ORIGINAL ARTICLE

The Effect of Resistance, Aerobic, and Concurrent Aerobic and Resistance Exercises on Inflammatory Markers of Metabolically Healthy Overweight or Obese Adults: A Systematic Review and Meta-analysis

John Patrick R. Lentejas, PTRP, MS,[1] Mark Anthony S. Sandoval, MD,[2] Teresita Joy Ples Evangelista, MD, MHA,[1] Myrna D. Buenaluz-Sedurante, MD, MSc[1] and Clarissa L. Velayo, MD, PhD[1]

[1]Department of Physiology, College of Medicine, University of the Philippines Manila
[2]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, College of Medicine and Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Objectives. To compare the effectiveness of different exercise interventions on improving adiposity-related inflammatory markers of metabolically healthy obese (MHO) adults.

Methods. This is a systematic review with meta-analysis of randomized controlled trials (RCTs) and quasi-experimental studies on the effects of exercise interventions in the inflammatory markers of sedentary adults with MHO phenotype. Systematic searches were performed in PubMed, Cochrane, CINAHL, and OVID from January 2021 to January 2022. The included studies were from 2000 to 2021. The inclusion criteria included: a) adults with obese phenotype, b) has physical activity or exercise as intervention, and c) inflammatory markers as outcome measure. Exclusion criteria included: a) pregnant women, b) adults with cardiovascular conditions or taking medications, c) participants having central obesity. The review was registered on PROSPERO (CRD42021249661). Risk of bias (RoB) assessment was performed using Revised Cochrane RoB tool for RCTs, and ROBINS-I tool for quasi-experimental studies. A meta-analysis was performed for inflammatory markers and body composition measurements using random effects model with forest plots presenting mean differences (MD) of outcome measures with 95% CI.

Results. Twenty-one RCTs and seven quasi-experimental studies with 1,117 participants were included in the review. For short-term intervention, aerobic exercises showed an increased trend in IL-6 levels, and both resistance and aerobic exercises reduced TNF-alpha and CRP levels, respectively. For long-term exercises, aerobic exercises showed a significant reduction in CRP (MD= -0.33, 95%CI, -0.57 to -0.09, p=0.006). Long-term concurrent training also showed a significant reduction in TNF-alpha (MD= -2.65, 95%CI, -4.13 to -1.18; p=0.0004). Meta-regression also found no direct association between body weight and fat mass, and changes in inflammatory markers.

Conclusion. Concurrent and aerobic exercises were both effective in reducing pro-inflammatory markers. Concurrent training was more effective in reducing BMI, body fat composition, and CRP compared to aerobic and resistance exercises. Furthermore, middle-aged women benefited from aerobic exercises to reduce IL-6 levels. These results indicate the need for both resistance and aerobic exercise in improving inflammatory levels of the body. This review has limitations in terms of degree of heterogeneity brought by different exercise protocol and assessment of inflammatory markers. More research is needed to identify possible outcome measures that can predict chronic inflammation in MHO people.

Keywords: metabolically healthy obese, aerobic exercise, resistance exercise, concurrent training, inflammatory markers

eISSN 2094-9278 (Online)
Published: November 29, 2024
https://doi.org/10.47895/amp.vi0.7315

Corresponding author: John Patrick R. Lentejas, PTRP, MS
Department of Physiology
College of Medicine, University of the Philippines Manila
547 Pedro Gil St., Ermita, Manila 1000, Philippines
Email: jrlentejas@up.edu.ph
ORCiD: https://orcid.org/0000-0002-5799-2421

INTRODUCTION

Currently, there have been investigations on a subtype of obesity called 'metabolically healthy obese' (MHO) which is a category for people with excess adiposity who do not exhibit cardiometabolic conditions.[1] Although considered as a healthier phenotype, MHO people still have a greater predisposition to cardiovascular conditions in the future due to their inflammation related to adiposity compared to their leaner counterparts.[2]

It has been shown that physical activity can induce anti-inflammatory effects.[3] This is supported by the meta-analyses performed by Garcia-Hermoso et al. and Alizaei Yousefabadi et al. which proved that exercises can reduce pro-inflammatory markers brought by excess weight in adolescents[4], and adults with metabolic syndrome[5], respectively. However, it is still unclear which type of physical activity intervention is more effective in improving adiposity-related inflammation in sedentary MHO adults.

According to Lin et al.[6], MHO people need a different set of interventions as they do not respond to the usual diet-induced weight loss given to obese individuals with metabolic syndrome. This is supported by Kantartzis et al.[7], who noted only slight improvements in insulin sensitivity in adults with MHO compared to adults with metabolic syndrome despite a significant decrease in visceral fat in both groups. More research is needed to find an effective treatment specifically for individuals with the MHO phenotype for the primary prevention of CVD and other metabolic conditions.[2,6]

With this, the systematic review will compare the effectiveness of resistance training, aerobic exercises, or a combination of both interventions in improving the inflammatory markers of sedentary metabolically healthy obese adults. The study will also help identify which body composition measurements are significantly associated with the changes in adiposity-related inflammatory markers.

METHODS

This systematic review followed the PRISMA guidelines as indicated in the study by Liberati et al.[8] It was registered at the University of the Philippines - Manila Research Grants Administration Office (RGAO) - RGAO-2021-1029. Compliance with research ethical guidelines including checking for plagiarism using Turnitin app was checked by the research panel of the Department of Physiology, College of Medicine, University of the Philippines Manila. The study proposal was also registered at the International Prospective Register of Systematic Reviews (PROSPERO) CRD42021249661. Amendments in the study protocol (i.e., clarifying research strategies, changing outcome measures, and adding data synthesis method) were made before the implementation of the review and can be accessed at the website https://www.crd.york.ac.uk/PROSPERO.

Data Search Terms and Search Strategy

The two authors (JPRL and TJPE) conducted individual systematic searching from January 2021 to January 2022. The search terms used are based on the PICO question: population ("overweight OR obese" AND "sedentary OR inactive" AND "adults", intervention and comparator exercise (“exercise” OR "physical activity” OR “training” OR “aerobic” OR “endurance” OR “resistance" OR “strengthening” OR “combined training” OR “concurrent training”), outcome measure ("inflammatory markers” OR “inflammation” OR “interleukin” OR c-reactive protein” OR “CRP”).

The authors performed systematic searches in the following databases: MEDLINE/PubMed, Cochrane, CINAHL, and OVID. To prevent publication bias, the authors performed hand searching of bibliographies of systematic reviews or meta-analyses, and conference proceedings on International Congress on Obesity. The authors also searched online repositories of international libraries and universities, websites of different health and research organizations, websites of health journals, and websites for online grey literature (google scholar, SCOPUS, proquest.com, science.gov, clinicaltrials.gov, and other related websites). The review included studies from the year 2000-2021.

Eligibility Criteria

Studies with adults (18 years old and above) with overweight or obese profile (based on BMI or other anthropometric measurement indicated), considered sedentary based on self-report survey or physical activity questionnaire, include physical activity, resistance exercise, or aerobic training, or sedentary breaks as intervention, outcome measures involve inflammatory markers, and with a control group that should be in sedentary condition or without exercise intervention, and the study type should be quasi-experimental or randomized controlled trials

Studies are excluded if they involve pregnant women or women taking hormonal replacement therapy; participants who have a central obesity or waist-hip ratio greater than 0.95 (women) and greater than 1.03 (men) (or waist circumference greater than 102 cm for men or greater than 88 cm for women)[9]; participants with diabetes mellitus, heart disease, active cancer, stroke, participants with active infection, or conditions with systemic inflammation; participants taking antihypertensives, anti-lipidemic, anti-diabetic drugs or NSAIDs; studies where intervention is only drug therapy or behavior change without quantified physical activity/exercise included; or studies that are not translated in English.

Data Extraction

All studies retrieved from the databases were stored and de-duplicated by a single researcher (JPRL) using Zotero reference manager.[10] Systematic title and abstract screening were performed by the same single researcher using Rayyan software.[11] After the abstract screening, the full texts of studies were retrieved and decided on which studies to be included based on the set of inclusion and exclusion criteria. Researchers of studies with missing data, no full-text, or no English translation of full-texts were contacted via email and requested the missing information, full-text copies, or English-translated copies. A separate spreadsheet was created to record the reasons for exclusion for the studies retrieved. The results of the abstract and full-text screening were verified by another researcher (TJPE).

The studies selected after full-text screening underwent a risk of bias assessment by two independent assessors (JPRL, TJPE). The assessors used the following risk-of-bias tools: for randomized controlled trials (parallel-group trials) - *Revised Cochrane risk-of-bias tool for randomized trials*; for randomized crossover trials *Revised Cochrane risk-of-bias tool for randomized crossover trials*; and for quasi-experimental studies - *Risk Of Bias In Non-randomized Studies - of Interventions* (ROBINS-I tool).[12,13] The results of the risk-of-bias assessment were compiled and summarized using an online robvis tool.[14] For disagreements between the assessment, discussions were conducted between the assessors until consensus was reached. For cases with no consensus on the disagreement, a third assessor (MSS) decided for the conflict in assessment.

For data extraction, a single data extractor (JPRL) used an MS Excel spreadsheet to document the data from each study. If the data is in graphical form, the Web Plot Digitizer was used independently by the two extractors, and the mean of (2) values gathered was considered the value for the outcome measure.[15] Missing data from studies were requested from the researchers by the data extractor. The data collected were counter-checked by another researcher (MSS).

Data Synthesis

A qualitative synthesis was performed and reported in the review containing PRISMA flow diagram.[16] The data collected were grouped into short-term exercise interventions (exercise interventions lasting for less than 6 weeks), and long-term exercise interventions (exercise interventions more than 6 weeks). For each group, the data were further classified according to the following classification of exercise intervention: aerobic or endurance exercise (any form of repetitive or sustained activity using large muscles of the body over a prolonged period of time e.g., walking, running, cycling, swimming[17]), resistance or strengthening (any form of exercise that results to muscle contraction against a resistance ("lifting, lowering, or controlling heavy loads for low number of repetitions or short period of time"[17]), and concurrent (combined aerobic and resistance exercise[18]).

A characteristic of experimental studies was also included with the following information: study author, type of study, participant characteristics (age, sex), sample size, control group (no exercise group or retain sedentary lifestyle), resistance and/or aerobic exercise – a specific type of exercise and equipment used, frequency, duration, and intensity of exercise, and the list of primary and secondary outcome measures. Lastly, a summary of the findings table was constructed in a Microsoft Excel sheet containing the data of outcome measures.

A quantitative analysis was also performed upon satisfying the following criteria: at least two experimental studies reporting a similar inflammatory marker, with a similar type of exercise intervention (resistance, aerobic, or concurrent); and the selected studies were considered "high level of evidence" based on the risk of bias assessment. The results of the studies with similar inflammatory markers and type of intervention were pooled together and meta-analyzed using RevMan Program Version 5.[19] The mean differences (MD) of CRP, IL-6, and TNF-alpha with 95% confidence interval were reported as the overall measure of effect size. The results of the meta-analysis were divided according to the duration of the intervention- short-term (less than 6 months) and long-term exercise interventions (more than 6 months). Studies with similar body composition measurements (weight, BMI, WHR, body fat mass, and lean body mass) and type of intervention were also pooled and meta-analyzed. A forest plot was generated using the RevMan Program Version 5[19] for each outcome measure and exercise intervention was presented. Random effects meta-analysis was used for the review to consider variability between studies. The association between inflammatory markers and body composition measurements was determined using meta-regression analysis of Stata 14 software.[20] Tests for heterogeneity (I^2 statistic), sub-group analyses of age, sex, and exercise intensity, and sensitivity analysis were also performed by the review. Lastly, the overall certainty of evidence were measured using GRADE tool[21] by two independent assessors (JPRL, TJPE).

RESULTS

Narrative review of study characteristics

The results of the screening of four databases (PUBMED, COCHRANE, CINAHL, and OVID) and other sources of grey literature produced 28 studies with 21 randomised controlled trials[18,22-41] and 7 quasi-experimental studies[41-48], with 1,117 MHO participants (Figure 1). The included studies can be stratified based on the duration of the studies: short-term exercise intervention (less than 6 weeks of exercise duration)[27,33,39-41,43], or long-term exercise intervention (more than 6 weeks)[18,22-26,28-32,34-38,42,45-48] (Tables 1 and 2). The summaries of findings were also created showing the results of each outcome measures in the studies included (Tables 3 and 4). Only studies with complete data were included in the study and used in the analysis.

For the studies under short-term term exercise intervention, the total number of participants was 181 adults. The age of participants ranged from young to older adulthood, with the majority belonging to the young adult population (60%). Most of the participants in the study were also male (80%). In terms of intervention, the studies only varied in type and intensity - with only the studies by Bizheh et al.[43] and Patrizi[33] having resistance exercises (low and high intensity, respectively), and the remaining studies used aerobic exercises (with both moderate and vigorous intensity). All exercise duration ranged from 25 mins to 1 hour, and most exercise frequencies lasted for one day, with the exception of the study of Koh et al.[27] which exercise intervention lasted for four weeks, with 3x/wk frequency.

For studies under long-term exercise interventions, the total number of participants was 936 participants: 481 (51%) are males, and 455 (49%) are females. In terms of the age group, the majority are middle-aged with 505 (54%) participants, followed by 328 (35%) young adults.

Despite having heterogeneous profiles (age and sex), all participants qualified under metabolically healthy obese phenotype based on the study of Zembic at el.[9] A subgroup analysis was performed for sex and age groups to determine possible sources of heterogeneity. A separate sub-group analysis for exercise intensity was also conducted to determine the level of effectiveness of each type of intervention on different sub-groups.

Another possible source of heterogeneity was the type of exercises performed.

They were further sub-grouped into resistance, endurance, and concurrent exercises. All resistance exercise interventions dealt with major muscle groups of the upper and lower extremities, with moderate intensity (8-10 repetitions, and 2-3 sets). The aerobic exercises also have similarities with the intervention type, varying only in intensity (low to high intensity). All of the exercise interventions lasted only for 40 minutes to 1 hour, with frequencies of 3-5 times per week, for 6 weeks to 12 months, with most studies (52%) conducted for 3 months.

Quality of the studies – Risk of bias assessment

Based on the Cochrane Collaboration's risk of bias tool for RCTs[12], out of 21 studies, there were two studies[26,37] with low risk of bias, and 17 studies[18,22-24,27-32,34-36,38-41] with some concerns regarding the randomization process and selection of outcome results, and two studies[25,33] with a high risk of bias. For the seven quasi-experimental studies, there were six studies[42-45,47,48] with only moderate risk of bias, and one study[46] with no information based on ROBINS-I tool[13].

Effects of short-term exercise intervention on changes in inflammatory markers

Short-term resistance exercise showed a significant increase in CRP levels with MD of 0.64 (95%CI, 0.05 to 1.23, p=0.03)[43], and a decrease in both TNF-alpha levels (MD=-280.67, 95%CI, -544.78 to -16.56, p=0.04)[33], and IL-6 levels compared to the control group (MD=-1.50,

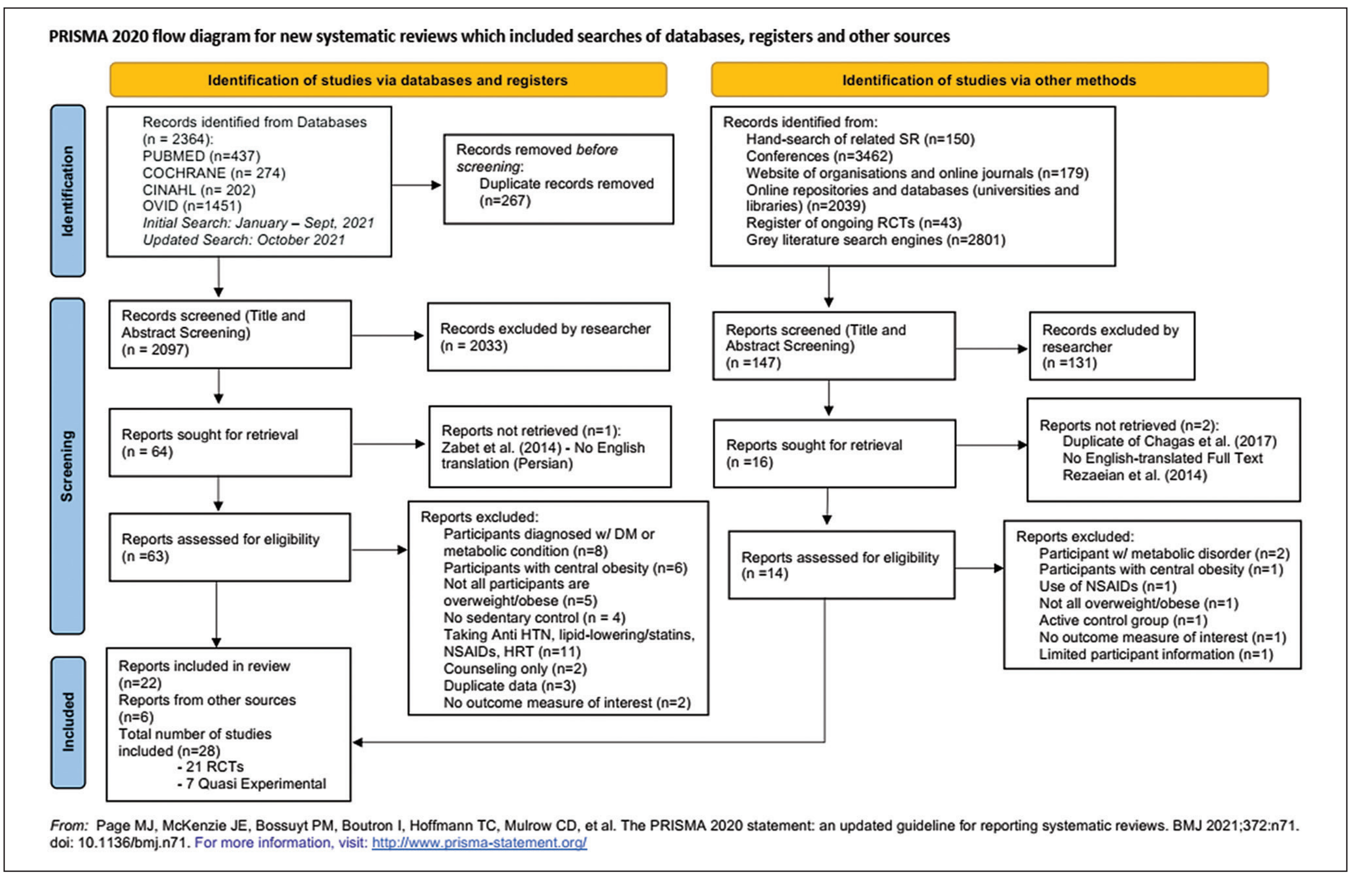

Figure 1. PRISMA flow chart.

95%CI, -1.85 to -1.15, p<0.00001)[33]. In contrast, short-term aerobic exercise only showed a significant decrease in CRP levels (MD= -1.43, 95%CI, -2.82 to -0.04, p=0.04)[27], with no significant decrease in TNF-alpha levels (MD=-2.08, 95%CI, -9.13 to 4.96, p=0.56; I^2=70%; p for heterogeneity=0.04)[27,40], and IL-6 levels compared to the control group (MD=4.37, 95%CI, -1.10 to 9.83, p=0.12; I^2=0%, p value for heterogeneity=1.00)[39-41].

Table 1. Characteristics of Experimental Studies: Short-term Studies

Study (Author, Year)	Participant Characteristics	Sex/Age	Sample Size (n=)	Exercise Intervention and Type of Exercise	Intensity	Frequency	Duration	Duration of Study (Pre-Post Test)	Outcome Measures
Bizheh et al., 2011 (Quasi Experimental)	Southwest Asians; healthy and inactive men; WHR: 0.93-0.94 (mean); nonsmokers, received no drugs and had no metabolic disease and physical impairment affecting their performance	M, MIDDLE-AGED Mean Age: 43-44 years	23	CONTROL (n=9) RESISTANCE (n=14): use of weights	RESISTANCE: LOW 35% of one repetition maximum	1x	10 whole-body exercises x 20 secs each x three circuits with 1 min rest between each set	1d	CRP BMI, Body Fat%
de Souza et al., 2018 (RCT)	Obese sedentary male; BMI 35.9 ± 4.9 kg/m^2, Not hypertensive No metabolic alterations *No reports of WC or WHR	M, YOUNG Mean Age: 28.5 ± 2.7 years	10 x 3 (cross over design)	CONTROL (n=10) AEROBIC: 2 groups treadmill HIIE (n=10) MICE (n=10)	AEROBIC: HIIE – high intensity 90% of MTV highest velocity sustained in 1 min MICE – MODERATE INTENSITY (CONTINUOUS) 65-75% HRmax	1x	25 min	1 day (60 minutes after exercise)	IL-6
Emerson et al., 2016 (RCT)	Caucasians; healthy, non-smoking, overweight (BMI: >25 kg/m^2), insufficiently active men, cross over design each trial after 7 days Not diagnosed with cardiovascular diseases No impaired glucose tolerance *No reports of WC or WHR	M, YOUNG Mean Age: 24.5 ± 5.1 years	12 x 3 trials (cross over design)	CONTROL (n=12) AEROBIC (n=12) (treadmill)	AEROBIC: VIGOROUS (60% VO_2 max)	1x	30 min, 60 min	1 day (1,2,4,6 and 8h post)	TNF-α, IL-6
Koh, Park et al., 2016 (RCT)	Caucasians; physically inactive, overweight or obese (body mass index >25.0 kg/m^2) No chronic conditions; Not taking any medication that can alter metabolic, cardiovascular or immune function	M(13), F(14) 18-65 years old	27	CONTROL (n=12) AEROBIC (n=15): (walking treadmill)	AEROBIC: MODERATE moderate intensity walking exercise on a treadmill for 60 min at 70% of maximal heart rate	3x/week	1 hour	1 month	CRP, TNF-α BMI, Body Fat%
Panissa et al., 2019 (RCT)	Hispanics; Inactive (lack of regular exercise, <150 min per week over the last 6 months), overweight men, No health problems or taking pharmacologic interventions affecting appetite or metabolic functions *No reports of WC or WHR	M, YOUNG Mean Age: 30.2 ± 4.1 years	14 x 5 trials (cross over design)	CONTROL (n=14) AEROBIC: 4 groups HIIE – 1 h and 2.5 h after breakfast (each group, n=14) Steady state exercise - cycling at 50% MAP - 1 h and 2.5 h after breakfast (each group, n=14)	AEROBIC: HIIE (VIGOROUS INTENSITY) 30s repetitions at MAP (70 rpm) Steady State (MODERATE INTENSITY) 50% of Maximum Aerobic Power	1x	30 min	1 day (1h, 1.75h, 2.5h and 3.25h)	IL-6
Patrizi, 2008 (RCT)	Caucasians; post-menopausal, obese women; 30 ≤ body mass index ≤ 40 kg/m^2; had not participated in a regular exercise program for the previous six months; No HRTs, severe arthritis, bedridden within three months of the study, central or peripheral nervous system disorders, previous stroke, use of antidepressant medications, acute or chronic infection, major affective disorder, HIV infection or auto-immune disorders, metabolic disorders (type I or type II diabetes mellitus), oral steroid use. Regular NSAID users were asked to refrain from taking their medication until after the experimental trials on test days	F, OLDER 60-70 years old	23	CONTROL (n=11) RESISTANCE (n=14): machine and free weights	RESISTANCE: HIGH (80% of their estimated 1-RM)	1x	10 exercises x 8 reps x 3 sets (with last set reps increased until fatigued) with 1.5 min rest period between sets	1d	IL-6, TNF-α

Table 2. Characteristics of Experimental Studies: Long-term Studies

Study (Author, Year)	Participant Characteristics	Sex/Age	Sample Size (n=)	Exercise Intervention and Type of Exercise	Intensity	Frequency	Duration	Duration of Study (Pre-Post Test)	Outcome Measures
Ahmadizad et al., 2015 (Quasi-experimental)	Southwest Asians; sedentary overweight men Healthy; Not taking any medications, No physical activity; WHR (0.87-0.88)	M, YOUNG (25±1 years)	30	CONTROL (n=10) AEROBIC: 2 GROUPS HIIT (n=10) and MCT-Moderate Exercise Group (n=10) (treadmill-run/jog)	AEROBIC: HIIT: VIGOROUS (90% VO_2 max) MCT: MODERATE (walking/jogging at 50-60% VO_2 max)	3x/week	HIIT 8 EXERCISE INTERVAL (1 min) with 2-3 min ACTIVE REST; MCT - 30-70 min	1.5 months (6 weeks)	TNF-α, IL-6 BMI, Body fat%, WHR
Auerbach et al., 2012 (RCT)	Sedentary Caucasian overweight men BMI 25-30 kg/m^2 with body fat percentage >25%, healthy, <140/90 mmHg blood pressure, took no medications Fasting capillary glucose <6.1 mM and no 1st degree relative with diagnosed T2DM WC mean: 98±1 cm	M, YOUNG Mean Age: 31±1 years	24	CONTROL (n=12) AEROBIC (n=12): (cycling, running, cross-training, or rowing)	AEROBIC: MODERATE-VIGOROUS ~65% HRR with High Intensity Training ~85% HR-reserve of 5-6 exercise bouts of 3-4 mins	3-4x/week	Not reported (equivalent to 600 kcal were utilized)	3 months	CRP, TNF-α, IL-6 BMI, whole body fat %, Free Fat Mass, WC (cm)
Cooper et al., 2016 (RCT)	Australians; sedentary men BMI >28 kg/m^2; No preexisting diabetes Not taking anti-hypertension medications, no cardiovascular disorders WHR of ~1.0, not taking lipid lowering medications or anti-inflammatory drugs	M, MIDDLE-AGED 40-60 years old	59	CONTROL (n=14) AEROBIC: 3 GROUPS ET - 50 TO 60 mins cycling (n=15) A-SIT - 4-10 x 30 secs sprint effort with active recovery (n=15) P-SIT - 4-10 x 30 secs sprint effort with passive recovery (n=15)	AEROBIC: ALL GROUPS VIGOROUS (80% HRmax)	3x/week	50-60 mins	3 months (12 weeks)	CRP, TNF-α, IL-6; Fat Mass %, Free Fat Mass (kg)
Domene et al., 2016 (RCT)	Australians; overweight (BMI 27.1±1.9) and physically inactive women; Not taking Anti HTN, mean arterial BP (90±8mmHg), not taking anti-inflammatory, anti-hyperlipidemia medications; not pregnant *blood glucose/insulin level not reported	F, YOUNG Mean Age: 34 years	20	CONTROL (n=10) AEROBIC (n=10): (zumba dance)	AEROBIC: VIGOROUS	1-2x/week	1 hour	2 months	CRP, IL-6 BMI, body fat %
Donges et al., 2013 (RCT)	Caucasians; BMI 30.4±4.1 kg/m^2 No pre-existing or new DM diagnosis No CV disease, renal or hepatic disorders, immunologic condition, COPD, or other systemic inflammatory condition, taking lipid-lowering, anti-hypertensive, and anti-inflammatory medications WHR: ~0.87	M, MIDDLE-AGED Mean Age: 48.1 ± 6.8 years	47	CONTROL (n=8) RESISTANCE n=13: (MACHINE) AEROBIC n=13: (cycle ergometry with elliptical cross training) COMBINED n=13: 50% completion of Resistance and Aerobic exercises protocol	RESISTANCE: MODERATE 75% of 1RM up to 80% 1RM AEROBIC: MODERATE TO VIGOROUS (75% HRmax to 80% HRmax)	3x/week	RESISTANCE: 10 exercises at 10 reps x 3 sets to 8 reps x 4 sets AEROBIC: 40-60 mins COMBINED: 60 mins	3 months	CRP, TNF-alpha, IL-6 BMI, WC (cm), WHR, Fat Mass%, Free Fat Mass (kg)
Gram et al., 2017 (RCT)	Caucasians; physically inactive, healthy, overweight and obese (BMI 25-35 kg/m^2) women and men; No metabolic or cardiovascular conditions, no habitual medications *No mentioning of central obesity on participants *No WHR or WC reported in study	M(45), F(50), YOUNG 20-45 years old	95	CONTROL (n=18) AEROBIC: 2 GROUPS MODERATE GROUP (n=39) AND VIGOROUS GROUP (n=38) - (running, cycling, rowing, step-machine, cross trainer, other aerobic exercise)	AEROBIC: MODERATE (50% VO_2 max) VIGOROUS (70% VO_2 max)	2-5x/week	30-75 mins (150 mins/ week)	3 months	CRP Body Composition (BMI)
Ho et al., 2013 (RCT)	Australians; overweight or obese sedentary men and women (BMI between 25 and 40 kg/m^2), not taking lipid lowering drugs, not pregnant or lactating -women, No diabetes mellitus Not taking any beta-blockers, blood pressure ~120/70 WHR (0.85-0.88)	M(16), F(81) MIDDLE-AGED 40-66 years with Mean Age: 52-55 years	97	CONTROL (n=16) RESISTANCE (n=16): machines and free weights AEROBIC (n=15): (treadmill) COMBINED (n=17): (15 mins of Aerobic, and 15 mins of Resistance)	RESISTANCE: MODERATE (10RM x 4 sets x 8-12 reps) progression increased weight AEROBIC: VIGOROUS 60% HRR COMBINED: combination of 2 types	5x/week	30 mins	3 months	TNF-α, IL-6 BMI, Body fat%, WC (cm)

Table 2. Characteristics of Experimental Studies: Long-term Studies *(continued)*

Study (Author, Year)	Participant Characteristics	Sex/Age	Sample Size (n=)	Exercise Intervention and Type of Exercise	Intensity	Frequency	Duration	Duration of Study (Pre-Post Test)	Outcome Measures
Mendham et al., 2014 (RCT)	Australians; Middle aged sedentary men; BMI (27 to 29 kg/m^2); not diagnosed with cardiovascular, metabolic and inflammatory disorders; not taking any medications, flu injections, or vitamin supplementation WHR: 0.95±0.05	M, MIDDLE-AGED (48.6±6.6 years)	33	CONTROL (n=11) AEROBIC: 2 GROUPS cycling (n=11), modified rugby session (n=11)	AEROBIC: VIGOROUS (80% HRmax)	3x/week	40-50 mins	2 months (8 weeks)	CRP, TNF-α, IL-6 BMI, WHR, Fat Mass %, Free Fat Mass (kg)
Mendham et al., 2015 (RCT)	Australian ancestry (BMI >27 kg/m^2) Not diagnosed with pre-existing metabolic or cardiovascular disorders, blood pressure ~120/70 mmHg WHR 0.96-0.97	M, MIDDLE-AGED (CONTROL: 36.1 ± 16.1 years EXP: Age 39.5 ± 10.6 years)	33	CONTROL (n=16) COMBINED n=17 (AEROBIC: cycling, running, rowing, ergometry; RESISTANCE: free weights; sports at final weeks)	COMBINED: MODERATE TO VIGOROUS (HRmax ONLY)	2-3x/week	45-60 mins	3 months (12 weeks)	CRP, TNF-α, IL-6 BMI, WC (cm), Waist/Hip Ratio
Moghadasi et al., 2012 (RCT)	Southwestern Asians; sedentary overweight and obese middle-aged men; Mean: 31.5±3.9 kg/m^2, 1) No diagnosed DM; 2) resting blood pressure <160/100 mmHg, not taking medications that can alter exercise performance, appetite or metabolism, including aspirin and lipid altering medications 3) WHR: 0.96-0.99	MIDDLE-AGED Age: 41.18±6.1 years	16	CONTROL (n=8) AEROBIC (n=8): (treadmill)	AEROBIC: VIGOROUS Moderate to vigorous endurance training (75–80% individual maximum oxygen consumption)	4x/week	45 mins	3 months	CRP BMI, WHR, Body fat %, Lean body mass (kg)
Mogharnasi et al., 2019 (Quasi-experimental)	Southwestern Asians; overweight and obese women; No chronic or acute conditions, not using dietary supplements or drugs, WHR (0.82-0.85)	F, YOUNG Age: 22.29 ± 2.49 years	34	CONTROL (n=10) RESISTANCE n=12 (free weights) AEROBIC n=12: (running)	RESISTANCE: MODERATE AEROBIC: VIGOROUS (20 mins with 65% HRmax up to 34 mins with 80% HRmax)	4x/week	RESISTANCE: training of major muscle groups at 8 stations for 2-4 sets x 8-12 reps (20-35 mins) AEROBIC: 20-34 mins	2 months	CRP BMI, Fat Mass (kg), WHR
Nikseresht, et al., 2014 (RCT)	Southwestern Asians; healthy sedentary men who are obese; No history of any kind of medical condition that would prevent from exercising; No regular consumption of medications; WC (cm) ~99-102	M, MIDDLE-AGED Age: 34–46 years	34	CONTROL (n=10) RESISTANCE n=12: (weights and machines) AEROBIC n=12: (treadmill)	RESISTANCE: LIGHT TO HEAVY (40-90% 1RM) AEROBIC: VIGOROUS (80-90% MHR Running on treadmill 4 sets of 4 mins with 3 mins recovery intervals at 55-65% MHR)	3x/week	40-65 mins	3 months	TNF-α Fat mass (kg)
Olson et al., 2007 (RCT)	Caucasians; overweight (BMI ≥25 kg/m^2) women, aged 25-44 years, sedentary; Not taking NSAIDS, Statins, and medications for hypertension for the past 6 months, Non hyperlipidemic and normoglycemic *No mentioning of central obesity on participants *No WC or WHR reported in the study	F, MIDDLE-AGED	28	CONTROL (n=12) RESISTANCE n=16 (isotonic variable machines, and free weights)	RESISTANCE: MODERATE	2x/week	RESISTANCE: Exercises for 8 major muscle groups 3 SETS x 8-10 REPS progressed with increased resistance/ weights	12 months	CRP, IL-6 BMI, body fat%, lean body mass(kg)
Puengsuwan et al., 2020 (RCT)	Southeast Asians; healthy sedentary adults aged 55-70 years, BMI mean: 25.6 kg/m^2; menopause, FBG ~ 95 mg/dL; WHR: 0.84±0.07 *blood pressure of participants not reported in study	M(11), F(45), OLDER Mean Age: 61 years	56	CONTROL (n=29) AEROBIC n=27 (weighted wand exercises)	AEROBIC: LOW (wand-assisted muscle stretching exercise and aerobic exercise on both the upper body and lower body)	5x/week	40 MINS	3 months (15 weeks)	CRP BMI, WHR, WC (cm), Body fat%, Free Fat Mass (kg)
Rohde et al., 2018 (RCT)	South Asians; physically inactive men (mean BMI: 27 kg/m^2) No T2DM diagnosis Blood pressure ~120/85 mmHg WC: 97-98 cm	M, MIDDLE-AGED CONTROL: 39.7(9.2) EXP: 35.8(6.1)	133	CONTROL (n=53) COMBINED n=80 (AEROBIC - floor ball/ football; RESISTANCE - strengthening)	COMBINED: MODERATE	2x/week	40 mins	5 months	CRP

Table 2. Characteristics of Experimental Studies: Long-term Studies *(continued)*

Study (Author, Year)	Participant Characteristics	Sex/Age	Sample Size (n=)	Exercise Intervention and Type of Exercise	Intensity	Frequency	Duration	Duration of Study (Pre-Post Test)	Outcome Measures
Sadeghi et al., 2019 (Quasi-experimental)	Southwest Asians; obese and overweight Iranian women; sedentary Lack of metabolic conditions Absence of chronic diseases e.g., cardiovascular and joint diseases *No mentioning of central obesity on participants *No WC, or WHR reported in the study	F, MIDDLE-AGED 35-45 years	22	CONTROL (n=11) AEROBIC (n=11): (slow-pace jogging and walking)	AEROBIC: LOW 50-55% HRmax	3-4x/week	30 mins progressed to 45 mins	2 months	CRP BMI Fasting glucose and insulin levels, HOMA-IR; Fasting blood lipid levels
Shabani et al., 2018 (RCT)	Southwest Asians; healthy sedentary overweight or obese (BMI ≥25 kg/m^2) females; lack of participation in any regular physical activity; No serious medical condition – stroke, heart attack, arthritis; No history of drug use Blood Pressure ~120/80 FBS ~99-102 mg/dL WHR ~0.90-0.91	F, OLDER Age: 50–60 years	22	CONTROL (n=10) COMBINED (n=12) (AEROBIC - running treadmill or ergometer; RESISTANCE)	COMBINED: MODERATE RESISTANCE; VIGOROUS AEROBIC EXERCISE RESISTANCE - 50%–75% of one-repetition maximum (1RM) AEROBIC - 50%–80% exercise target HR (THR)	3x/week	90 mins	2 months (8 weeks)	CRP BMI, WHR CRF; fasting glucose, fasting lipid profile (TC, TG, LDL, HDL)
Shahram et al., 2016 (Quasi-experimental)	Southwest Asians; healthy overweight women *No mentioning of central obesity on participants *No WC, or WHR reported in the study	F, YOUNG Mean Age: 22 years	30	CONTROL (n=10) RESISTANCE (n=10): circuit weight training AEROBIC (n=10): running program	RESISTANCE: MODERATE (50-60% 1RM x 12 reps x 4 sets) AEROBIC: VIGOROUS (60-65 TARGET HR to 70-75 THR)	3x/week	RESISTANCE: 11 stations aerobic: running time not reported	3 months	TNF-α, IL-6 BMI, Body fat% IL-10
Shahrekordi et al., 2017 (Quasi-experimental)	Southwest Asians; old-aged healthy women No hypertension No Diabetes Mellitus WHR (088-0.91)	F, OLDER Age: 55–70 years	40	CONTROL (n=9) COMBINED 4 GROUPS Resistance after Aerobic (n=9) Resistance prior to Aerobic (n=10) Interval Resistance and Aerobic (n=12)	Not reported	3x/week	50 mins	2 months	CRP, IL-6 BMI, Body Fat%, WC (cm), WHR
Soltani et al., 2020 (Quasi Experimental)	Southwest Asians; sedentary overweight and obese females No diagnosed conditions, or taking medications* *No mentioning of central obesity on participants *No WC or WHR reported in the study	F, YOUNG 18-25 years	30	CONTROL (n=15) COMBINED (AEROBIC - cycling; RESISTANCE - free weights and machine)	COMBINED: For Resistance - MODERATE (40-50% 1RM to 50-70% 1RM) For Aerobic - VIGOROUS (50-70% to 75-90% HRMax)	4x/week	~30 mins	2.5 months (10 weeks)	TNF-α BMI IL-10; Adiponectin; Fasting glucose, fasting insulin, HOMA-IR; Pentraxin 3 (PTX3); Fasting lipid profile (TG, LDL, HDL)
Swisher et al., 2015 (RCT)	Caucasians; survivors of triple-negative breast cancer* with BMI >25 kg/m^2 No diagnosis of DM No significant cardiac or renal disease that would prohibit exercise WHR: 0.87-0.9	F, MIDDLE-AGED CONTROL: 53.6 (36-71) years EXP: 53.8 (43-65) years	23	CONTROL (n=10) AEROBIC (n=13): (stationary biking, elliptical trainer, treadmill, walking as home exercise)	AEROBIC: MODERATE (supervised, moderate-intensity aerobic exercise 60-75% Max HR)	5x/week	30 mins	3 months	CRP, TNF-α, IL-6 BMI, Waist/hip ratio, Body fat% Leptin, Adiponectin, Fasting insulin; QOL (FACT-B)
Yoon et al., 2018 (RCT)	East Asians; obese post-menopausal women with 30% body fat percentage; not taking medications due to heart conditions, sex hormonal drugs or HRT Normal blood pressure (baseline) Relatively normal fasting glucose (baseline) WC> 82 cm	F, MIDDLE-AGED Mean Age: 52-53	30	CONTROL (n=10) RESISTANCE (n=10): machines and free weights AEROBIC (n=10): (treadmill)	RESISTANCE: MODERATE 60% OF 1RM AEROBIC: VIGOROUS HRR 60-80%	3x/week	40 mins	3 months	CRP BMI, Body Fat%, WC (cm)

Effects of long-term exercise intervention on changes in inflammatory markers

C-reactive protein

For long-term aerobic exercises, there were 12 arms with 348 participants included in the analysis. The pooled results showed a significant decrease in CRP levels with MD of -0.33 (95%CI, -0.57 to -0.09, p=0.006; I^2=93%, p for heterogeneity <0.00001)[18,22-25,28,30,34,37,38,45] (Figure 2). In comparing different exercise types in decreasing CRP levels, concurrent exercise was a better intervention in reducing CRP levels compared to aerobic exercises (p=0.0002)[18], and resistance exercises (p=0.0002).[18]

TNF-alpha

For long-term concurrent exercises, there were 4 arms with 117 participants included in the analysis. Based on the pooled results, concurrent training caused a significant reduction of TNF-alpha levels with MD of -2.65 (95%CI, -4.13 to -1.18, p=0.0004; I^2=88%, p for heterogeneity <0.0001)[18,26,29,48] (Figure 3). In comparing the effectiveness of different exercise interventions in decreasing TNF-alpha, the studies did not show significant difference between aerobic and resistance (p=0.11)[18,26,31,46], aerobic and concurrent (p=0.21)[18,26], and concurrent and resistance (p=0.19)[18,26].

IL-6

For IL-6, no significant reduction was observed in all of the exercise interventions (Figure 4). In comparing different exercise interventions in terms of decreasing IL-6 levels, aerobic training caused significant reduction of IL-6 levels compared to concurrent exercises (p<0.00001)[18,26] (Figure 5).

Effects of long-term exercise intervention on body composition measurements

Weight

There were 25 study arms with 650 participants used to investigate the effectiveness of exercise interventions to changes in weight. It was observed that only long-term vigorous aerobic exercise caused a significant weight loss with MD of -1.30 (95%CI, -2.31 to -0.28, p= 0.01; I^2=25%, p for heterogeneity = 0.22)[23-25,28,30,31,38,42,46]. In terms of comparison of exercise types, the pooled data showed that concurrent training was more effective in reducing weight compared to aerobic exercise (p<0.0001).[18]

Table 3. GRADE evidence profile: Long-term exercise effects on inflammatory markers for MHO adults

Quality of evidence								Summary of findings: No. of patients			Overall certainty of evidence
Intervention	No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Risk of Reporting Bias	Control	Exercise	MD (95% CI)	
CRP											
Aerobic	11	10 RCT, 1 Quasi-experimental	Not serious	Serious	Not serious	Not serious	Undetected	141	207	-0.33 (-0.57, -0.09)	⊕⊕⊕◯ MODERATE
Resistance	3	3 RCTs	Not serious	Very Serious	Not serious	Serious	Undetected	30	39	0.04 (-0.34, 0.41)	⊕◯◯◯ VERY LOW
Concurrent	5	4 RCTs, 1 Quasi-experimental	Not serious	Not serious	Not serious	Serious	Undetected	96	132	-0.05 (-0.42, 0.32)	⊕⊕⊕◯ MODERATE
TNF-alpha											
Aerobic	9	8 RCTs, 1 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	101	121	-0.91 (-1.92, 0.10)	⊕⊕◯◯ LOW
Resistance	4	3 RCTs, 1 Quasi-experimental	Not serious	Very Serious	Not serious	Serious	Undetected	44	51	-1.45 (-3.11, 0.20)	⊕◯◯◯ VERY LOW
Concurrent	4	3 RCTs, 1 Quasi-experimental	Not serious	Very Serious	Not serious	Not serious	Undetected	55	62	-2.65 (-4.13, -1.18)	⊕⊕◯◯ LOW
IL-6											
Aerobic	9	7 RCTs, 2 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	101	119	-0.42 (-2.07, 1.24)	⊕⊕◯◯ LOW
Resistance	4	3 RCTs, 1 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	46	55	-1.20 (-4.11, 1.71)	⊕⊕◯◯ LOW
Concurrent	4	3 RCTs, 1 Quasi-experimental	Not serious	Very Serious	Not serious	Very Serious	Undetected	49	57	0.14 (-0.99, 1.27)	⊕◯◯◯ VERY LOW

Table 4. GRADE evidence profile: Long-term Exercise Effects on Body Composition Measurements for MHO Adults

Quality of evidence								Summary of findings			Overall certainty of evidence
								No. of patients		MD (95% CI)	
Intervention	No. of studies	Design	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Risk of Reporting Bias	Control	Exercise		
Body Weight											
Moderate Intensity Aerobic	6	4 RCTs, 2 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	81	113	-0.89 (-3.73, 1.95)	⨁⨁◯◯ LOW
Vigorous Intensity Aerobic	9	7 RCTs, 2 Quasi-experimental	Not serious	Not serious	Not serious	Not serious	Undetected	96	124	-1.30 (-2.31,-0.28)	⨁⨁⨁⨁ HIGH
Resistance	5	4 RCTs, 1 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	50	61	-0.30 (-3.78, 3.17)	⨁⨁◯◯ LOW
Concurrent	5	3 RCTs, 2 Quasi-experimental	Not serious	Not serious	Not serious	Serious	Undetected	58	67	-1.64 (-5.07, 1.79)	⨁⨁⨁◯ MODERATE
BMI											
Moderate Intensity Aerobic	4	3 RCTs, 1 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	68	90	-1.01 (-2.45, 0.42)	⨁⨁◯◯ LOW
Vigorous Intensity Aerobic	8	6 RCTs, 2 Quasi-experimental	Not serious	Not serious	Not serious	Not serious	Undetected	93	114	-0.24 (-0.32,-0.15)	⨁⨁⨁⨁ HIGH
Resistance	5	3 RCTs, 2 Quasi-experimental	Not serious	Not serious	Not serious	Not serious	Undetected	58	64	0.07 (0.00, 0.13) Favours control	⨁⨁⨁⨁ HIGH
Concurrent	5	3 RCTs, 2 Quasi-experimental	Not serious	Serious	Not serious	Not serious	Undetected	66	71	-1.90 (-3.48, -0.31)	⨁⨁⨁◯ MODERATE
WHR											
Aerobic	5	3 RCTs, 2 Quasi-experimental	Not serious	Not serious	Not serious	Not serious	Undetected	68	78	-0.02 (-0.04, -0.01)	⨁⨁⨁⨁ HIGH
Resistance	1	1 Quasi-experimental	Serious	Unknown	Not serious	Not serious	Undetected	10	12	-0.03 (-0.06, 0)	*Insufficient*
Concurrent	3	2 RCTs, 1 Quasi-experimental	Not serious	Not serious	Not serious	Serious	Undetected	35	39	-0.01 (-0.05, 0.03)	⨁⨁⨁◯ MODERATE
Body fat composition											
Moderate Intensity Aerobic	4	3 RCTs, 1 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	57	63	-0.35 (-2.56, 1.86)	⨁⨁◯◯ LOW
Vigorous Intensity Aerobic	10	7 RCTs, 3 Quasi-experimental	Not serious	Serious	Not serious	Not serious	Undetected	109	113	-1.72 (-2.70, -0.74)	⨁⨁⨁◯ MODERATE
Resistance	7	5 RCTs, 2 Quasi-experimental	Not serious	Serious	Not serious	Serious	Undetected	76	89	-0.92 (-2.42, 0.57)	⨁⨁◯◯ LOW
Concurrent	3	2 RCTs, 1 Quasi-experimental	Not serious	Not serious	Not serious	Not serious	Undetected	33	40	-1.19 (-1.36, -1.02)	⨁⨁⨁⨁ HIGH
Lean Body Mass											
Aerobic	6	6 RCTs	Not serious	Serious	Not serious	Not serious	Undetected	82	86	-1.43 (-2.31, -0.55)	⨁⨁⨁◯ MODERATE
Resistance	2	2 RCTs	Not serious	Not serious	Not serious	Serious	Undetected	20	29	-2.26 (-4.52, 0.01)	⨁⨁⨁◯ MODERATE
Concurrent	1	RCT	Not serious	Unknown	Not serious	Not serious	Undetected	8	13	-4.80 (-7.46, -2.14)	*Insufficient*

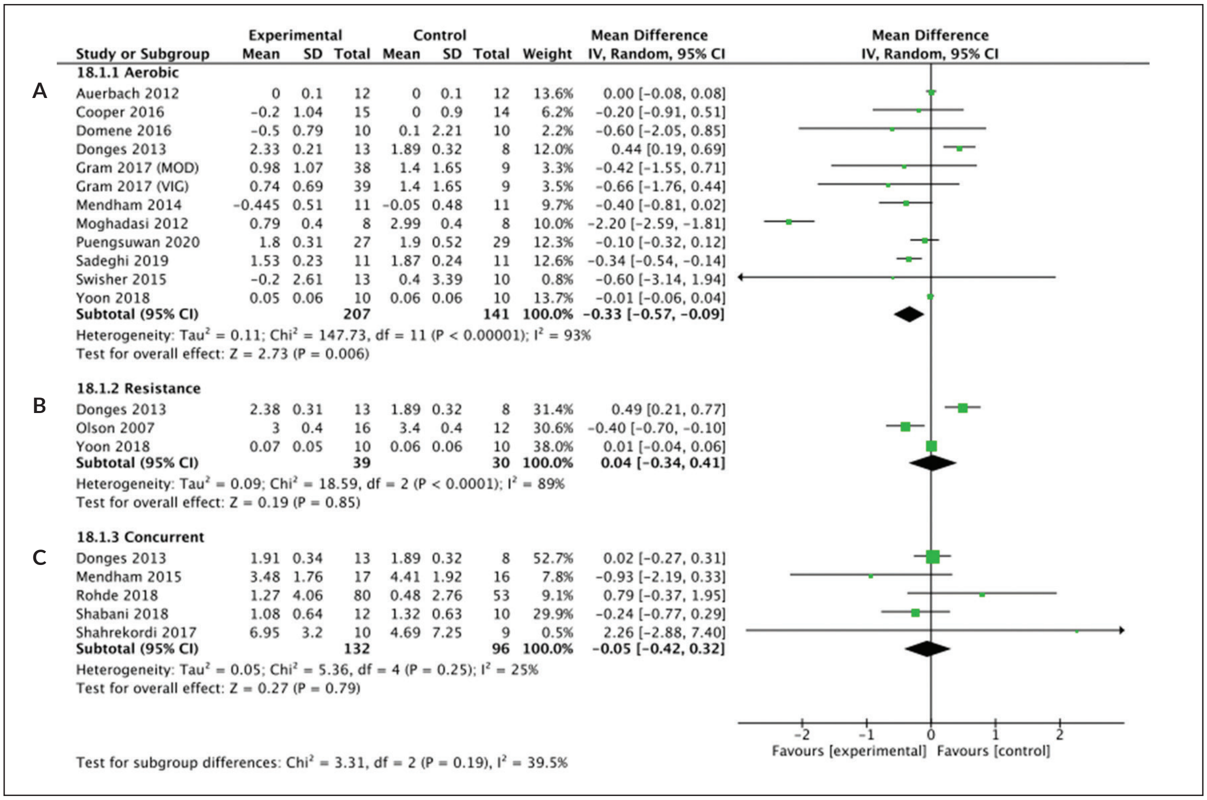

Figure 2. Forest plot of long-term exercise and its effect on C-reactive protein levels: **(A)** long-term aerobic exercise, **(B)** long-term resistance exercise, and **(C)** long-term concurrent aerobic and resistance exercise.

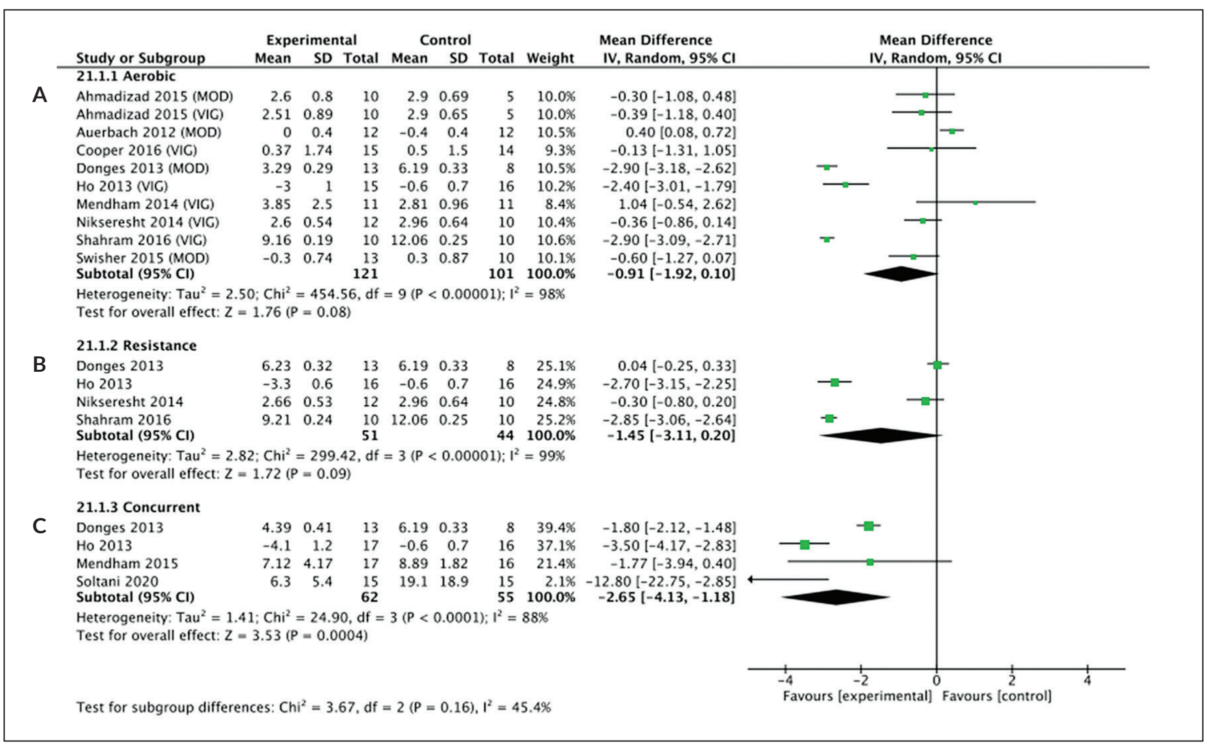

Figure 3. Forest plot of long-term exercise and its effect on TNF-alpha levels: **(A)** long-term aerobic exercise, **(B)** long-term resistance exercise, and **(C)** concurrent long-term aerobic and resistance exercise.

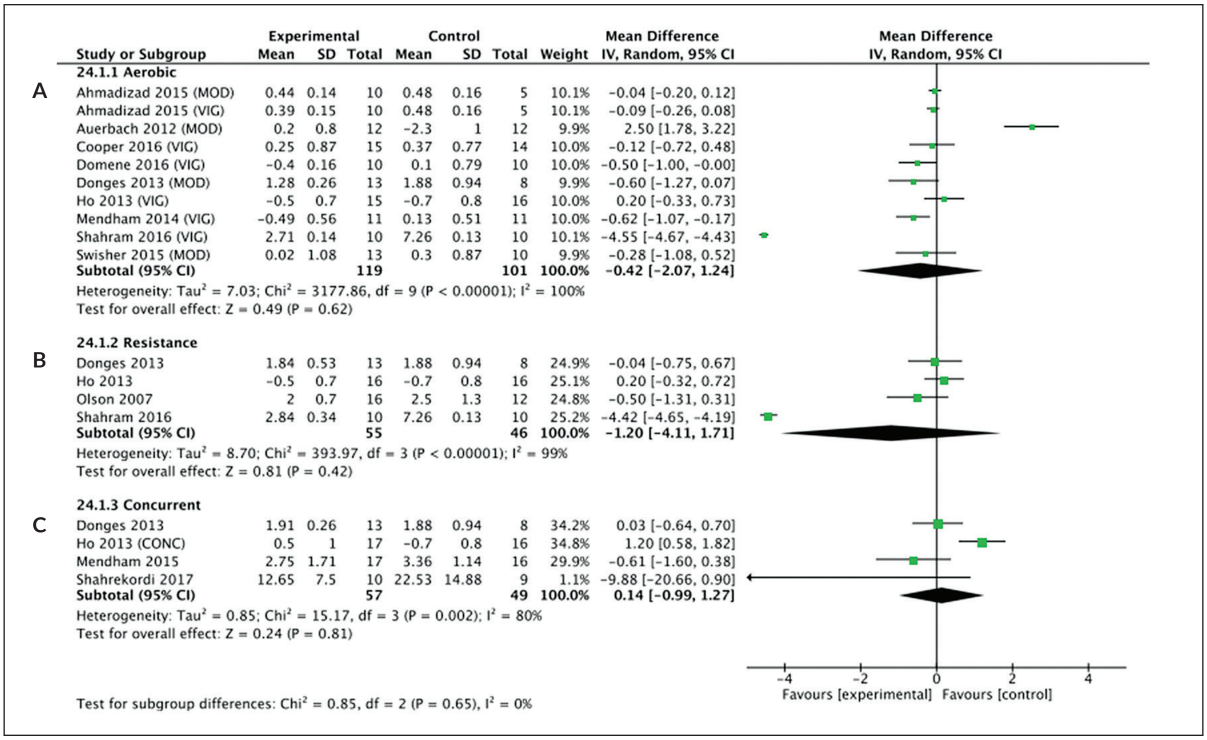

Figure 4. Forest plot of long-term exercise and its effect on IL-6 levels: **(A)** long-term aerobic exercise, **(B)** long-term resistance exercise, and **(C)** long-term concurrent training.

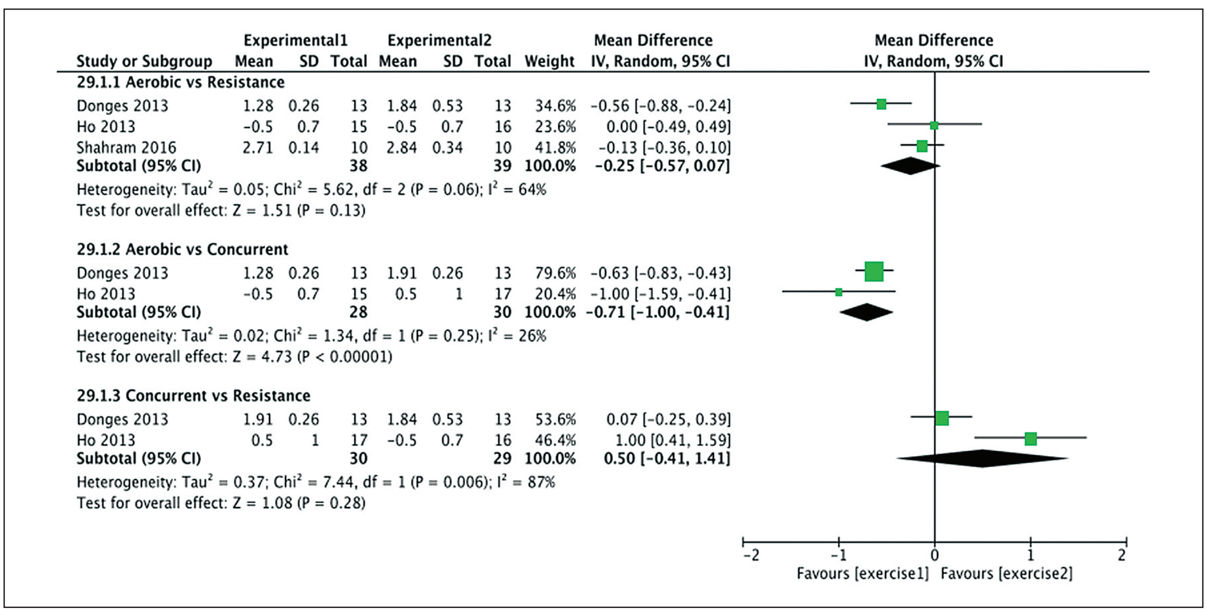

Figure 5. Forest plot of comparison of different types of long-term exercises in terms of effects on IL-6 levels.

Body Mass Index

There were 22 study arms with 624 participants included for the analysis of the effectiveness of exercise in changing BMI. Vigorous aerobic exercises (MD=-0.24, 95%CI, -0.32 to -0.15, p<0.00001, I^2=0%, p for heterogeneity=0.75)[24-26,28,30,38,43,46], and concurrent training (MD=-1.90, 95%CI, -3.48 to -0.31, p=0.02, I^2=87%, p for heterogeneity<0.00001)[26,29,36,47,48] resulted in significant reduction of BMI compared to control group. In terms of exercise type comparison, it showed aerobic exercises to be more effective than resistance exercises (p<0.00001) in reducing BMI.[26,38,44,46] Pooled data also showed that concurrent intervention was more effective than aerobic exercises in changing BMI (p=0.006).[26]

Waist-Hip Ratio

There were 10 study arms with 242 participants included for the analysis of the effectiveness of exercise in changing the WHR. Resistance exercises (MD=-0.03, 95%CI, -0.03 to 0, p=0.02)[44], and aerobic exercises (MD=-0.02, 95%CI, -0.04 to -0.01, p<0.00001, I^2=39%, p for heterogeneity= 0.14)[28,30,34,42,44] were found effective in decreasing WHR. However, concurrent training had no significant effect in reducing WHR (MD=-0.01, 95%CI, -0.05 to 0.03, p=0.56, I^2=53%, p for heterogeneity=0.12).[29,36,47]

Body fat composition

There were 24 study arms with 580 participants included for the analysis of the effectiveness of exercises in changing body fat mass. Only long-term vigorous aerobic exercises[23,24,26,28,30,31,38,42,44,46] (MD=-1.72, 95% CI, -2.70 to -0.74, p=0.0006, I^2=85%, p for heterogeneity<0.00001), and concurrent training[18,26,47] (MD=-1.19, 95% CI, -1.36 to -1.02, p<0.00001, I^2=0%, p for heterogeneity=0.55) were found to be effective in decreasing body fat mass compared to control groups. In terms of exercise type comparison, there were no significant differences found between aerobic and resistance[18,26,31,38,44,46] (p=0.63), aerobic and concurrent[18,26] (p=0.25), and concurrent and resistance exercises[18,26] (p=0.20).

Lean body mass

There were 9 study arms with 238 participants included for the analysis of the effectiveness of exercises in improving lean body mass. All exercise interventions were found to be effective in improving lean body mass compared to the control group: resistance exercise[18,32] (MD=2.26, 95%CI, -0.01 to 4.52, p=0.05, I^2=0%, p for heterogeneity=0.42), aerobic exercise[18,22,23,28,30,34] (MD=1.43, 95%CI, 0.55 to 2.31, p=0.001, I^2=80%, p for heterogeneity=0.0001), and concurrent training[18] (MD=4.80, 95%CI, 2.14 to 7.46, p=0.0004).

Meta-regression for CRP, TNF-alpha, and IL-6 levels

No significant association was found between inflammatory markers and weight and body fat mass of participants. Other body composition measurements have insufficient observations to be included in the meta-regression.

Funnel plot assessment for meta-analysis

The funnel plot showed moderate asymmetry in the meta-analyses of the effects of long-term aerobic exercises on CRP, weight, BMI, WHR, and body fat mass, and the effects of long-term concurrent training on CRP and IL-6, possibly due to publication bias. The other meta-analyses have significant asymmetry due to small-study effects with limited methodological design or small sample sizes.

Test for heterogeneity

Meta-analyses of the effects of short-term aerobic exercises on IL6 and TNF-alpha, and meta-analyses for secondary outcome measures (weight, WHR and BMI) showed low to moderate heterogeneity (I^2=0-70%). However, meta-analyses for long-term exercises on inflammatory markers, body fat mass, and lean body mass showed moderate to high heterogeneity (I^2=80-100%). Sub-group analyses and sensitivity analyses were performed to determine the factors affecting the heterogeneity of results

Subgroup analysis

Subgroup analysis for TNF-alpha showed that sex has a significant effect on subgroup differences in both long-term aerobic, resistance, and concurrent training, with women having a larger reduction in the inflammatory marker compared to men. Age was also a significant factor that also affected changes in TNF-alpha during concurrent training. For IL-6 levels, age was considered a significant factor that affected the changes in the inflammatory marker for resistance exercise. In terms of concurrent training, sex was a significant factor that affected the results. Also, middle-aged participants of aerobic exercises had a significant reduction of IL-6 levels (MD=-0.44, 95%CI, -0.73 to -0.16, p=0.003, I^2=0%, p for heterogeneity=0.545) compared to the control group.

Sensitivity analysis

After removing two studies[26,46] with a high risk of bias and possible data outlier, there were significant improvements in the heterogeneity of meta-analyses for TNF-alpha levels and IL-6 on concurrent training, and IL-6 levels on resistance intervention.

DISCUSSION

Currently, studies have reported conflicting evidence on the effects of exercise on inflammatory markers. In terms of exercise duration, both short-term and long-term exercises showed different effects on inflammatory markers. For short-term exercise sessions, aerobic exercise showed an increase in IL-6 levels compared to the control group. This pulsatile increase in IL-6 levels during exercise possibly has an anti-inflammatory effect as it also stimulates the production of another anti-inflammatory cytokine, IL-10.[49] This is in support of this review, as TNF-alpha levels were reduced in both resistance and aerobic training, and CRP levels in aerobic exercises. In terms of long-term exercise programs, only aerobic exercises were found to cause a significant reduction in CRP levels with a moderate level of evidence. This reduction in CRP after long-term aerobic exercise can be attributed to the reduction in fat mass.[50]

Another important finding of the review is the significant reduction of TNF-alpha caused only by long-term concurrent exercises with a low level of evidence. This highlights the recommendation of improving muscle mass and not just targeting weight loss when performing exercise interventions. This is supported by Khalafi et al.[51], which proposed gaining muscle mass as another mechanism for fighting adiposity-related inflammation during exercise. Another study by Nicklas & Brinkley found that the improvement in muscle mass from the chronic exercise intervention resulted in decreased levels of CRP in active participants.[52] Although this study is contradicted by Strandberg et al. who did not find a significant reduction in CRP or IL-6 levels after an increase in muscle mass in healthy elderly women.[53] This remains to be elucidated whether gain in muscle mass has a direct correlation with changes in inflammatory markers for adults with MHO.

In terms of intensity of exercise, a better reduction of pro-inflammatory markers was observed in vigorous intensity compared to moderate intensity aerobic exercises for MHO people. Although this result is not significant, more studies are needed to prove its effectiveness.

For exercise type, only a few studies performed a direct comparison of different exercise interventions. Based on this review, concurrent exercises were found to be more effective in reducing body weight, BMI, and CRP levels in people with MHO compared to aerobic, and resistance exercises, with moderate level of evidence. This may be due to its mechanisms to improve muscle mass and reduce body fat mass. However, as seen in the meta-regression of this review, body weight reduction and body fat mass may not be significant mechanisms for changing pro-inflammatory levels in MHO people. This is in support of the study by Shin et al. which reported that despite significant changes in weight and visceral fat mass by diet interventions, MHO people did not experience a significant reduction in CRP levels.[54] Another study by Barron-Cabrera et al. also supported that changes in pro-inflammatory levels were seen in the exercise group compared to diet-only intervention, regardless of weight loss experienced by both groups.[55]

Lastly, personal factors are also at play in changes in adiposity-related inflammatory markers. The review found that women had a greater reduction in pro-inflammatory levels compared to men. This is because most of the women in the study were of postmenopausal age (45 and above). According to the study by Sinatora et al.[56], women of post-menopausal age have an increased predisposition for increased weight and adiposity due to a decrease in estrogen hormone. Thus, they can benefit more from exercise intervention compared to males of the same age group. Age can also be considered a factor due to the increased predisposition to pro-inflammatory markers, a concept called inflammaging.[57]

CONCLUSION

Changes in inflammatory markers for MHO people are directly affected by different exercise protocols and personal factors. In terms of duration of exercise, short-term exercises showed a general trend toward an acute increase in IL-6 levels and reduction in TNF-alpha. This can be explained by the production of myokine IL-6 from contracting muscles, resulting in the anti-inflammatory effect of exercise. The study also found that long-term aerobic and concurrent exercises are effective in reducing pro-inflammatory markers (CRP and TNF-alpha) in people with MHO.

In terms of exercise type, concurrent training was found to be the most effective intervention in reducing body weight, BMI, and CRP levels with a moderate level of evidence. The possible mechanisms behind its effectiveness are visceral fat reduction and muscle mass build-up. Despite body weight and body fat mass showing no correlation with changes in inflammatory markers, it is imperative to continue improving physical activity levels, as chronic muscle contraction could be the possible mechanism to decrease inflammatory markers for MHO people.

In terms of personal factors, the review found that middle-aged women benefit more from exercise than men possibly due to their susceptibility to chronic inflammation caused by the lack of estrogen during menopause. It remains to be elucidated if older people with MHO phenotype can benefit more from exercises to counteract the effects of *inflammageing* in their bodies.

Recommendations

This review has limitations in terms of publication bias and degree of heterogeneity brought by methodological differences in measuring inflammatory markers, and exercise parameters. More studies that focus on MHO population, and that directly compare the effects of resistance, aerobic, and concurrent training on chronic inflammation are needed to provide more significant results. The review also has limited data for correlation and regression analysis. Further research is needed to find the actual relationship between different body composition measurements and changes in inflammatory markers. More research is needed to identify possible outcome measures that can predict chronic inflammation for people with MHO.

Lastly, more experimental studies focused on comparing the effectiveness of exercise interventions in sedentary Filipino MHOs are needed to know which intervention would be appropriate in our setting.

Acknowledgments

The primary author would like to thank DOST-ASTHRDP and the UPCM Department of Physiology for providing him the means to pursue this study.

Data Availability

The data collection forms, data extracted, and data analyses can be accessed upon request from the corresponding author.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

This review received DOST-SEI thesis allowance as part of the primary author's DOST-ASTHRDP scholarship.

REFERENCES

1. Blüher M. Metabolically healthy obesity. Endocr Rev. 2020 May;41(3):bnaa004. doi: 10.1210/endrev/bnaa004.
2. Efremov L, Lacruz ME, Tiller D, Medenwald D, Greiser KH, Kluttig A, et al. Metabolically healthy, but obese individuals and associations with echocardiographic parameters and inflammatory biomarkers: results from the CARLA study. Diabetes Metab Syndr Obes. 2020 Jul;13:2653-65. doi: 10.2147/DMSO.S263727.
3. Pedersen L, Pilegaard H, Hansen J, Brandt C, Adser H, Hidalgo J, et al. Exercise-induced liver chemokine CXCL-1 expression is linked to muscle-derived interleukin-6 expression. J Physiol. 2011 Mar;589(Pt 6):1409-20. doi: 10.1113/jphysiol.2010.200733.
4. García-Hermoso A, Sánchez-López M, Escalante Y, Saavedra JM, Martínez-Vizcaíno V. Exercise-based interventions and C-reactive protein in overweight and obese youths: a meta-analysis of randomized controlled trials. Pediatr Res. 2016 Apr;79(4):522–7. doi: 10.1038/pr.2015.274.
5. Alizaei Yousefabadi H, Niyazi A, Alaee S, Fathi M, Mohammad Rahimi GR. Anti-inflammatory effects of exercise on metabolic syndrome patients: a systematic review and meta-analysis. Biol Res Nurs. 2021 Apr;23(2):280-92. doi: 10.1177/1099800420958068.
6. Lin H, Zhang L, Zheng R, Zheng Y. The prevalence, metabolic risk and effects of lifestyle intervention for metabolically healthy obesity: a systematic review and meta-analysis: A PRISMA-compliant article. Medicine. 2017 Nov;96(47):e8838. doi: 10.1097/MD.0000000000008838.
7. Kantartzis K, Machann J, Schick F, Rittig K, Machicao F, Fritsche A, et al. Effects of a lifestyle intervention in metabolically benign and malign obesity. Diabetologia. 2011 Apr;54(4):864-8. doi: 10.1007/s00125-010-2006-3.
8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul;339:b2700. doi: 10.1136/bmj.b2700.
9. Zembic A, Eckel N, Stefan N, Baudry J, Schulze MB. An empirically derived definition of metabolically healthy obesity based on risk of cardiovascular and total mortality. JAMA Netw Open. 2021 May;4(5):e218505. doi: 10.1001/jamanetworkopen.2021.8505.
10. Takats S. (Director). Zotero [Computer software]. Corporation for Digital Scholarship; 2021 [cited 2021 Jan]. Available from: https://Zotero.org
11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid, A. Rayyan — a web and mobile app for systematic reviews. Syst Rev. 2016 Dec;5(1):210. doi: 10.1186/s13643-016-0384-4.
12. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug;366:l4898. doi: 10.1136/bmj.l4898.
13. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct;355:i4919. doi: 10.1136/bmj.i4919.
14. McGuinness LA, Higgins JP. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Methods. 2021 Jan;12(1):55-61. doi: 10.1002/jrsm.1411.
15. Rohatgi A. Web Plot Digitizer; 2017 [cited 2021 Jan]. Available from: https://automeris.io/ WebPlotDigitizer
16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar;372:n71. doi: 10.1136/bmj.n71.
17. Kisner C, Colby L. Resistance exercise for impaired muscle performance. In: Kisner C, Colby L. Therapeutic Exercise: Foundations and Techniques. 6th ed. Philadelphia, Pennsylvania: F.A. Davis Company; 2013. pp.157-158.
18. Donges CE, Duffield R, Guelfi KJ, Smith GC, Adams DR, Edge JA. Comparative effects of single-mode vs. duration-matched concurrent exercise training on body composition, low-grade inflammation, and glucose regulation in sedentary, overweight, middle-aged men. Appl Physiol Nutr Metab. 2013 Jul;38(7):779–88. doi: 10.1139/apnm-2012-0443.
19. Review Manager. (RevMan) [computer software]. Copenhagen, Denmark: Cochrane Collaboration; 2011 [cited 2021 Jan]. Available from: https://training.cochrane.org/online-learning/core-software/revman/revman-5-download
20. StataCorp. Stata 14 Base Reference Manual. College Station, Texas: Stata Press; 2015 [cited 2021 Jan]. Available from: https://download.stata.com/download/
21. Schünemann H, Brożek J, Guyatt G, Oxman AD. The GRADE handbook [Internet]. Ontario, Canada: The Cochrane Collaboration. 2013 [cited 2021 Jan 4]. Available from: http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html
22. Auerbach P, Nordby P, Bendtsen LQ, Mehlsen JL, Basnet SK, Vestergaard H, et al. Differential effects of endurance training and weight loss on plasma adiponectin multimers and adipose tissue macrophages in younger, moderately overweight men. Am J Physiol Regul Integr Comp Physiol. 2013 Sep;305(5):R490-8. doi: 10.1152/ajpregu.00575.2012.
23. Cooper JHF, Collins BEG, Adams DR, Robergs RA, Donges CE. Limited effects of endurance or interval training on visceral adipose tissue and systemic inflammation in sedentary middle-aged men. J Obes. 2016;2016:2479597. doi: 10.1155/2016/2479597.
24. Domene PA, Moir HJ, Pummell E, Knox A, Easton C. The health-enhancing efficacy of Zumba fitness: An 8-week randomised controlled study. J Sports Sci. 2016 Aug;34(15):1396–404. doi: 10.1080/02640414.2015.1112022.
25. Gram AS, Bladbjerg EM, Quist JS, Petersen MB, Rosenkilde M, Stallknecht B. Anti-inflammatory effects of active commuting and leisure time exercise in overweight and obese women and men: A randomized controlled trial. Atherosclerosis. 2017 Oct;265:318-24. doi: 10.1016/j.atherosclerosis.2017.06.923.
26. Ho SS, Dhaliwal SS, Hills AP, Pal S. Effects of chronic exercise training on inflammatory markers in Australian overweight and obese individuals in a randomized controlled trial. Inflammation. 2013 Jun;36(3):625–32. doi: 10.1007/s10753-012-9584-9.

27. Koh Y, Park KS. Responses of inflammatory cytokines following moderate intensity walking exercise in overweight or obese individuals. J Exerc Rehabil. 2017 Aug;13(4):472–6. doi: 10.12965/jer.1735066.533.
28. Mendham AE, Duffield R, Marino F, Coutts AJ. Small-sided games training reduces CRP, IL-6 and leptin in sedentary, middle-aged men. Eur J Appl Physiol. 2014 Nov;114(11):2289–97. doi: 10.1007/s00421-014-2953-3
29. Mendham AE, Duffield R, Marino F, Coutts AJ. A 12-week sports-based exercise programme for inactive Indigenous Australian men improved clinical risk factors associated with type 2 diabetes mellitus. J Sci Med Sport. 2015 Jul;18(4):438-43. doi: 10.1016/j.jsams.2014.06.013.
30. Moghadasi M, Mohebbi H, Rahmani-Nia F, Hassan-Nia S, Noroozi H, Pirooznia N. High-intensity endurance training improves adiponectin mRNA and plasma concentrations. Eur J Appl Physiol. 2012 Apr;112(4):1207–14. doi: 10.1007/s00421-011-2073-2.
31. Nikseresht M, Agha-Alinejad H, Azarbayjani MA, Ebrahim K. Effects of nonlinear resistance and aerobic interval training on cytokines and insulin resistance in sedentary men who are obese. J Strength Cond Res. 2014 Sep;28(9):2560-8. doi: 10.1519/JSC.0000000000000441.
32. Olson TP, Dengel DR, Leon AS, Schmitz KH. Changes in inflammatory biomarkers following one-year of moderate resistance training in overweight women. Int J Obes. 2007 Jun;31(6):996–1003. doi: 10.1038/sj.ijo.0803534.
33. Patrizi RM. The influence of acute resistive exercise on inflammatory markers in the blood of obese, postmenopausal women [Internet]. Harris College of Nursing and Health Sciences; 2008 [cited 2021 Jan]. Available from: https://repository.tcu.edu/handle/116099117/4093
34. Puengsuwan P, Kuo CH, Chaunchaiyakul R, Nanagara R, Leelayuwat N. Wand stretching exercise decreases abdominal obesity among adults with high body mass index without altering fat oxidation. Front Physiol. 2020 Oct;11:565573. doi: 10.3389/fphys.2020.565573.
35. Rohde C, Polcwiartek C, Andersen E, Vang T, Nielsen J. Effect of a physical activity intervention on suPAR levels: A randomized controlled trial. J Sci Med Sport. 2018 Mar;21(3):286-90. doi: 10.1016/j.jsams.2017.06.018.
36. Shabani A, Shabani R, Dalili S, Hassanzadeh Rad A. The effect of concurrent endurance and resistance training on cardio-respiratory capacity and cardiovascular risk markers among sedentary overweight or obese post-menopausal women. J Nurs Midwifery Sci. 2018;5(4):123-9. doi: 10.4103/JNMS.JNMS_34_18
37. Swisher AK, Abraham J, Bonner D, Gilleland D, Hobbs G, Kurian S, et al. Exercise and dietary advice intervention for survivors of triple-negative breast cancer: effects on body fat, physical function, quality of life, and adipokine profile. Support Care Cancer. 2015 Oct;23(10):2995–3003. doi: 10.1007/s00520-015-2667-z.
38. Yoon JR, Ha GC, Ko KJ, Kang SJ. Effects of exercise type on estrogen, tumor markers, immune function, antioxidant function, and physical fitness in postmenopausal obese women. J Exerc Rehabil. 2018 Dec;14(6):1032–40. doi: 10.12965/jer.1836446.223.
39. de Souza DC, Matos VAF, dos Santos VOA, Medeiros IF, Marinho CSR, Nascimento PRP, et al. Effects of high-intensity interval and moderate-intensity continuous exercise on inflammatory, leptin, IgA, and lipid peroxidation responses in obese males. Front Physiol. 2018 May;9:567. doi: 10.3389/fphys.2018.00567.
40. Emerson SR, Kurti SP, Snyder BS, Sitaraman K, Haub MD, Rosenkranz SK. Effects of thirty and sixty minutes of moderate-intensity aerobic exercise on postprandial lipemia and inflammation in overweight men: a randomized cross-over study. J Int Soc Sports Nutr. 2016 Jun;13:26. doi: 10.1186/s12970-016-0137-8.
41. Panissa VLG, Julio UF, St-Pierre DH, Tavares da Silva Gomes A, Caldeira RS, Lira FS, et al. Timing of high-intensity intermittent exercise affects ad libitum energy intake in overweight inactive men. Appetite. 2019 Dec;143:104443. doi: 10.1016/j.appet.2019.104443.
42. Ahmadizad S, Avansar AS, Ebrahim K, Avandi M, Ghasemikaram M. The effects of short-term high-intensity interval training vs. moderate-intensity continuous training on plasma levels of nesfatin-1 and inflammatory markers. Horm Mol Biol Clin Investig. 2015 Mar;21(3):165-73. doi: 10.1515/hmbci-2014-0038.
43. Bizheh N, Jaafari M. The effect of a single bout circuit resistance exercise on homocysteine, hs-CRP and fibrinogen in sedentary middle aged men. Iran J Basic Med Sci. 2011 Nov;14(6):568–73.
44. Mogharnasi M, TaheriChadorneshin H, Abbasi-Deloei N. Effect of exercise training type on plasma levels of vaspin, nesfatin-1, and high-sensitivity C-reactive protein in overweight and obese women. Obes. Med. 2019 Mar;13:34–8 doi: 10.1016/j.obmed.2018.12.006
45. Sadeghi M, Mohammadi A, Khajehlandi A. The effect of aerobic exercise training on oxidized LDL cholesterol (Ox-LDL) levels and some cardiovascular risk factors in women with obesity. Jundishapur J Health Sci [Internet]. 2019;11(2):e87511. doi: 10.5812/jjhs.87511.
46. Shahram S, Elham Y, Abdolali B. The effect of endurance and resistance training on inflammatory cytokines in sedentary young women. Acta Med Mediterr. 2016;32:999- 1002.
47. Mardanpour Shahrekordi Z, Banitalebi E, Faramarzi M. The effect of resistance training on levels of interlukine-6 and high-sensitivity C - reactive protein in older-aged women. Elder Health J. 2017 Jun;3(1):35–41.
48. Soltani N, Marandi SM, Kazemi M, Esmaeil N. Meta-inflammatory state and insulin resistance can improve after 10 weeks of combined all-extremity high-intensity interval training in sedentary overweight/obese females: a quasi-experimental study. J Diabetes Metab Disord. 2020 Jul;19(2):717–26. doi: 10.1007/s40200-020-00550-z.
49. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985). 2005 Apr;98(4):1154-62. doi: 10.1152/japplphysiol.00164.2004.
50. Dunn SL, Vera DL, Weaver KF, Garcia JV. Relationships between inflammatory and metabolic markers, exercise, and body composition in young individuals. J Clin Transl Res. 2021 May;7(3):289-96.
51. Khalafi M, Malandish A, Rosenkranz SK. The impact of exercise training on inflammatory markers in postmenopausal women: A systemic review and meta-analysis. Exp Gerontol. 2021 Jul;150:111398. doi: 10.1016/j.exger.2021.111398.
52. Nicklas BJ, Brinkley TE. Exercise training as a treatment for chronic inflammation in the elderly. Exerc Sport Sci Rev. 2009 Oct;37(4): 165-70. doi: 10.1097/JES.0b013e3181b7b3d9.
53. Strandberg E, Edholm P, Ponsot E, Wåhlin-Larsson B, Hellmén E, Nilsson A, et al. Influence of combined resistance training and healthy diet on muscle mass in healthy elderly women: a randomized controlled trial. J Appl Physiol (1985). 2015 Oct;119(8):918-25. doi: 10.1152/japplphysiol.00066.2015.
54. Shin MJ, Hyun YJ, Kim OY, Kim JY, Jang Y, Lee JH. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. Int J Obes. 2006 Oct;30(10):1529–34. doi: 10.1038/sj.ijo.0803304.
55. Barrón-Cabrera E, González-Becerra K, Rosales-Chávez G, Mora-Jiménez A, Hernández-Cañaveral I, Martínez-López E. Low-grade chronic inflammation is attenuated by exercise training in obese adults through down-regulation of ASC gene in peripheral blood: a pilot study. Genes Nutr. 2020 Aug;15(1):15. doi: 10.1186/s12263-020-00674-0.
56. Sinatora RV, Chagas EFB, Mattera FOP, Mellem LJ, de Oliveira Dos Santos AR, Pereira LP, et al. Relationship of inflammatory markers and metabolic syndrome in postmenopausal women. Metabolites. 2022 Jan;12(1):73. doi: 10.3390/metabo12010073
57. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018 Sep;15(9):505–22. doi: 10.1038/s41569-018-0064-2.