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Effect of low-volume exercise on hepatic steatosis in adults with obesity plus normal glucose, prediabetes or type 2 diabetes: a randomised controlled trial

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ABSTRACT

Objectives This study aimed to evaluate the effects of a novel, low-volume combined high-intensity interval training (HIIT) and progressive resistance training (PRT) in overweight/obese adults.

Methods This randomised control trial compared the effect of regular supervised HIIT combined with PRT (Exercise) with an unsupervised stretching intervention (Control), in previously inactive adults with either normal glucose (NG), pre-diabetes or type 2 diabetes (T2DM) with body mass index of >25 kg/m^2. Participants were randomly allocated (1:1) to receive low-volume exercise or control by an online randomisation tool. The primary outcome was the difference in change of hepatic steatosis between Exercise and Control. A prespecified sensitivity analysis was undertaken for weight stable participants (<5% change in bodyweight from baseline). Secondary outcomes were change in hepatic steatosis within the glucose groups, glycaemic control, cardiorespiratory fitness, muscle strength and body composition.

Results Between June 2018 and May 2021, 162 participants were randomly assigned (NG: 76, pre-diabetes: 60, T2DM: 26) and 144 were included in the final analysis. Mean absolute change in hepatic steatosis was −1.4% (4.9) in Exercise (n=73) and −0.1% (7.2) in Control (n=71)(p=0.25). By preplanned sensitivity analysis, the mean change in hepatic steatosis with Exercise (n=70) was −1.5% (5) compared with 0.7% (4.6) with Control (n=61) (p=0.017). Subgroup analysis within the glucose groups showed that exercise reduced hepatic steatosis in those with pre-diabetes but not NG or T2DM (pre-diabetes: −1.2% (4.4) in Exercise and 1.75% (5.7) in Control, p=0.019).

Conclusion These findings show that low-volume HIIT with PRT yields improvements in muscle strength and cardiorespiratory fitness and may have a small effect on hepatic steatosis.

Trial registration number The trial was prospectively registered with the ANZCTR (ACTRN12617000552381).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Metabolic dysfunction-associated liver disease (MASLD) affects ~1 in 4 people globally. People with MASLD are at increased risk of developing type 2 diabetes, cardiovascular disease and some cancers.

⇒ Most physical activity guidelines recommend aerobic exercise, either of vigorous intensity or moderate intensity, and resistance training, however the effect of this exercise type on hepatic steatosis has not been examined.

⇒ Low-volume high-intensity aerobic exercise can improve cardiometabolic health and may represent a more time efficient method of exercise than moderate intensity aerobic exercise or traditional high-intensity interval training.

WHAT THIS STUDY ADDS

⇒ This type of combined low-volume exercise training was not effective for reducing hepatic steatosis. Within glucose strata, only people with pre-diabetes observed a reduction in hepatic steatosis with Exercise—those with normal glucose and type 2 diabetes did not reduce hepatic steatosis with Exercise.

⇒ Low-volume exercise training may elicit other metabolic benefits such as increased cardiorespiratory fitness and muscular strength while reducing risk of atherosclerotic cardiovascular disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Low-volume exercise training may not be the optimal exercise prescription for reducing hepatic steatosis, however, this type of exercise may be suitable for people with a history of limited exercise engagement to improve cardiometabolic health.

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide with a reported current global prevalence of 25.2%.[1] While hepatic steatosis without concomitant metabolic disease is associated with a mild increase in the risk of liver morbidity, including fibrosis and cirrhosis, hepatic steatosis significantly increases the risk of cardiovascular disease

(CVD) and cancer mortality.[2] In adults with hepatic steatosis in the presence of obesity and insulin resistance, the risk of fibrosis is significantly increased.[3] High hepatic steatosis levels have also been shown to be mechanistically involved in insulin resistance and contribute to the progression from obesity with normal glycaemic control and insulin sensitivity to insulin resistance and type 2 diabetes (T2DM).[4] As the global epidemic of obesity and T2DM are realised, it is, therefore, expected that the prevalence of MASLD will increase.[5] The future burden of MASLD is expected to be considerable, and there is a great need to establish effective treatments for MASLD, particularly for adults with comorbid obesity and insulin resistance.

Lifestyle intervention, involving regular exercise (training) is well known to have a wide range of health benefits including improving cardiorespiratory fitness, muscular function and reducing risk of CVD and some cancers.[6] Exercise training enhances insulin sensitivity and glycaemic control in those with normal glycaemia and overweight/obesity.[7] In people with pre-diabetes, exercise training significantly reduces risk of progression to T2DM in addition to improving fitness and reducing CVD risk factors.[8] In those with T2DM, regular exercise improves glycaemic control, fitness, CVD risk and a range of diabetes-related complications.[9] Consequently, despite some differences between specific exercise guidance, the consensus from major international authorities is that adults with overweight/obesity and/or pre-diabetes/T2DM should engage in regular bouts of aerobic and resistance type exercise.[10 11]

There are limited pharmacological interventions that are effective and safe for reducing hepatic steatosis.[12] Despite generally small studies and sample sizes, collectively the available evidence demonstrates that exercise training alone (in the absence of dietary modification) can improve hepatic steatosis in adults with obesity,[13] those with prediabetes[14] and those with T2DM.[15] Furthermore, exercise can reduce hepatic steatosis without meaningful reduction in body weight,[16] this is important because, although weight loss consequent to lifestyle intervention is known to significantly reduce hepatic steatosis,[17] meaningful weight loss is difficult for most people to achieve and sustain.[10] Yet, despite the emphasis on combined aerobic and resistance exercise in current guidelines,[10] all studies to date have used exclusively aerobic or resistance training interventions to examine the therapeutic effect of exercise training on hepatic steatosis, and the vast majority of these have involved exclusive aerobic exercise interventions in small experimental samples. These data have demonstrated that aerobic exercise involving either moderate-intensity continuous training (MICT) and/or HIIT may be beneficial for reducing hepatic steatosis. Furthermore, low-volume HIIT may reduce hepatic steatosis[15] and may yield similar improvements in cardiorespiratory fitness and glycaemia while being more time effective than traditional HIIT.[18] Low-volume HIIT may be more a more achievable method of exercise for some people who experience a lack of time as a barrier to engaging in exercise.[19] The combination of low-volume HIIT and resistance training may improve hepatic steatosis, glycaemia and body composition. However, the effect of resistance training on hepatic steatosis remains unclear in a small number of trials, which may be related to the length of the intervention and participants insulin sensitivity.[20 21] The effect of combined low-volume high-intensity aerobic exercise with progressive resistance training (PRT) on hepatic steatosis is not known.

Given its possible efficacy for reducing hepatic steatosis, and the established multiplicity of its health benefits, the primary aim of this study was to examine the utility of combined high-intensity aerobic exercise and resistance training on hepatic steatosis in adults with overweight/obesity. Secondary aims were to examine the effects of the intervention on cardiometabolic health, to conduct a sensitivity analysis of weight stable participants and to examine subgroups of participants based on glucose status. To investigate this, a randomised controlled trial was employed, involving regular low-volume HIIT and resistance training and serial measurement of hepatic steatosis and cardiometabolic outcomes in a large sample of previously inactive adults with obesity and either normal glucose (NG), pre-diabetes or newly diagnosed T2DM.

RESEARCH DESIGN AND METHODS

Study design and population

The PACE-G study was a randomised controlled trial undertaken in a community healthcare centre in Sydney, Australia. Eligible participants were those who provided written informed consent, were aged ≥18, had a body mass index (BMI) of ≥25.0 kg/m^2 and reported completing less than 150 min of moderate-intensity exercise or 75 min of vigorous intensity exercise per week. Individuals were excluded if they had type 1 diabetes, or T2DM with disease duration >2 years, had a cardiovascular event in the previous 6 months had alcohol intake of >140 g per week, had an active foot ulcer, were currently pregnant, breast feeding or were planning pregnancy in the next 3 months, had liver cirrhosis or had weight change of >5% in the past 3 months. NG was defined as fasting plasma glucose (FPG) <5.6 mmol/L and glycated haemoglobin (HbA1c) level <5.7% NGSP units. Pre-diabetes was either of FPG of 5.6–6.9 mmol/L or HbA1c of 5.7%–6.4%. Newly diagnosed T2DM was defined within 2 years of entering the trial as either FPG >6.9 mmol/L or HbA1c >6.5% or prior diagnosis of T2DM by a medical doctor within the last 2 years.

Randomisation and masking

After stratification by glucose group, participants were randomly assigned to supervised exercise (Exercise) or unsupervised sham control (Control) in a 1:1 ratio for the duration of the study. Block permutation randomisation was carried out by a study investigator using an online tool (sealedenvelope.com). Data analysis was carried out

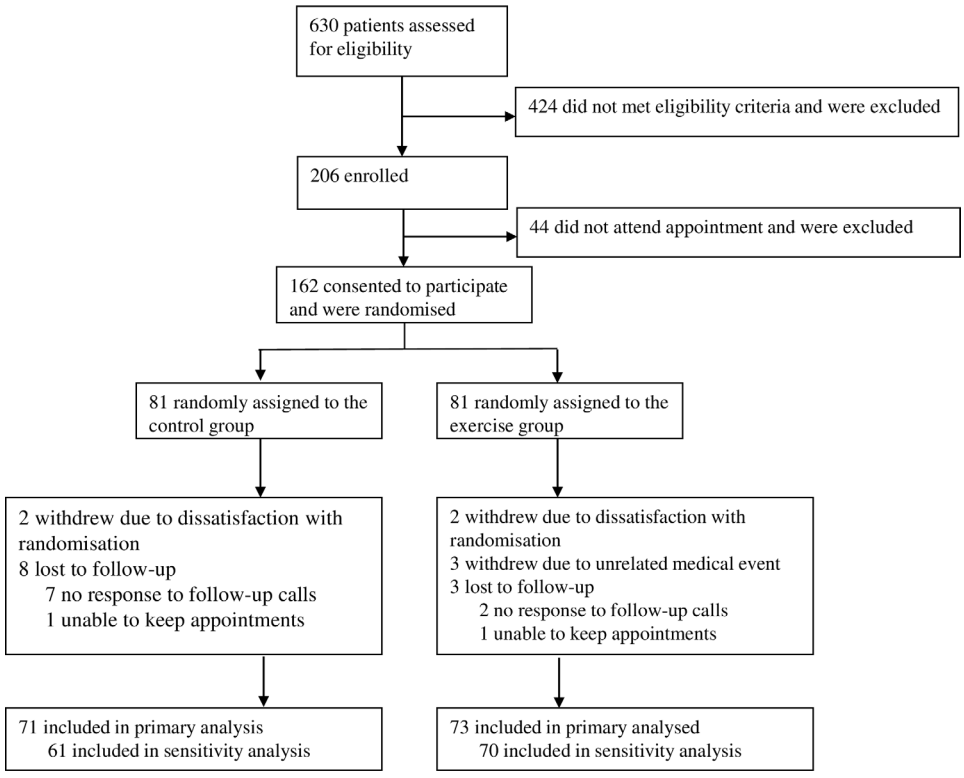

Figure 1 Consolidated Standards of Reporting Trials flow diagram of participants through the phases of the study.

by a study investigator blinded to the participants' group allocation.

Procedures

Potentially eligible participants responded to advertising in local newspapers, online or were referred by medical clinics. Participants were initially screened for eligibility via telephone and once written consent was provided the final eligibility of participants was established before randomisation.

Participants in the supervised exercise group completed 12 weeks of two times weekly supervised exercise at the Charles Perkins Centre Royal Prince Alfred Clinic at the University of Sydney, and one unsupervised weekly session completed at participant's home. Supervised exercise sessions consisted of stationary cycling on an upright ergometer (Monark Exercise AB, Vansbro, Sweden) followed by nine machine-based resistance exercises (Keiser Corporation, California, online supplemental table 3). The exercise arm involved a 2-week phase to gradually progress physical activity levels - commencing aerobic exercise intensity at 65% of age predicted heart rate maximum and PRT at 60% of 1-repetition maximum (1-RM). During the following 10 weeks, participants completed two times weekly supervised exercise sessions, consisting of one bout of 4 min of HIIT at 85%–95% of age-predicted heart rate maximum and also resistance exercises involving two sets of 8–12 repetitions at 80% of 1RM. The 1RM was retested for each exercise at week 6 of the intervention and strength machine resistance settings were increased progressively as participants strength gains occurred throughout the intervention. Supervised exercise sessions were supervised by an accredited exercise physiologist. In addition, participants were provided a heart rate monitor and instructed to undertake one (unsupervised) HIIT session using a modality of exercise available to them. This HIIT session consisted of one 4 min high-intensity interval at 85%–95% of age-predicted heart rate maximum.

Participants in the control group were instructed to complete an unsupervised stretching protocol that consisted of four stretches targeting major muscle groups for 15 min, three times per week for 12 weeks. Participants in both groups were asked to maintain their habitual dietary patterns.

Outcomes

The primary outcome, change in hepatic steatosis, was quantified by non-invasive proton magnetic spectroscopy (^{1}H-MRS). Localised ^{1}H-MRS was undertaken using a 1.5 Tesla Achieva whole-body system (Philips Medical Systems, Best, The Netherlands), with participants supine. Point resolved spectroscopy technique (PRESS) (TR=5000 ms, TE=34 ms, 32 measurements, 1024 sample points) was used; with spectra acquired from the right lobe of the liver (voxel size 3.0×2.0×2.0 cm) using the whole-body (Q body) coil and a torso coil (flex M multichannel surface). As detailed elsewhere,[22] spectral data were analysed by magnetic resonance user interface software (jMRUI V.5.2) by a technician blinded to participant's allocation.

Table 1 Baseline characteristics

	Control (n=81)	Exercise (n=81)	P
Age (years)*	57.8 (21.7–80.4)	59.1 (23.7–79.9)	0.48
Male:female (%female)	33:38 (53.5%)	30:43 (58.9%)	0.63
BMI (kg/m^2)	32±0.6	31.9±0.5	0.89
Weight (kg)	91.0±1.9	90.3±1.9	0.81
Waist circumference (cm): females	101±2	101±2	0.88
Males	108±1	108±2	0.91
Hepatic steatosis (%)	9.8±1.7	11.2±1.5	0.53
FPG (mmol/L)	5.1±0.1	5.2±0.1	0.77
HbA1c (%)	5.7±0.1	5.6±0.1	0.48
Fructosamine (µmol/L)	263.2±3.9	261.5±3.5	0.75
Insulin (pmol/L)	62±4.2	71.9±7.7	0.26
HOMA-IR	2.5±0.2	3±0.4	0.34
ALT (U/L)	31±2.5	29.9±1.5	0.70
AST (U/L)	25.7±1	25.8±1.1	0.97
GGT (U/L)	30.8±2.4	26.2±1.8	0.14
Cholesterol (mmol/L)	5.3±0.1	5.2±0.1	0.57
Triglycerides (mmol/L)	1.4±0.1	1.6±0.1	0.11
LDLC (mmol/L)	3.2±0.1	3.1±0.1	0.52
HDLC (mmol/L)	1.5±0	1.5±0	0.64
Systolic BP (mm Hg)	132±2	134±2	0.75
Diastolic BP (mm Hg)	79±1	79±1	0.86
ASCVD 10-year risk (%)	8.8±1	9.9±1.2	0.50
1-RM leg press (N)	2017±70	1943±73	0.47
1-RM seated row (N)	351±15	329±14	0.31
1-RM chest press (N)	475±18	438±18	0.15
VO_2peak (mL/kg/min)	30.7±0.9	29.9±1.1	0.61
Body fat (%)	40.6±1.0	40.5±0.9	0.94
Lean mass (kg)	5.1±1.2	5.0±1.1	0.70
Current cigarette smoking	7	10	0.62
Quality of Life (AqoL-8D Total Score)	65.1±1.6	63.1±1.6	0.37
Self-Efficacy for Exercise (SEE Score)	67.9±1.9	65.5±2.2	0.41
Depressive Symptoms (PHQ-9)	4.1±0.5	3.9±0.4	0.68
Medications: anti-hyperglycaemic	12	14	0.87
Anti-hypertensive	16	27	0.08
Lipid lowering	14	20	0.36
Glycaemic status at baseline: NG	39 (50.7%)	37 (47.9%)	
Pre-diabetes	29 (36.6%)	31 (34.2%)	
T2DM	13 (12.7%)	13 (17.8%)	

Data are mean (SD) or n (%).
P values are for between-groups comparisons at baseline.
*Years (range).
ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease risk; AST, aspartate transaminase; BP, blood pressure; FPG, fasting plasma glucose; GGT, gamma glutamyl transferase; HDCL, high density lipoprotein level; HOMA-IR, homoeostasis model assessment-insulin resistance; LDLC, low density lipoprotein level; NG, normal glucose; 1-RM, 1 repetition maximum; T2DM, type 2 diabetes.

Body composition was measured by dual-energy X-ray absorptiometry (Hologic Discovery, Wisconsin), Height was measured with a stadiometer (seca Model 220; seca, Hamburg, Germany) to the nearest 0.5 cm. Waist circumference was measured to the nearest 0.5 cm midway between the inferior margin of the ribs and the superior border of the iliac crest. Body weight was measured with a digital platform scale (Tanita BC-418 Body Composition Analyzer; Tanita Corporation, Tokyo, Japan). After an overnight fast venous blood was collected by a train phlebotomist. Blood analysis for blood lipids and biochemistry was performed in a commercial laboratory on the same day as data collection. Insulin sensitivity measured by homoeostasis model assessment-insulin resistance (HOMA-IR). Quality of life, self-efficacy for exercise and depressive symptoms were assessed by questionnaires (AQoL-8D, SEE and PHQ-9, respectively). Cardiorespiratory fitness (VO_2peak) was estimated from a graded treadmill exercise test until volitional fatigue (Bruce protocol),[23] and muscular strength was measured by 1-repetition maximal (1-RM) strength testing.[23] Estimated 10-year atherosclerotic cardiovascular disease risk (ASCVD) was calculated using the ASCVD risk calculator.[24]

Statistical analysis

By power calculation, 90 participants per glucose category of pre-diabetes, recent onset T2DM and NG groups were needed to have 90% power at 0.05 significance level to test the primary outcome. We anticipated a 3% mean difference (SD 4%) in hepatic steatosis between groups after the intervention period and accounted for a 15% dropout rate from previous studies.[13]

Changes from baseline were compared by use of between-group analysis of co-variance (ANCOVA) where baseline hepatic steatosis values were used as a covariate. The primary and secondary outcomes were analysed in all randomly assigned participants who attended the follow-up visit. A prespecified sensitivity analysis was conducted whereby participants with more than 5% change in body weight from baseline were excluded, as such change likely indicates lifestyle change external to the study.[16] For binary outcomes, Fischer's exact test was used to compare groups. Relationship between blood lipids, hepatic steatosis, ASCVD risk and VO_2peak were calculated by Pearson's correlation. Missing data values for the follow-up visit were imputed by mean imputation method. Analyses were performed in R, V.3.5.2 (R Core Team 2021, Vienna, Austria).

The trial was approved by Sydney Local Health District HREC with oversight by a data monitoring and safety committee who reviewed the study at ~50% recruitment. Over the course of this trial, the unfolding COVID-19 pandemic resulted in amendments to the trial. As Sydney was under stay-at-home orders for two periods in 2020 and 2021, a maintenance home exercise protocol was delivered via telehealth for some Exercise participants (online

supplemental figure 1). This amendment was approved by the Human Research Ethics Committee of The University of Sydney. Participants in the trial during lock-down periods had the remaining duration of their intervention period paused until the end of the lockdown period and resumed once government health orders allowed for the trial to recommence. As study recruitment was markedly impacted and delayed owing to the COVID-19 pandemic, participant numbers were revised to n=160, which would enable a calculated 80% power at a 0.05 significance level to test the primary outcome, still anticipating a 3% mean difference (SD 4%) in hepatic steatosis between groups and still accounting for a 15% dropout rate.

Data resource availability

The datasets generated during and/or analysed in the current study are available from the corresponding author on reasonable request.

RESULTS

Between June 2018 and May 2021, 630 potential participants were assessed for eligibility, 162 were randomised to Exercise (n=81) and Control (n=81). A total of 144 participants completed follow-up (n=73 Exercise, n=71 Control) and were included in the primary analysis. Of the 162 included participants, 131 participants (n=70 Exercise and n=61 Control) remained weight stable (<5% body weight change in 12 weeks) and were included in the sensitivity analysis (figure 1).

Baseline characteristics

Baseline characteristics were similar between the two groups (table 1). The study cohort was 58% women, the mean (SD) age was 58.2 years (12.2) and mean BMI (SD) was 32.0 kg/m^2 (5.2). Mean (SD) absolute hepatic steatosis in participants with T2DM was 24.5% (17.7), pre-diabetes 11.4% (12.8) and NG 5.4% (9.0) (figure 2A). Across the glucose categories, 46.9% of participants had NG, 37.0% had pre-diabetes and 16.0% had newly diagnosed T2DM. The exercise intervention was well attended, with 80% of all supervised sessions attended by participants. There were no adverse events related to the intervention.

Primary outcome

Between baseline and 12 weeks, the mean change in absolute hepatic steatosis of participants from baseline was −1.3% (4.9) in Exercise and 0.1% (7.1) in Control (p=0.22) (figure 2, table 2). Three participants (two

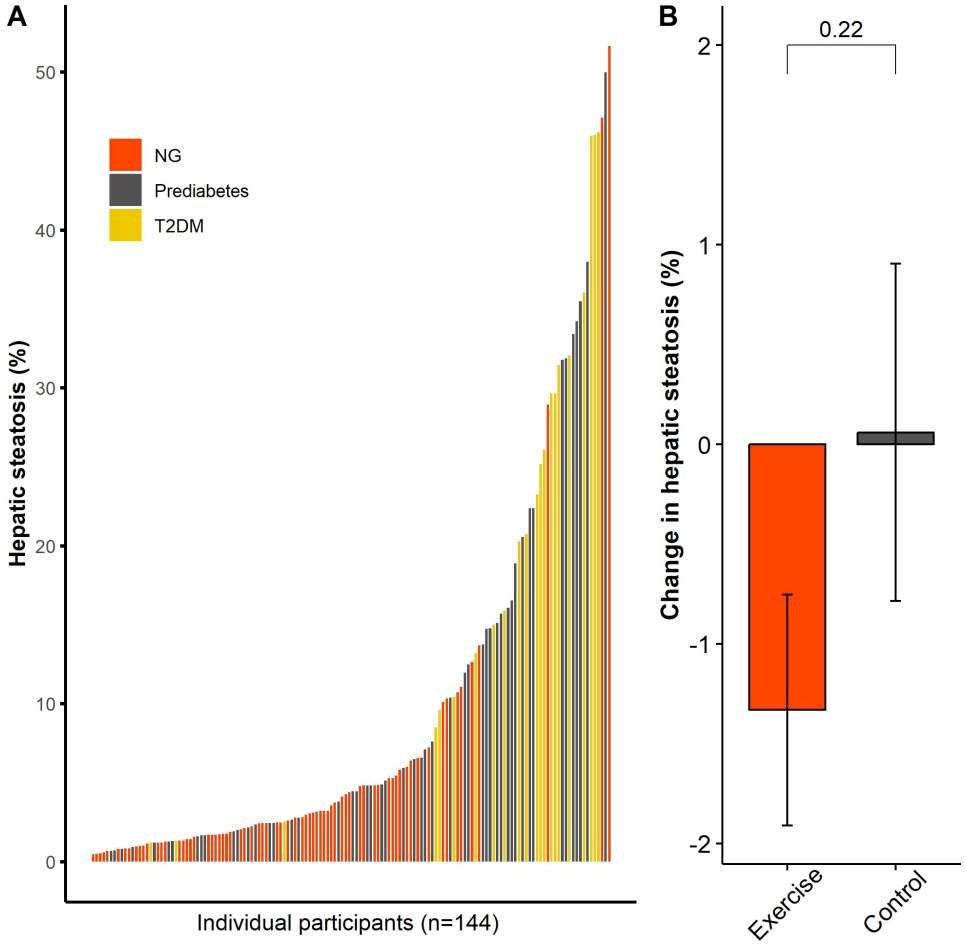

Figure 2 (A) Individual participants hepatic steatosis at baseline. Participants with normal glucose are in orange, pre-diabetes are in grey and T2DM are in gold. (B) Absolute change in hepatic steatosis. Data are mean and error bars show one standard error of the mean (SEM). NG, normal glucose; T2DM, type 2 diabetes.

Table 2 Comparison of mean differences within and between groups at the end of the intervention

	Control (n=71)			Exercise (n=73)			
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	P value
Primary outcome: hepatic steatosis (%)	9.3±12.5	9.4±13	0.1±7.1	10.5±12.3	9.2±10.6*	−1.3±4.9	0.22
BMI (kg/m^2)	31.6±5.6	31.4±5.7	−0.2±1.4	31.9±4.7	31.7±4.8*	−0.2±0.8	0.98
Weight (kg)	39.7±8.7	40±9.5	0.2±7	40±8.2	40.4±9.3	0.5±5.4	0.78
Waist circumference (cm): females	101±13	9±14	−2±5	101±11	100±12	−1±4	0.306
Males	108±9	108±14	1±12	108±11	105±10	−2±3	0.282
FPG (mmol/L)	5.0±1.1	5.1±1.2	0.1±0.9	5.1±1.4	5.0±1.2	−0.1±0.7	0.041
HbA1c (%)	5.6±0.8	5.7±0.9	0.1±0.4	5.6±0.7	5.6±0.7	0.0±0.2	0.471
Fructosamine (µmol/L)	263.5±35.2	266.9±36.4	3.5±29.2	261±33.1	264.3±28.7	3.3±26.4	0.79
Insulin (pmol/L)	31.5±22.5	30.5±21.1	−1.0±9.1	26.2±17.4	24.3±14.3*	−1.9±6.9	0.12
HOMA-IR	2.3±1.7	3.1±4	0.8±3.4	3.0±4	2.6±2	−0.4±3	0.067
ALT (U/L)	31±23.3	33.8±30.1	2.8±13.5	30.4±14	28.4±11.8	−2.0±9.6	0.016
AST (U/L)	25.8±9.5	26.8±12.2	1.0±7.7	26.0±9.7	24.3±7.0*	−1.7±6.2	0.018
GGT (U/L)	31.5±22.5	30.5±21.1	−1.0±9.1	26.2±17.4	24.3±14.3*	−1.9±6.9	0.119
Cholesterol (mmol/L)	5.3±1.3	5.2±1.3	−0.1±0.9	5.1±1.0 .	5.0±1.0*	−0.2±0.6	0.32
Triglycerides (mmol/L)	5.0±1.1	5.1±1.2	0.1±0.9	5.1±1.4	5.0±1.2	−0.2±0.7	0.041
LDLC (mmol/L)	3.2±1.2	3.3±1.1	0.1±0.5	3.0±1.0	2.9±0.9*	−0.1±0.5	0.092
HDLC (mmol/L)	1.5±0.4	1.6±0.4	0.1±0.2	1.4±0.3	1.5±0.3	0.0±0.2	0.92
Systolic BP (mm Hg)	132±15	133±17	1±12	133±17	132±16	−1±13	0.31
Diastolic BP (mm Hg)	79±8	79±7	0±7	79±9	78±8	−1±8	0.61
ASCVD 10-year risk (%)	8.7±9.5	9.3±10.7*	0.5±2.2	9.8±10.8	9.6±11.2	−0.2±2	0.015
1-RM leg press (N)	1959±537	1986±618	27.5±326	1959±662	2320±757*	361±383	<0.001
1-RM seated row (N)	464±148	470±159	6±61	443±160	557±210*	113±98	<0.001
1-RM chest press (N)	346±123	343±125	−2±35	333±132	400±161*	67.3±55.4	<0.001
VO_2peak (mL/kg/min)	30.7±7.9	31.6±7.7	0.8±6.2	30.2±9.5	33±10*	2.9±7.3	0.079
Body fat (%)	39.7±8.7	40±9.5	0.2±7	40±8.2	40.4±9.3	0.5±5.4	0.80
Lean mass (kg)	5.2±1.0	5.0±1.0	−0.3±1.8	5.1±1.0	5.1±1.0	0.0±1.6	0.24

Data are mean (SD). P value obtained with analysis of covariance adjusted for baseline scores.
*P<0.05 within group.
P values are for between-groups comparisons at baseline.
HDLC is high density lipoprotein; LDL is low density lipoprotein
ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease risk; AST, aspartate transaminase; BP, blood pressure; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HOMA-IR, homoeostasis model assessment-insulin resistance; NG, normal glucose; 1-RM, 1 repetition maximum.

Control and one Exercise) had a hepatic steatosis change of >3 SDs from the mean; post hoc exclusion of these participants resulted in mean hepatic steatosis change of −1.0% (4.0) in Exercise and 0.3% (3.4) in Control (p=0.062) (data not shown).

Secondary outcomes

Compared with Control, Exercise reduced FPG (although minimally) (Exercise: −0.1±0.7 vs Control: 0.1±0.9, p=0.041), triglycerides (Exercise: −0.2±0.7 vs Control: 0.1±0.9, p=0.041), ASCVD 10-year predicted risk (Exercise: −0.2±2.0 vs Control: 0.5±2.2, p=0.015), and liver enzymes ALT and AST (Exercise: −2.0±9.6 vs Control: 2.8±13.5, Exercise: 1.7±6.2 vs Control: 1.0±7.7, respectively, both p<0.05). Compared with Control, Exercise increased 1-RM strength leg press, seated row and chest press (table 2). After the intervention, there was no difference between groups in body weight, BMI or body composition. Subgroup analysis within the glucose groups showed that exercise reduced hepatic steatosis in those with pre-diabetes but not NG or T2DM (NG Exercise: −0.8±3.6 vs Control −1.0±8.2, p=0.88. Pre-diabetes Exercise: −1.2±4.4 vs Control: 1.7±5.7, p=0.019. T2DM Exercise: −3.2±8.2 vs Control −0.5±5.8, p=0.13) (figure 3, online supplemental table S1). In the preplanned

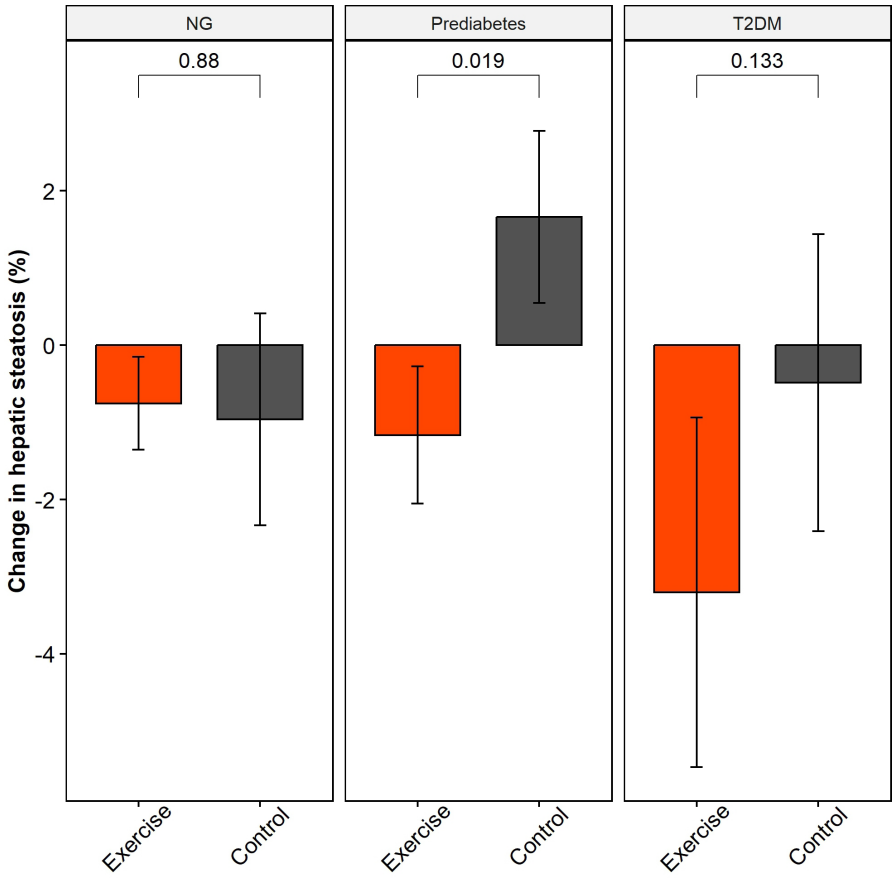

Figure 3 Absolute change in hepatic steatosis within glucose groups. Data are mean and error bars show one standard error of the mean (SEM). NG, normal glucose; T2DM, type 2 diabetes.

sensitivity analysis, excluding those with more than 5% body weight change from baseline (10 Control and 3 Exercise participants with mean weight change of −4.1 kg (10.03) and −1.6 kg (6.7), respectively), adherence to the supervised exercise sessions was similar between those who were weight stable and those who did reduce bodyweight (79.1% *vs* 80.0%, p=0.94). In the sensitivity analysis, mean change in absolute hepatic steatosis was −1.5% (5) with Exercise and 0.7% (4.6) with Control (p=0.017) (table 3). In the sensitivity analysis, Exercise also reduced FPG, HOMA-IR and increased cardiorespiratory fitness (VO_2peak) (table 3). Changes in hepatic steatosis and VO_2Peak were correlated with changes in 10-year predicted ASCVD risk and body weight (online supplemental table S2).

CONCLUSION

The purpose of this study was to examine the utility of combined high-intensity aerobic exercise and resistance training on hepatic steatosis and cardiometabolic health outcomes in adults. The primary finding from this study was that in overweight/obese adults, regular HIIT combined with progressive resistance exercise for 12 weeks did not significantly reduce hepatic steatosis. The treatment benefit was similar among those with NG and T2DM, however those with pre-diabetes did realise a statistically significant reduction in hepatic steatosis. As others have observed, there was significant variation between participants in baseline hepatic steatosis and in response to the intervention.[15 25] In a sensitivity analysis, in which participants who experienced significant body weight change (suggestive of confounding diet on physical activity modification) were excluded, hepatic steatosis was reduced by the exercise intervention compared with the sham intervention.

Despite the impact of the COVID-19 pandemic on global research efforts and associated challenges with recruiting participants with newly diagnosed T2DM, the sample size was large for a supervised exercise trial and withdrawal/lost to follow-up rates were similar to other comparable studies done before the COVID-19 era.[13 15 20] There was no difference in effect sizes (or baseline characteristics) for people who had their study involvement impacted by COVID-19 lockdowns (data not shown).

The exercise intervention in this study was selected based on current physical activity guidelines for adults with overweight/obesity, pre-diabetes and T2DM, which recommend regular bouts of aerobic and resistance exercise.[10 11] Low-volume HIIT may yield similar results to traditional forms of HIIT and thus be a time-efficient method to engage in aerobic exercise. The effect of combined low-volume high-intensity aerobic exercise and PRT on hepatic steatosis has not been examined. Several studies with small sample sizes have investigated

Table 3 Sensitivity analysis (participants with bodyweight change<5%): comparison of mean differences within and between groups at the end of the intervention

	Control (n=61)			Exercise (n=70)			
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	P value
Hepatic steatosis (%)	9.1±11.9	9.8±13	0.7±4.6	10.9±12.4	9.4±10.7*	−1.5±5	0.017
BMI (kg/m^2)	31.8±5.8	31.8±5.7	0±0.7	32±4.7	31.8±4.8*	−0.2±0.7	0.30
Weight (kg)	90.7±17.7	90.6±18	0±1.9	91±16.3	90.5±16.2*	−0.5±1.9	0.18
FPG (mmol/L)	5.1±1.2	5.2±1.3	0.1±1	5.1±1	4.9±0.9	−0.1±0.6	0.038
HbA1c (%)	5.7±0.8	5.7±0.9	0±0.5	5.6±0.6	5.6±0.6	0±0.2	0.46
HOMA-IR	2.4±1.7	3.3±4.2*	0.9±3.6	3±4.1	2.6±2.1	−0.4±3	0.041
ASCVD 10-year risk (%)	8.9±9.7	9.5±11*	0.6±2.2	9.9±10.9	9.7±11.3	−0.3±2	0.008
VO_2peak (mL/kg/min)	30.5±8.1	31.4±7.7	0.9±5.9	30±9.6	33.2±10.1*	3.2±7.2	0.047
Body fat (%)	39.9±8.2	40.3±9.4	0.4±7.2	39.9±8.3	40.5±9.5	0.5±5.5	0.91
Lean mass (kg)	5.1±1.0	5.2±1.0	−0.3±1.5	5.1±1.0	5.1±1.	0.4±1.6	0.20

Data are mean (SD). P value obtained with analysis of covariance adjusted for baseline scores.
*P<0.05 within group.
P values are for between-groups comparisons at baseline.
ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease risk; AST, aspartate transaminase; FPG, fasting plasma glucose; GGT, gamma-glutamyl transferase; HOMA -IR, homoeostasis model assessment-insulin resistance; NG, normal glucose; 1-RM, 1 repetition 561 maximum; T2DM, type 2 diabetes.

different MICT aerobic exercise and HIIT interventions with weekly supervised session frequency of three or four supervised sessions per week. Meta-analysis of these studies has shown that both modalities reduce hepatic steatosis to a similar extent MICT[26] although these studies have small sample sizes and are often underpowered.[27] Resistance exercise training can improve muscle strength and function and is of particular use as a therapy to offset sarcopenia and frailty associated with ageing.[28] Resistance training can also reduce HbA1c, however, when resistance training is combined with aerobic exercise the effect on HbA1c may be more pronounced.[29] We did not observe a meaningful difference in HbA1c with combined low-volume exercise. Low-volume combined exercise may require greater frequency than 2–3 times per week to elicit an improvement in HbA1c.

The impact of resistance exercise training on hepatic steatosis is unclear. Our previous study of three times per week PRT for 8 weeks did not reduce hepatic steatosis in adults with NG and overweight/obesity were instructed to maintain their habitual diet.[20] In contrast, others have shown a positive effect of three times per week of resistance training on hepatic steatosis in adults with T2DM who also received nutrition counselling prior to the study commencing.[21] We observed minimal impact of combined high-intensity aerobic and resistance training suggesting that this volume of exercise may be at or close to the threshold *dose* to reduce hepatic steatosis without dietary modification.

To our knowledge, this is the largest supervised exercise study investigating hepatic steatosis by ^{1}H-MRS in adults with overweight/obesity and either NG, pre-diabetes, or T2DM. Despite rising global prevalence of pre-diabetes and strong associations between hepatic steatosis and insulin resistance,[30] this patient group with pre-diabetes is understudied. Exercise can reduce risk of conversion from pre-diabetes to T2DM,[8] however the impact of exercise on hepatic steatosis in adults with pre-diabetes has not been robustly investigated. In this large-scale randomised control trial of supervised exercise, the primary analysis showed no effect of combined exercise on hepatic steatosis, however clinically meaningful improvements in aerobic fitness and muscle strength were observed.

Aerobic fitness predicts CVD risk, all-cause mortality and risk of T2DM.[31] Exercise training may reduce all-cause mortality by ~25% per metabolic equivalent (1MET=3.5 mL/kg/min) increase in aerobic fitness.[31] HIIT can increase aerobic fitness with less time intensive training required than traditional MICT interventions. In weight-stable adults, our combined HIIT and PRT, even though of quite low volume, increased aerobic fitness by ~1 MET and this change in aerobic fitness inversely correlated with change in ASCVD predicted risk. This increase in aerobic fitness is clinically meaningful and may result in reduced risk of CVD mortality.

Our study has specific strengths, including a randomised controlled design, a relatively large sample size, and gold standard non-invasive quantitation of hepatic steatosis by ^{1}H-MRS. Additionally, the combined HIIT and PRT was a novel exercise intervention where most exercise interventions focus on moderate intensity continuous training of 150 min per week for reducing hepatic steatosis.[16] The supervised exercise intervention was safe with no adverse events related to the study despite a study population that were sedentary and at high risk of CVD, supervision of exercise sessions is recommended for people with high

cardiovascular risk.[32] Several limitations of this study should be acknowledged. First, COVID-19 lockdowns in Sydney, Australia, resulted in pausing of the exercise intervention and delivery of a maintenance home exercise protocol via telehealth for some participants in the exercise intervention. Second, while adherence to the supervised exercise sessions was measured, the once weekly unsupervised HIIT session by participants in the exercise intervention was not measured. Third, participants were able to modify lifestyle habits, which may influence hepatic steatosis and metabolic health; at baseline, participants were instructed to maintain habitual dietary habits, however, several participants in the control arm reduced body weight over their study involvement (10 Control participants achieved >5% change in bodyweight). Finally, participants were not blinded to their intervention.

This study adds further evidence for muscular and cardiorespiratory benefit from low-volume exercise training for people with overweight/obesity and insulin resistance—without dietary modification. This type of exercise may be suitable for people with a history of limited exercise engagement. Future studies are needed to further investigate the role of HIIT and PRT in those with newly diagnosed T2D.

In conclusion, our trial showed that combined high-intensity aerobic exercise and PRT for 12 weeks improved muscle strength and aerobic fitness yet is below the minimal volume of exercise required to reduce hepatic steatosis. Combined HIIT and PRT, in a modest exercise volume, may be of clinical utility in overweight/obese adults with NG and pre-diabetes as a method to increase aerobic fitness and muscle strength.

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Contributors SMT, NAJ and YB conceived and designed the study. CB, SLH, XW, JG and AS collected data. CJB and AS supervised exercise sessions. CB, NAJ and LM analysed the data. SMT, NAJ, DM and CB interpreted the data. All authors drafted, revised and approved the final versions of the manuscript. SMT (guarantor) takes responsibility for the work, including study design, access to data and the decision to submit for publication.

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