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Original Paper

Modified high-intensity interval training reduces liver fat and improves cardiac function in non-alcoholic fatty liver disease: a randomized controlled trial

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Abstract

Although lifestyle changes encompassing weight loss and exercise remain the cornerstone of non-alcoholic fatty liver disease (NAFLD) management, the effect of different types of exercise on NAFLD is unknown. This study defines the effect of modified high-intensity interval training (HIIT) on liver fat, cardiac function and metabolic control in adults with NAFLD. Twenty-three patients with NAFLD [age 54 ± 10 years, body mass index (BMI) 31 ± 4 kg/m^2, intra-hepatic lipid >5%) were assigned to either 12 weeks HIIT or standard care (controls). HIIT involved thrice weekly cycle ergometry for 30–40 min. MRI and spectroscopy were used to assess liver fat, abdominal fat and cardiac structure/function/energetics. Glucose control was assessed by oral glucose tolerance test and body composition by air displacement plethysmography. Relative to control, HIIT decreased liver fat (11 ± 5% to 8 ± 2% compared with 10 ± 4% to 10 ± 4% $P = 0.019$), whole-body fat mass (35 ± 7 kg to 33 ± 8 kg compared with 31 ± 9 kg to 32 ± 9 kg, $P = 0.013$), alanine (52 ± 29 units/l to 42 ± 20 units/l compared with 47 ± 22 units/l to 51 ± 24 units/l, $P = 0.016$) and aspartate aminotransferase (AST; 36 ± 18 units/l to 33 ± 15 units/l compared with 31 ± 8 units/l to 35 ± 8 units/l, $P = 0.017$) and increased early diastolic filling rate (244 ± 84 ml/s to 302 ± 107 ml/s compared with 255 ± 82 ml/s to 251 ± 82 ml/s, $P = 0.018$). There were no between groups differences in glucose control. Modified HIIT reduces liver fat and improves body composition alongside benefits to cardiac function in patients with NAFLD and should be considered as part of the broader treatment regimen by clinical care teams. ISRCTN trial ID: ISRCTN78698481.

Key words: cardiac function, exercise, magnetic resonance imaging, non-alcoholic fatty liver disease.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum from isolated fatty liver through progressive non-alcoholic steatohepatitis (NASH) and hepatic fibrosis to cirrhosis, with an overall prevalence of NAFLD in Western countries of 20%–33% [1,2]. Patients with simple fatty liver have a relatively 'benign' liver prognosis with a 1%–2% risk of developing evidence of cirrhosis over 15–20 years [3], whereas up to 5%–11% of those with NASH develop end-stage liver disease [4]. NAFLD is closely associated with the development of type 2 diabetes (T2DM) [4,5] and cardiovascular disease (CVD) [3–5]. More than 90% of obese people with T2DM have NAFLD [6]. NAFLD is also associated with early left ventricular (LV) diastolic dysfunction [7,8] and NAFLD characterized by elevated serum γ-glutamyltransferase (GGT) is independently associated with heart failure [9,10]. As such, protection of both metabolic and cardiac health is as relevant to people with liver disease and their care teams as liver health.

In the absence of approved pharmacotherapy for NAFLD, lifestyle interventions focusing on weight loss remain the cornerstone for NAFLD management [11]. However, weight loss is

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC; area under the curve; BMI, body mass index; CVD, cardiovascular disease; ECG, electrocardiogram; GGT; γ-glutamyltransferase; HbA_{1c}, glycated haemoglobin; HIIT, high-intensity interval training; HOMA2; homoeostasis model assessment 2; IHL, intrahepatic lipid; LV, left ventricular; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; REE, resting energy expenditures; RPE, rate of perceived exertion;T2DM, type 2 diabetes; VCO_2 volume of carbon dioxide; VO_2, volume of oxygen; VO_{2peak}, oxygen consumption at peak work rate.

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difficult to achieve and sustain even in well conducted and resourced behavioural interventions [12]. Cross-sectional studies report that more physically active people and/or those with greater cardiorespiratory fitness are less likely to have NAFLD [13] or have a less advanced form [14]. Despite these associations, studies reporting the effect of exercise-based lifestyle interventions in NAFLD are lacking, preventing its routine and effective use in clinical care [15,16].

Small scale exercise-only interventions demonstrate that moderate-intensity aerobic [17] or resistance training [18] reduce intrahepatic lipid (IHL) independently of weight change and dietary modification. Previous reports suggest that high-intensity interval training (HIIT), exercise divided into high-intensity bouts and recovery periods, can provide comparable or greater benefits to cardiorespiratory fitness than continuous moderate-intensity exercise of longer duration [19] and that volunteers prefer HIIT to continuous exercise routines [20,21] as it is less time consuming. However, there is no consensus in the literature as to what constitutes a true HIIT protocol and all-out interval training may be deemed to be inappropriate and potentially unsafe to use in certain patient groups [22]. Thus we designed a modified HIIT protocol which would be realistic and safe for our participants to complete taking into consideration baseline fitness, unfamiliarity with exercising and comorbidities. To date, no studies have reported the effects of HIIT on IHL in people with NAFLD limiting its clinical use.

The primary aims of the present study were to determine the effect of a modified HIIT programme on IHL and cardiac function in adults with NAFLD. The secondary aims were to determine the effect of HIIT on mediators of IHL and cardiac risk: glucose control, abdominal adiposity and body composition.

PATIENTS AND METHODS

Trial design and recruitment

This was a single-centre parallel design randomized trial conducted at Newcastle University in Newcastle upon Tyne, U.K. The study was approved by the Newcastle and Northeast Tyneside Local Research Ethics Committees. All participants provided written informed consent. Participants were recruited from secondary care (Freeman Hospital) and by advertising in local newspapers between September 2010 and February 2013. All the authors have had access to the data, reviewed and approved the final manuscript.

Participants and randomization

Exclusion criteria included: inability to give informed consent, heart or kidney disease, viral hepatitis, uncontrolled thyroid conditions, haemochromatosis, drug-related steatosis, implanted ferrous material, pre-existing medical conditions preventing participation in the exercise programme; medication for T2DM other than metformin and self-reported weekly alcohol intake above 21 units for men or 14 units for women.

Twenty-nine sedentary ($\leqslant$60 min moderate-vigorous activity per week) adults with clinically-defined non-advanced NAFLD were randomly assigned to HIIT (n=15) or standard care (n=14). Excess liver fat was defined as >5% and advanced liver disease was ruled out by including only volunteers with a NAFLD fibrosis score of $\leqslant -1.455$, corresponding to a negative predictive value of 88%–93% for advanced (Kleiner F3/4) fibrosis [23]. Participant flow is shown in Figure 1. Randomization was undertaken via a random allocation sequence (www.randomization.com).

Study intervention

Participants completed a cycle ergometer-based HIIT protocol three times per week on non-consecutive days for 12 weeks. Intensity was based on the 6–20 point Borg rating of perceived exertion (RPE) [24]. Participants were provided with a portable audio device (iPod shuffle, Apple Inc.) containing pre-recorded and written instructions to guide them through each session. Sessions consisted of a 5-min warm up progressing from an RPE of 9–13 ('very light' to 'somewhat hard') followed by five intervals of cycling at an RPE of 16–17 ('very hard') interspersed with 3-min recovery periods and followed by a 3-min cool down after the last interval. Each interval was 2-min long in the first week with 10 s added per week, so that intervals were 3 min and 50 s long by week 12. Sessions therefore lasted 30–40 min. Recovery periods included 90 s of passive recovery, 60 s of light band resisted upper body exercise and 15 s each to transition off and on the ergometer. One upper body exercise was performed per recovery period in the following order: face-pull, horizontal push, horizontal pull and 30° push. Exercise was performed at commercial fitness facilities, with the first two sessions supervised by one of the investigators. Participants were asked to retain their current diets and monitor and maintain their body weight within 1% of baseline. Adequate adherence was defined as attendance of at least 33 of a possible 36 sessions assessed by an exercise diary. Participants who missed one or more weeks of exercise had additional weeks added to their programme to allow them to finish the requisite number of exercise sessions.

Standard care consisted of volunteers continuing any prescription medication and going for regular monitoring of their condition(s) with their normal general practitioner and/or consultant(s).

Experimental protocol

Following an initial screening visit, glucose control, resting metabolism, abdominal lipid depots, IHL and cardiac function were measured at baseline and post-intervention; at least 48 h following the last bout of exercise.

Safety and eligibility screening

At baseline, a medical history, physical examination and progressive exercise test were used to screen for undiagnosed cardiac disease. Resting 12-lead electrocardiogram (ECG; Custo med GmbH) and blood pressure (Suntech Tango+, Suntech Medical Ltd) were measured in a seated position to determine normal cardiac function. VO_{2peak} (oxygen consumption at peak work rate) was determined during an ECG and blood pressure monitored progressive maximal exercise test using an electronically braked recumbent cycle ergometer (Corival Lode BV), as previously described [18]. Expired gases were collected using a Hans Rudolf

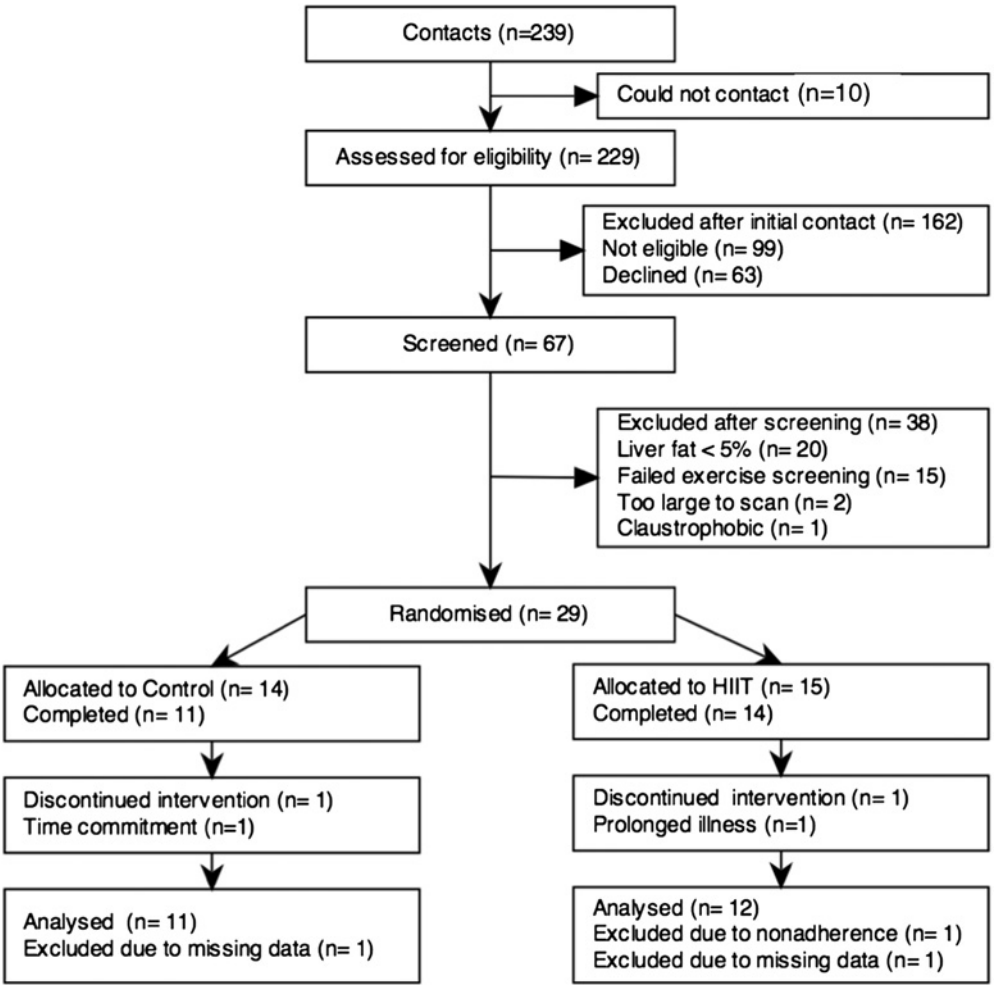

Figure 1 Participant flow

breathing mask and analysed online for VO_2 (volume of oxygen), VCO_2 (volume of carbon dioxide) and ventilation (CORTEX Biophysik).

Body composition and anthropometry

Body weight and body composition were measured using an electronic scale and air displacement plethysmography (BodPod, Life Measurement Inc.). Height was measured using a stadiometer (SECA 799; SECA).

MRI and spectroscopy

Magnetic resonance assessments were performed using a 3.0 Tesla Philips Achieva scanner with a six channel cardiac array (both from Philips; specific procedures are described in Supplementary Document 1). In brief, IHL was assessed by ^{1}H-magnetic resonance spectroscopy in a $3 \times 3 \times 3$ cm voxel and abdominal visceral fat area was measured at the L4/L5 junction using a three-point Dixon sequence. Cardiac structure, function and energetics were assessed by ECG-gated MRI of the cardiac cycle, cardiac-cine tagging along the short axis and ^{31}P-magnetic resonance spectroscopy respectively.

Resting metabolism

Volunteers lay supine on a bed for 30 min while expired gases were collected using a Hans Rudolf breathing mask and analysed online for VO_2, VCO_2 and ventilation (CORTEX Biophysik). Results from the first 10 min and last 5 min were discarded and means calculated. Resting energy expenditures (REE) were calculated using the Weir equation [25].

Glucose, insulin and blood lipid assessment

A frequently sampled oral glucose tolerance test was conducted using previously described techniques [18]. Samples were analysed for whole blood glucose (YSI 2300 Stat Plus-D, Yellow Springs Instruments) and plasma insulin (Coat-A-Count Insulin RIA kit, Diagnostic Products Corporation). Area under the curve (AUC) for the resulting glucose response profile was calculated using the trapezoidal rule [26] and insulin resistance and β-cell function determined using the homoeostasis model assessment 2 (HOMA2; HOMA2 Calculator, University of Oxford) [27]. Fasting plasma was analysed for: alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, total cholesterol, high-density lipoprotein cholesterol, estimated low-density

Table 1 Baseline comparisons (mean ± S.D.)
Abbreviation: WR_{peak}, peak work rate.

Parameter	Control (n=12)	HIIT (n=11)	P
Age (years)	52 ± 12	54 ± 10	0.621
BMI (kg/m^2)	31 ± 5	31 ± 4	0.893
Weight (kg)	90 ± 11	90 ± 14	0.973
Height (m)	1.70 ± 0.08	1.69 ± 0.08	0.668
IHL (%)	10.3 ± 4.4	10.6 ± 4.9	0.882
ALT (units/l)	47 ± 22	52 ± 29	0.705
AST (units/l)	31 ± 8	36 ± 18	0.405
Fasting glucose (mmol/l)	5.4 ± 1.2	5.8 ± 1.8	0.544
2-h glucose (mmol/l)	7.7 ± 3.5	10.4 ± 4.0	0.119
VO_{2peak} (l/min)	2.2 ± 0.5	1.9 ± 0.8	0.215
VO_{2peak} (ml/kg/min)	24.6 ± 5.7	21.9 ± 6.2	0.288
VO_{2peak} (ml/kg$_{lean\ mass}$/min)	37.8 ± 6.5	32.9 ± 8.0	0.123
WR_{peak} (W)	154 ± 35	149 ± 45	0.749

lipoprotein cholesterol, triacylglycerol and glycated haemoglobin A1c (HbA_{1c}), as previously described [18].

Statistical analysis

Prior data indicated that the S.D. of IHL in a population similar to that of the study was between 7.4% and 9.1% [18]. Assuming a S.D. of 9.0 and no change in IHL in the control group, an 80% chance of detecting a 10% relative between group change in liver IHL at a one-sided 0.05 significance required n=11 per group. Normality of data was assessed by the Shapiro–Wilk test. Between-group comparisons were made using analysis of covariance using the baseline value as the covariate. Comparisons of key baseline variables were made using independent sample $t$tests. Within group changes were assessed by paired-sample $t$test. Statistical significance was set at 0.05 and data are mean ± S.D., unless otherwise stated.

RESULTS

Participants and baseline comparison

Participant flow is shown in Figure 1. Sixty-seven volunteers underwent clinical screening with 29 eligible subsequently randomized. Eleven people were included for final analysis in the control group and 12 in the HIIT group. Age, body mass index (BMI), weight, height and peak oxygen consumption were similar between groups (Table 1). Baseline measures of IHL, liver enzymes, metabolic control and abdominal adiposity were similar between groups (Tables 1 and 2).

Intrahepatic lipid, anthropometry, body composition and liver enzymes

Compared with control, HIIT was associated with a reduction in IHL and improvements in body composition (Figure 2; Table 2). Specifically, there was a significant improvement in steatosis (−2.8 ± 4.0% compared with 0.1 ± 3.1%, P = 0.01; Figure 2) which was accompanied by biochemical changes consistent with decreased inflammatory activity characterized by lower ALT (−10 ± 13 units/l compared with 4 ± 12 units/l, P = 0.016) and AST (−4 ± 5 units/l compared with 4 ± 7 units/l, P = 0.017). Improvements in fat mass (−1.8 ± 1.5 kg compared with 0.3 ± 2.0 kg, P = 0.013; Figure 2) and body fat percentage (−1.2 ± 1.6% compared with 0.4 ± 2.0%, P = 0.027) were also observed with HIIT. However, visceral fat area did not change within or between groups (Table 2).

Glucose, insulin and blood lipids

Within group comparisons showed a reduction in 2-h glucose (10.4 ± 4.0 to 8.8 ± 3.8 mmol/l, P = 0.036; Table 3) and suggested a trend toward reduced fasting insulin (108 ± 53 to 91 ± 45 mmol/l, P = 0.055; Table 3) and HOMA2-IR (HOMA2 of insulin resistance; 2.4 to 2.1, P = 0.061; Table 3). Between and within groups comparisons showed no change in HbA_{1c}, 2-h insulin or fasting total cholesterol and triacylglycerol (Table 3). HOMA2-β and HOMA2-S also appeared unchanged (result not shown).

Metabolic flexibility and resting energy expenditure

Resting respiratory quotient appeared unaffected by the intervention. However there was a trend towards an increase in REE in the HIIT relative to the control group [1718 ± 390 to 1847 ± 398 kcal/day compared with 2046 ± 313 to 1826 ± 430, P = 0.055; Table 3].

Cardiac morphology, function and metabolism

HIIT improved diastolic function in adults with NAFLD. Early diastolic filling rate increased by 24% in the exercise group but not in control (Table 4; Figure 2). Exercise decreased peak cardiac torsion (Table 4; Figure 2) but had no effect on morphology, systolic function or cardiac energetics (Table 4).

DISCUSSION

This is the first study to assess the effects of a modified HIIT programme in patients with clinically-defined NAFLD. This is also the first study to assess the effects of any form of exercise on cardiac function in people with NAFLD. The major findings are that HIIT performed three times per week for 12 weeks led to: (1) a 27% reduction in IHL; (2) reduced plasma ALT and AST; and (3) an improvement in cardiac diastolic function. These changes were accompanied by mean 1.8 kg reduction in fat mass but with an absence of a substantive effect on glycaemic control or body weight. Combined, these results suggest that HIIT may deliver improvements to both liver health and cardiovascular function for people with NAFLD.

The data show that HIIT provided a 27% relative reduction in IHL, in people with clinically defined NAFLD. The changes following HIIT compare favourably with the 10%–21% previously reported following aerobic or resistance exercise only interventions [17,18,28] and comparable to several weight reduction trials [16]. It should be noted that the changes in IHL with HIIT are

Table 2 Changes in anthropometry, IHL and liver biochemistry (mean ± S.D.)

	Control			HIIT			*P* Time ×
	Baseline	Post-treatment	*P*	Baseline	Post-treatment	*P*	Treatment interaction
IHL (%)	10.3 ± 4.4	10.4 ± 3.9	0.955	10.6 ± 4.9	7.8 ± 2.4	0.032*	0.019#
ALT (units/l)	47 ± 22	51 ± 24	0.318	52 ± 29	42 ± 20	0.032*	0.016#
AST (units/l)	31 ± 8	35 ± 8	0.093	36 ± 18	33 ± 15	0.042*	0.017#
GGT (units/l)	53 ± 37	58 ± 51	0.365	37 ± 14	33 ± 17	0.555	0.678
BMI (kg/m^{-2})	31.2 ± 4.8	31.2 ± 4.6	0.971	31.5 ± 4.1	31.0 ± 4.1	0.001**	0.046#
Weight (kg)	90.1 ± 10.6	90.1 ± 10.0	0.976	89.9 ± 13.6	88.5 ± 13.5	0.001**	0.037#
Visceral adipose tissue (cm^2)	149 ± 48	145 ± 37	0.543	151 ± 52	159 ± 62	0.388	0.299
Fat mass (kg)	31.4 ± 8.9	31.7 ± 9.2	0.642	34.7 ± 7.4	32.9 ± 7.6	0.002**	0.013#
Lean body mass (kg)	58.7 ± 6.5	58.4 ± 7.3	0.595	55.2 ± 10.5	55.6 ± 11.1	0.365	0.052
Body fat (%)	34.5 ± 7.0	34.8 ± 7.9	0.565	38.4 ± 6.4	37.2 ± 6.9	0.024*	0.026#

*significant difference baseline versus post-intervention ($p < 0.05$).
**significant difference baseline versus post-intervention ($p < 0.01$).
#significant difference time x treatment interaction ($p < 0.05$).

Table 3 Metabolic changes (mean ± S.D.)
Abbreviations: AUGC, area under the glucose curve; REE, resting energy expenditure; RQ, respiratory quotient.

	Control			HIIT			*P* Time ×
	Baseline	Post-treatment	*P*	Baseline	Post-treatment	*P*	Treatment interaction
Fasting glucose (mmol/l)	5.4 ± 1.2	5.4 ± 1.3	0.984	5.8 ± 1.8	5.6 ± 1.6	0.533	0.663
Fasting insulin (pmol/l)	90.1 ± 44.6	91.0 ± 34.1	0.891	108.0 ± 53.1	91.4 ± 45.1	0.055	0.322
2-h glucose (mmol/l)	7.7 ± 3.5	7.5 ± 3.9	0.601	10.4 ± 4.0	8.8 ± 3.8	0.036*	0.165
2-h insulin (pmol/l)	578.3 ± 455.3	669.3 ± 429.0	0.317	772.5 ± 464.9	872.0 ± 484.4	0.426	0.517
2-h AUGC	1046 ± 299	1103 ± 369	0.198	1197 ± 376	1140 ± 407	0.342	0.138
HOMA2-IR	1.9 ± 0.9	1.9 ± 0.6	0.789	2.4 ± 0.8	2.1 ± 0.8	0.061	0.418
HbA1c (%)	6.6 ± 1.8	6.7 ± 2.0	0.135	6.6 ± 1.2	6.5 ± 1.2	0.347	0.107
Total cholesterol (mmol/l)	5.4 ± 1.2	5.2 ± 1.3	0.253	5.1 ± 1.0	5.0 ± 0.9	0.416	0.981
Triacylglycerol (mmol/l)	1.5 ± 0.6	1.7 ± 0.8	0.103	1.7 ± 0.6	1.7 ± 0.5	1.000	0.306
REE (kcal/day)	2046 ± 313	1826 ± 430	0.061	1718 ± 390	1847 ± 398	0.104	0.055
Resting RQ	0.88 ± 0.06	0.93 ± 0.08	0.018	0.89 ± 0.05	0.89 ± 0.08	0.962	0.140

*significant difference baseline versus post-intervention ($p < 0.05$).

modest when compared with more substantive weight loss programmes, which can deliver a ∼80% reduction in IHL with 8% loss of body weight [29]. However, substantive weight loss is difficult for some patients to achieve and exercise, now including modified HIIT, may provide another therapeutic option. Furthermore, exercise training may also deliver additional benefits to cardiovascular function which are less pronounced with weight loss alone.

The impact of NAFLD clearly extends beyond the liver. People with NAFLD are exposed to double the risk of CVD compared with people without NAFLD [30]. Indeed, recent studies report significant changes in cardiac structure and function in adults with NAFLD in the apparent absence of cardiac metabolic changes or overt cardiac disease [8]. The current study shows that HIIT significantly improved diastolic function as demonstrated by a 24% increase in early diastolic filling rate. The direct effect of exercise on cardiac function is of particular interest given recent reports suggesting LV diastolic dysfunction in NAFLD [7,8], T2DM [31,32], obesity [33,34] and increased risk of heart failure with elevated GGT [9,10], a presentation in 43% of our cohort. These data suggest that exercise may hold the potential to target diastolic dysfunction in NAFLD and lay the foundation for further exploration. Other studies using echocardiography or impedance cardiography have shown that HIIT reduced heart rate in sedentary overweight/obese women [35] and improved ejection fraction and blood pressure in hypertensive women [36]. HIIT did not have an effect on cardiac energetics, blood pressure, heart rate or systolic function in the present group. Combined, these data show a positive, but modest impact of HIIT on cardiac function in a clinical group who are at risk of CVD.

Although HIIT holds greater patient acceptability over continuous forms of exercise [20,21], due to its time-efficient nature, the metabolic effects of more vigorous exercise differ from more moderate intensities of exercise and should be considered. The current data show that despite benefits to IHL and cardiac function, there was no substantive effect on measures of glucose control. Previous reports of the effects of HIIT on glucose control are mixed, with any effects on glucose control predominately in postprandial periods [37,38]. Other studies have also demonstrated that more vigorous types of exercise have limited effects on glucose control compared with more moderate levels of

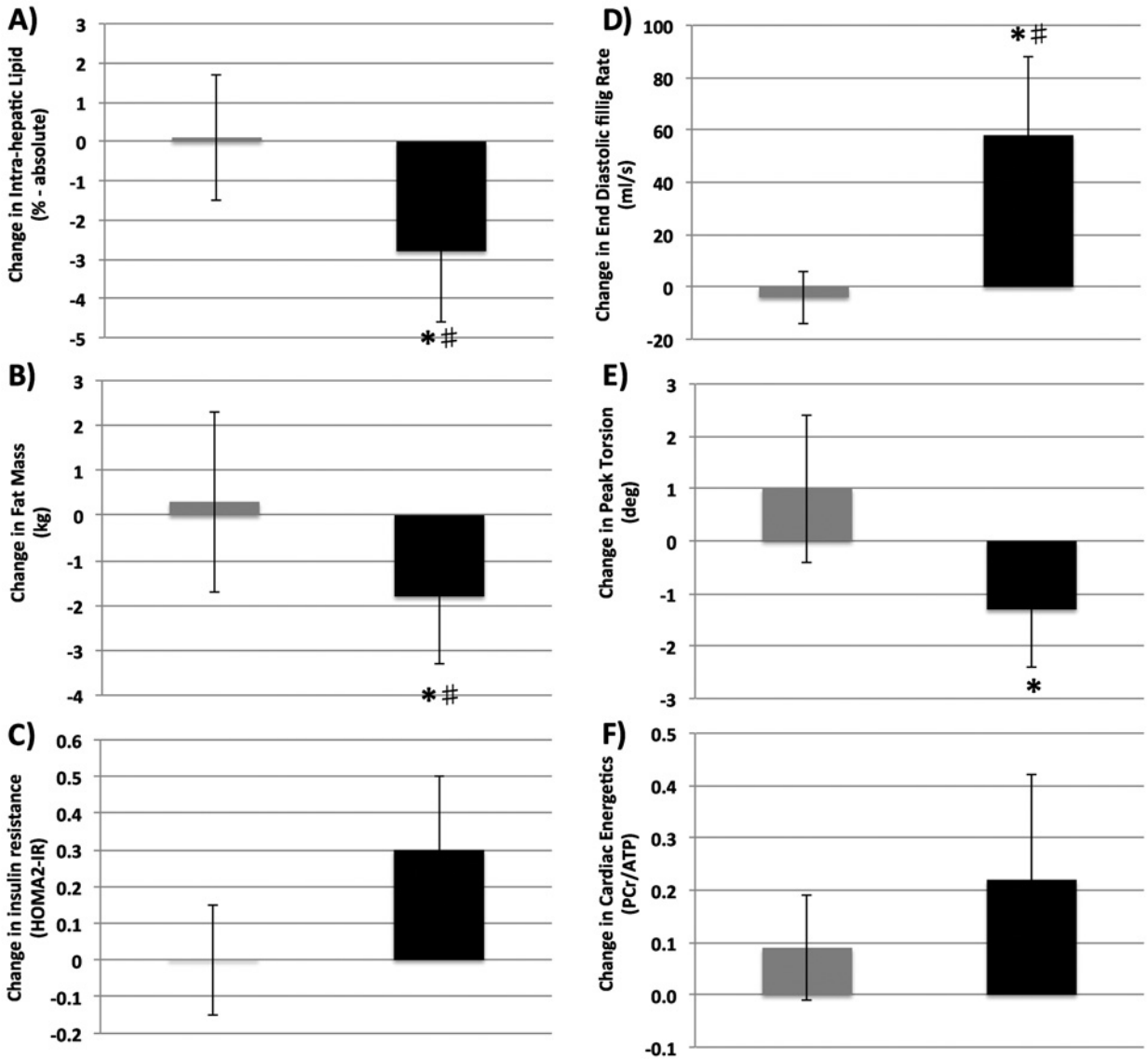

Figure 2 **Change in IHL (A), whole-body fat mass (B), fasting insulin resistance (C), end diastolic filling rate (D), peak torsion (E) and cardiac energetics (F) following control (grey) or HIIT (black); *within group difference ($P < 0.05$) #between group difference ($P < 0.05$); (mean ± S.D.)**

exercise in overweight people [39,40]. This raises the possibility that the benefits of HIIT types of exercise upon glucose control are acutely after exercise. The stability of fasting measures of insulin and glucose in the present dataset indicate that hepatic insulin sensitivity has not been affected, despite the reduction in IHL. Although no previous reports have investigated HIIT and IHL, studies have shown a reduction in hepatic secretion of very-low density lipoprotein triacylglycerol [41] and reduced postprandial plasma triacylglycerol concentrations [42] following HIIT. Thus, despite promising effects of HIIT upon hepatic and cardiac health, the effects on glycaemic control appear limited. The stability of glucose control following HIIT in NAFLD is of particular clinical significance given the growing links between NAFLD and dysglycaemia [5].

Interestingly, the data also show that HIIT produced a change in IHL without any apparent change in visceral fat content. There is increasing evidence that the two depots tend to reflect adiposity and are not mechanistically linked [43]. Previous findings from the Framingham Heart Study show IHL to be associated with the dyslipidaemia and dysglycaemia independently of visceral fat [44]. However, there is potentially a stronger role for visceral fat in the progression of NAFLD to more advanced forms of liver disease [45], stressing the importance of future work in this area.

The study was not without limitations. The groups in this explorative study were small and were heterogeneous with respect to sex and some biochemical, anthropometric and cardiac parameters. All but the first 1–2 exercise sessions were unsupervised and programme adherence assessed by self-report. This reflects

Table 4 Cardiac structure, function, torsion, strain and energetics (mean ± S.D.)
Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; deg, degrees, PCr/ATP, phosphocreatine/adenosine triphosphate ratio; SBP, systolic blood pressure.

	Control			HIIT			
Parameter	Baseline	Post-Treatment	*P*	Baseline	Post-Treatment	*P*	Time × Treatment interaction
SBP (mmHg)	141 ± 16	141 ± 15	0.926	141 ± 11	140 ± 14	0.849	0.880
DBP (mmHg)	89 ± 8	87 ± 9	0.165	89 ± 13	92 ± 10	0.493	0.243
Heart rate (bpm)	67 ± 8	67 ± 8	0.582	67 ± 8	64 ± 6	0.063	0.236
Stroke volume (ml)	58 ± 14	54 ± 13	0.103	59 ± 17	60 ± 15	0.753	0.069
Cardiac output (l/min)	3.8 ± 0.8	3.7 ± 0.7	0.710	3.8 ± 0.8	3.8 ± 0.7	0.826	0.640
End diastolic volume (ml)	96 ± 25	88 ± 22	0.048	96 ±38	94 ± 27	0.708	0.097
End systolic volume (ml)	40 ± 12	34 ± 12	0.098	37 ± 24	34 ± 14	0.899	0.691
Wall mass (g)	107 ± 25	107 ± 22	0.876	100 ± 30	104 ± 24	0.416	0.648
LV mass (g)	121 ± 25	120 ± 24	0.661	113 ± 34	121 ± 30	0.106	0.152
Wall thickness systole (mm)	13.9 ± 2.6	14.1 ± 2.6	0.850	14.0 ± 3.0	13.3 ± 2.6	0.268	0.342
Wall thickness diastole (mm)	8.1 ± 1.4	8.4 ± 1.0	0.474	8.1 ± 1.2	8.4 ± 1.0	0.494	0.987
Longitudinal shortening (%)	13.3 ± 2.5	14.8 ± 3.1	0.100	14.1 ± 2.5	15.3 ± 3.6	0.280	0.908
Eccentricity ratio (g/ml)	1.30 ± 0.35	1.42 ± 0.39	0.106	1.23 ± 0.28	1.31 ± 0.25	0.247	0.551
Early diastolic filling rate (ml/s)	255 ± 82	251 ± 82	0.787	244 ± 84	302 ± 107	0.008**	0.018#
Late diastolic filling rate (ml/s)	241 ± 107	266 ± 81	0.343	246 ± 43	257 ± 57	0.500	0.655
Peak endocardial circumferential strain (%)	25.2 ± 4.4	24.4 ± 4.8	0.637	28.2 ± 3.5	26.7 ± 4.7	0.076	0.823
Peak whole wall circumferential strain (%)	17.0 ± 3.5	16.9 ± 3.2	0.957	18.7 ± 2.1	17.9± 3.1	0.393	0.788
Peak torsion (deg)	5.76 ± 1.27	6.76 ± 1.86	0.178	7.8 ± 1.8	6.5 ± 1.9	0.001**	0.132
Torsion strain ratio	0.42 ± 0.17	0.49 ± 0.15	0.171	0.48 ± 0.09	0.43 ± 0.11	0.040*	0.070
E/A ratio	1.32 ± 0.88	1.05 ± 0.47	0.236	1.05 ± 0.50	1.27 ± 0.62	0.069	0.080
PCr/ATP	1.61 ± 0.35	1.70 ± 0.27	0.494	1.71 ± 0.39	1.93 ± 0.57	0.247	0.385

*significant difference baseline versus post-intervention ($p < 0.05$).
**significant difference baseline versus post-intervention ($p < 0.01$).
#significant difference time x treatment interaction ($p < 0.05$).

the likely scenario in a clinical setting, but does not optimize adherence. RPE was used to guide exercise intensity as this was a practical method and could be used by the patient to gauge their activities beyond the time that they were included in the trial. However, intensity guided by the use of heart rate monitors may have proved more accurate. Although the time-frame of IHL change following exercise is not known, exercise-induced improvements in glucose tolerance and insulin sensitivity are most marked within the first 24–48 h post exercise and tend to decline markedly after 72 h [46]. Thus, efficacy of the HIIT protocol in terms of glucose control may have been underestimated due to most patients being assessed between 48 and 72 h after their final session. Furthermore, given the modest reduction in body weight observed in the present study (0.5 kg), it remains to be determined whether exercise has a direct effect on IHL or whether the changes were due to the negative energy balance created by exercise. Irrespective of the mechanisms underpinning adaptation, the data suggest that modified HIIT remains an effective way of positively influencing IHL and its mediators in NAFLD.

In conclusion, these novel results show that a modified HIIT programme performed three times per week over 12 weeks significantly reduces IHL, circulatory liver enzymes and body fat in adults with NAFLD independent of substantive weight loss. These changes were accompanied by improvements in diastolic function, which warrants further exploration, but with limited impact on glucose control. Combined, these data suggest that clinical care teams should consider modified HIIT as part of the therapeutic management of liver fat and early cardiac changes in adults with NAFLD.

CLINICAL PERSPECTIVES

- Weight loss and exercise remains the cornerstone of NAFLD management; however, the effect of different types of exercise on NAFLD is unknown. This is the first study to assess the effects of a modified HIIT programme in patients with NAFLD.
- HIIT significantly reduced liver fat, circulatory liver enzymes and body fat independent of substantive weight loss. These changes were accompanied by improvements in cardiac function.
- Clinical care teams should consider modified HIIT as part of the therapeutic management of liver fat and early cardiac changes in adults with NAFLD.

AUTHOR CONTRIBUTION

The study was designed by Michael Trenell, Christopher Day, Kieren Hollingsworth and Kate Hallsworth. Christian Thoma, Kate Hallsworth, Sophie Cassidy, Quentin Anstee and Kieren Hollingsworth collected the data. Christian Thoma, Kate Hallsworth, Kieren Hollingsworth and Michael Trenell analysed the data. All authors helped write the manuscript and viewed the final version of the manuscript.

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