Loughborough University

Full title

The Impact of Type 2 Diabetes and Exercise on Liver Fat Quality

Short title

Diabetes, Exercise and Liver Fat (DELIVER)

Confidentiality Statement

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Mr Scott Willis
Mrs Sundus Malaikah

Sponsor: Loughborough University

Ethics Ref (IRAS Project ID): 241046

Funders: Diabetes UK (ref no. 17/0005659); NIHR Nottingham & Leicester Biomedical Research Centres

Date and Version No: 23/09/21
Version 6

Authors

1. Dr James King
2. Professor Guruprasad Aithal
3. Dr David Webb
4. Professor Melanie Davies
5. Professor Penny Gowland
6. Professor David Stensel
7. Dr Tom Yates
8. Dr Stephen Bawden
9. Dr Ghazala Waheed
10. Mr Jack Sargeant
11. Mr Scott Willis
12. Mr Aron Sherry
13. Mrs Sundus Malaikah

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Date:
23/09/2021

Name: Dr JAMES KING

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1. AMENDMENT HISTORY

Protocol version 1 – 1/5/2018
Protocol version 2 – 14/11/2018
Protocol version 3 – 19/02/2020
Protocol version 4 – 20/05/2020
Protocol version 5 – 09/09/2020
Protocol version 6 – 23/09/2021

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
2	2	14/11/18	James King, Aron Sherry	In our protocol, in relation to pre-exercise screening, we have used the term 'medical professional' which should be 'healthcare professional'. The subtle change in terminology clarifies that the individual responsible for the pre-exercise assessment is not necessarily a doctor but can be another suitably qualified healthcare professional – in our case a specialist cardiac nurse
3	2	14/11/18	James King, Aron Sherry	The 'medical exam' or 'physical exam' referred to in protocol v1 is actually an optional part of the Leicester BRC's pre-exercise screening process. When writing the protocol we misinterpreted the BRC pre-exercise screening SOP (that all medical evaluations include a physical exam). In effect, our SOP states that all participants undergo a medical history, resting BP and 12-lead ECG; but a physical exam only occurs if the healthcare professional dictates it is necessary – based on the history, ECG and BP. If the physical exam is needed, this is performed by a doctor.
4	3	19/02/20	James King, Aron Sherry, Scott Willis	In protocol v2, a participant inclusion criterion stipulated "Inactive (low or medium score on IPAQ-short form)" and an exclusion criterion stipulated "Excessively active (score of high on IPAQ-short form)". These items have now been removed from the eligibility criteria and the IPAQ-short form has been removed as a screening tool. Instead, within the exclusion criteria, an item has been added which excludes individuals who regularly take part in purposeful exercise training of vigorous intensity. This change was to more effectively screen out individuals who are too physically fit for the purpose of the study.
5	4	20/05/2020	James King, Scott Willis	The inclusion criteria for Part B of the study has now been changed to the recruitment of both patients with pre-diabetes and type 2 diabetes. The involved reducing the inclusion criterion for HbA1c from 6.5% to 6.0% and changing references to this group as 'individuals with type 2 diabetes/prediabetes'. The change was to enable a wider pool of patients to be recruited from in order to complete the study in a timely fashion due to ongoing difficulties with patient recruitment. Mrs Sundus Malaikah has also been added as a co-investigator on the study.

6	5	09/09/2020	James King, Scott Willis	The requirement of participants to complete three supervised and one unsupervised exercise training session per week has been altered so that participants are now required to complete four exercise training sessions per week, of which at least one session will be supervised by a member of the research team. This change is to reduce the number of visits participants make to study sites in order to reduce potential exposure to COVID-19. Participants will also now be contacted via telephone after each unsupervised session for support and to ensure compliance with the prescribed exercise intensity and duration. Site-specific COVID-19 symptom screening questionnaires have also been added which will be administered verbally by a member of the research team within 72 hours of each visit to study sites and on the day of each visit.
7	6	23/09/2021	James King, Scott Willis	The expiration date for the NHS ethical approval was extended from 31/12/2021 to 31/12/2022. This was in response to an 18 month delay due to the COVID-19 pandemic to allow more time for participant recruitment and data collection to hit the study recruitment targets.

2. KEY STUDY CONTACTS

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3. STUDY SUMMARY

Full study title	The Impact of Type 2 Diabetes and Exercise on Liver Fat Quality
Internal ref. no. (or short title)	Diabetes, Exercise & Liver Fat (DELIVER)
Study Design	Part A: cross-sectional study Part B: randomised controlled trial (RCT)
Scientific abstract	Non-alcoholic fatty liver disease (NAFLD) is characterised by an excessive accumulation of liver fat which is intricately linked to type 2 diabetes (T2DM), cardiovascular and renal disease. Recent research suggests that liver fat quality i.e. the composition of fat stored in the liver (saturated, unsaturated, polyunsaturated), may represent a key link between excess liver fat and adverse metabolic health outcomes. The proposed research contains a cross-sectional component (Part A) that will explore whether liver fat quality differs in male NAFLD patients with (*n* = 26) or without T2DM (*n* = 14); and a randomised controlled trial (Part B) (one exercise training and one control group) that will determine if exercise (150 - 200 min per week, 6 weeks) can beneficially modify liver fat quality in NAFLD patients with T2DM/prediabetes (n = 26, 13 per group). Liver fat quality will be assessed in both studies via magnetic resonance (3T) spectroscopy (^{1}H-MRS) using validated methods. This research will investigate whether liver fat quality is a novel therapeutic target for T2DM patients with NAFLD and determine whether exercise is able to favourably modify liver fat quality.
Study Participants	Part A (cross-sectional study): 14 obese men with non-alcoholic fatty liver disease (NAFLD) and 26 obese men with NAFLD and T2DM Part B (RCT): 26 obese men with NAFLD and T2DM/prediabetes
Planned Study Period	1st September 2018 to 31st December 2022 (52 months)

Research aims and objectives	The research outlined in this proposal seeks to determine the impact of T2DM on liver fat quality in patients with NAFLD and to characterise changes in liver fat quality in response to a supervised exercise training programme. The specific objectives of this work are to: • characterise the liver fat phenotype (saturation, unsaturation and polyunsaturation indices) and associated metabolic parameters in obese men with NAFLD and T2DM versus non-diabetic obese men with NAFLD • determine the impact of six weeks supervised exercise training on liver fat quality (saturation, unsaturation and polyunsaturation indices) and associated metabolic parameters in obese men with NAFLD and T2DM/prediabetes.

4. FUNDING AND SUPPORT IN KIND

FUNDER(S)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
Diabetes UK Wells Lawrence House 126 Back Church Lane London E1 1FH Phone: 0345 123 2399 Email: info@diabetes.org Fax: 020 7424 1001	Early Career Small Grant (Dr James King - Chief Investigator) - £15,000
The NIHR Nottingham Biomedical Research Centre Contact: Prof Guruprasad Aithal (Liver Theme Lead) Queens Medical Centre Hospital, West Block, E floor, Room 1418 Nottingham UK NG7 2UH Phone: 0115 823 1149 Email: Guru.Aithal@nottingham.ac.uk Fax: 0115 970 9012	• Funding support for additional MRI scans (see breakdown in section 20) • Clinical Research Fellow support
The NIHR Leicester Biomedical Research Centre Contact: Mr Tim Skelton (BRC manager) Diabetes Research Centre Leicester General Hospital	• Funding support for travel expenses (participants and study investigators) and metabolic analyses (see breakdown in section 20) • Research Associate (0.5 WTE, 2 years) • PhD student

Gwendolen Road Leicester LE5 4PW Phone: 0116 258 8128 Email: tim.skelton@uhl-tr.nhs.uk	• Research Administrator • Cardiac Nurse • Clinical Research Fellows • Leicester Diabetes Centre Exercise Team

5. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BMI	Body Mass Index
BRC	NIHR Biomedical Research Centre
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CRO	Contract Research Organisation
CT	Clinical Trials
EC	Ethics Committee (see REC)
GCP	Good Clinical Practice
GP	General Practitioner
^{1}H-MRS	Protein Magnetic Resonance Spectroscopy
ICF	Informed Consent Form
IRAS	Integrated Research Application System
MRI	Magnetic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PIL	Participant/ Patient Information Letter
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee
T2DM	Type 2 Diabetes Mellitus

6. PEER REVIEW

The research outlined in this protocol document has been peer reviewed by four independent experts in the research field during the Diabetes UK grant award process (competitive funding process). Within this process, the chief investigator was required to amend or rebut reviewer's comments and the final protocol has therefore been refined based on this critique. A diabetes-focussed PPI group at the Leicester General Hospital (organised by the NIHR Leicester BRC) also provided detailed comments on this research study during the development of the Diabetes UK funding application.

7. BACKGROUND AND RATIONALE

Non-alcoholic fatty liver disease (NAFLD) is often described as the hepatic manifestation of the metabolic syndrome and is defined as the excessive accumulation of fat within the liver (hepatic steatosis) in individuals who do not consume excessive alcohol or possess viral hepatic pathology [1]. The global prevalence of NAFLD is high and rising owing to the pandemics of obesity and inactivity which are leading risk factors. The most recent estimates suggest that NAFLD is present in approximately 25% of adults and up to 75% of those who are obese [2]. These statistics are concerning given that changes in metabolism that occur with NAFLD are heavily implicated in the development and progression of type 2 diabetes (T2DM), cardiovascular and renal disease [3].

The pathophysiology of NAFLD is complex and not completely understood; however, it is recognised that insulin resistance is integral to disease initiation and progression [4]. In effect, hepatic steatosis is strongly associated with insulin resistance in the liver, skeletal muscle and adipose tissue (body fat) [5]. This pathology helps explain the high prevalence of NAFLD in individuals with T2DM (up to 90%) and the more aggressive trajectory witnessed in this patient group [6]. Notably, approximately 40% of T2DM patients with NAFLD have non-alcoholic steatohepatitis (NASH) [6]; a more progressive form of NAFLD characterised by liver inflammation and injury that predisposes to premature cardiovascular and liver-related mortality [7]. This knowledge underlines the need to identify effective methods to prevent the inception and progression of NAFLD for those with, and at risk of, T2DM.

Although there is a strong link between the liver inflammation and injury associated with NASH and adverse clinical consequences; including substantially higher rates of decompensated cirrhosis, liver cancer, all-cause mortality and cardiovascular events [8], no such relationship exists between the amount of liver fat and clinical outcomes. However, recent research has identified liver fat quality (lipid species proportions) as being central to the metabolic derangements associated with NAFLD; with a higher proportion of saturated lipids, and a lower proportion of unsaturated lipids, being linked to adverse metabolic phenotypes e.g. insulin resistance and dyslipidaemia [9,10]. It is possible that elevated proportions of saturated hepatic lipids may contribute to the more aggressive NAFLD trajectory seen in patients with T2DM. This hypothesis is supported by the knowledge that hepatic *de novo* lipogenesis; a significant contributor to the hepatic fat pool in NAFLD [11]; exclusively produces saturated lipids [12] and is stimulated directly by hyperinsulinemia and hyperglycemia [12]. Liver fat quality may therefore represent a new therapeutic target for patients with NAFLD and T2DM.

The importance of liver fat quality within the pathophysiology of NAFLD has been identified within studies that have analysed liver tissue specimens collected via surgical biopsy [9,10]. Liver biopsy is a highly invasive procedure that carries significant risks to the patient. Alternatively, a MRI based procedure has been validated as a technique that is able to non-invasively determine liver fat quality indices (saturated,

unsaturated and polyunsaturated indexes) [13]. In this original paper, several lipids of known composition were analysed via proton magnetic resonance spectroscopy and were shown to assess liver fat quality with a high degree of accuracy and precision. Additionally, the researchers also identified higher saturated fat and lower unsaturated fat indices in obese individuals with clinically elevated hepatic steatosis verses obese and lean individuals without elevated liver fat. The MRI technique detailed in this research study provides a useful tool for researchers to investigate the importance of liver fat quality in the pathophysiology of NAFLD (and associated disease) and to scrutinise the efficacy of disease management therapies.

A small feasibility study in patients with NAFLD has demonstrated that seven consecutive days of moderate-intensity brisk walking is able to increase the proportion of polyunsaturated lipids within the liver and improve insulin sensitivity [14]. This beneficial change in liver fat quality occurred independently of body weight change and was directly associated with an increase in circulating adiponectin. These preliminary findings suggest that exercise may directly improve hepatic fat quality and metabolic outcomes in patients with NAFLD but further research is now required to investigate this possibility. It is intriguing that formal exercise training provides robust metabolic health benefits for patients with NAFLD, despite conferring a relatively modest weight-independent reduction in total liver fat [15,16]. This research project will explore the possibility that the quality of liver fat may contribute to the adverse metabolic profile seen in individuals with T2DM and NAFLD as well as examining the potential for regular exercise training to elicit favourable changes in liver fat quality. This research will therefore expand knowledge relating to the pathophysiology of NAFLD and T2DM; and the efficacy of exercise as a non-pharmacological therapy.

8. OBJECTIVES

Co-primary objectives

To determine: a) whether differences exist in the liver saturated fat index between obese men with NAFLD, with versus without, T2DM; b) the impact of six weeks exercise training on these outcomes in obese men with NAFLD and T2DM/prediabetes.

Secondary objectives

- To characterise potential differences in the following outcomes between obese men with NAFLD and T2DM versus non-diabetic obese men with NAFLD
    - Liver unsaturated fat index
    - Liver polyunsaturated fat index
    - Total liver fat percentage
    - Liver inflammation
    - Visceral adipose tissue
    - Circulating cardiometabolic biomarkers
    - Circulating liver enzymes
    - Circulating hepatokines
    - Objectively measured sedentary time and physical activity
    - Energy and macronutrient intake
    - Body weight & body fat percentage
    - Blood pressure
    - Aerobic fitness (peak oxygen uptake)
- To determine the impact of six weeks moderate-intensity exercise training on the following outcomes in obese men with NAFLD and T2DM/prediabetes
    - Liver unsaturated fat index
    - Liver polyunsaturated fat index
    - Total liver fat percentage
    - Liver inflammation
    - Visceral adipose tissue
    - Circulating cardiometabolic biomarkers
    - Circulating liver enzymes
    - Circulating hepatokines

- Objectively measured sedentary time and habitual physical activity
- Energy and macronutrient intake
- Body weight and body fat parentage
- Blood pressure
- Aerobic fitness (peak oxygen uptake)

9. STUDY DESIGN

Summary of trial design

This study consists of two parts: a cross-sectional component (Part A) and a randomised controlled trial (RCT) (Part B). All participants will complete Part A (non-diabetic obese men with NAFLD and obese men with NAFLD & T2DM/prediabetes); however, only one of the two study groups will progress to Part B (obese men with NAFLD and T2DM/prediabetes) (see Figure 1).

All prospective study participants will undergo a telephone interview in order to verbally assess potential study eligibility. This conversation will be conducted by a member of the study team and is anticipated to last up to 30 minutes. Participants wishing to take part and who appear eligible will subsequently be invited to attend the first face-to-face study assessment visit (visit one).

Study assessment visit one will occur at the Sir Peter Mansfield Imaging Centre located on the University of Nottingham Campus. Written informed consent shall be obtained at the beginning of this visit. After this, several questionnaires relating to health status and lifestyle habits will be completed before anthropometric measurements are taken. Participants will then undergo an MRI scan of the liver and abdominal region. Before participants leave the centre they shall be familiarised with a wrist worn (watch-like) physical activity monitor that they will wear continuously for the next seven days; and a food diary that they will complete on two week and one weekend day.

Participants will be invited to attend a second assessment visit if their MRI scan shows that they meet the criteria for clinically elevated liver fat (> 5.56%). Visit two will take place at the Queens Medical Centre Hospital (Nottingham) or the Leicester General Hospital (depending on participant preference). During this session a fasting blood sample will be taken and a healthcare professional will perform a medical exam that will include an ECG. Finally, participants will complete a symptom limited peak oxygen uptake test on a treadmill. Vital signs will be monitored throughout this test by a healthcare professional.

Participants' involvement in this study will end after visit two for those only taking part in Part A. At this point, participants destined to progress to Part B of the study will be randomised to one of two six week interventions (1:1) (exercise training or control) by the trial statistician. Participants will be notified of their assignment by telephone.

Participants randomised to control will receive no interventions and will be requested to maintain their habitual lifestyle during the six week intervention phase. Ahead of week five, participants will be posted a wrist worn physical activity monitor to wear continuously for the final two weeks of the study.

Participants will also complete a food diary during this time (two week and one weekend day in week five and six).

Participants randomised to the exercise training intervention will complete 24 moderate-intensity exercise training sessions over the subsequent six weeks (four times per week; ~50 min per session). Each week, at least one of the four exercise training sessions will be supervised by the research team. The remainder of the sessions each week will be unsupervised but monitored objectively using a heart rate monitor. Post- intervention assessments will be completed 48 h - 72 h after the final exercise training session.

After the intervention phase, participants will attend two final assessment sessions to obtain post-intervention data. Assessment visit three will be a repeat of assessment visit one whilst assessment visit four will be a repeat of assessment visit two (minus the medical examination).

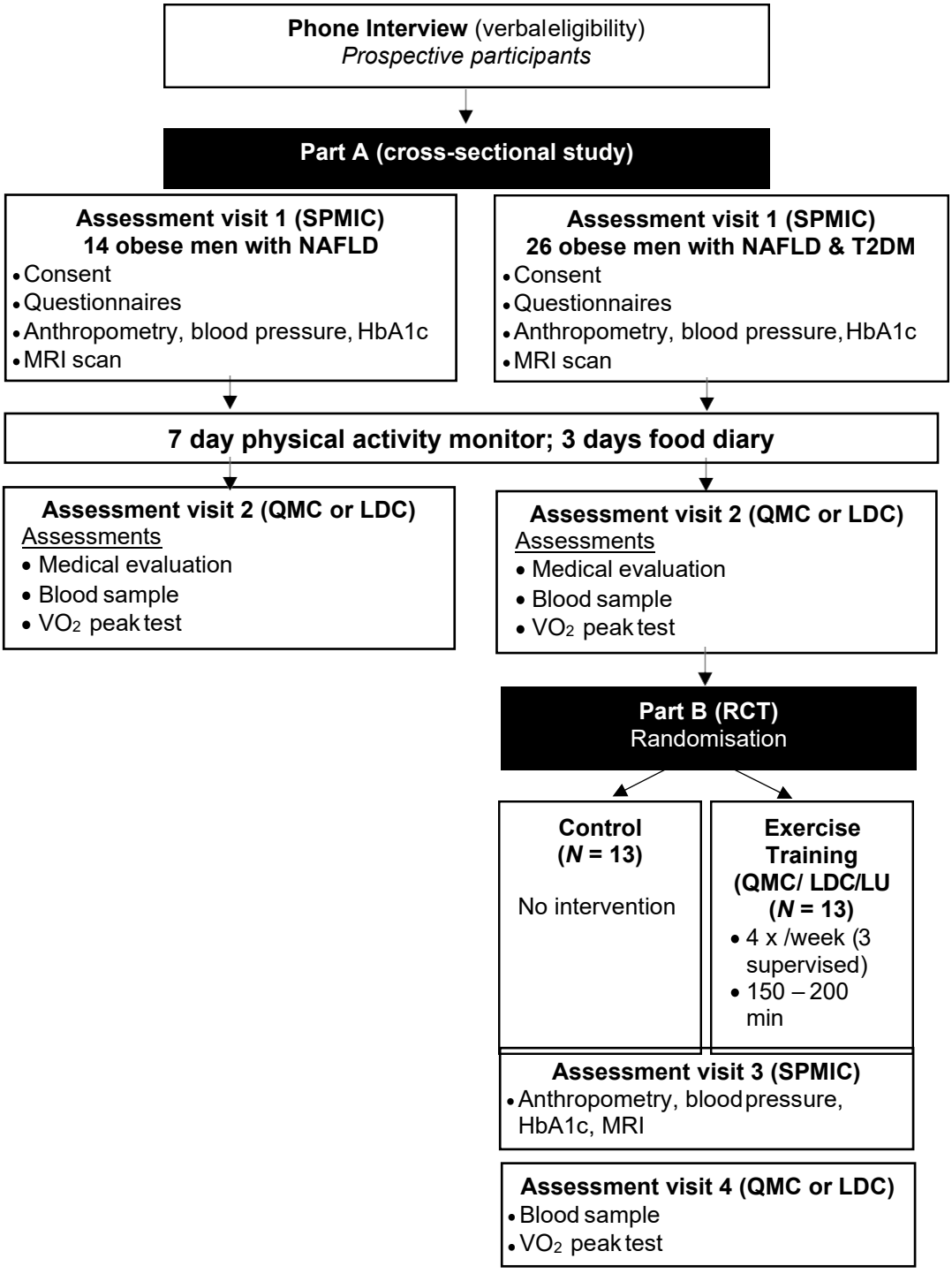

Figure 1: flow diagram of the study protocol
SPMIC – Sir Peter Mansfield Imaging Centre; QMC – Queens Medical Centre, Nottingham; LDC – Leicester Diabetes Centre; LU – Loughborough University

Primary and secondary endpoints / outcome measures

Co-primary outcomes: Liver saturated lipid index (%) determined by proton magnetic resonance spectroscopy (^{1}H-MRS) using a 3T MRI scanner

1) Comparison between obese men with NAFLD verses obese men with NAFLD and T2DM (Part A)
2) Response to the six week exercise training intervention (Part B)

Secondary outcomes:

- Liver unsaturated lipid index (%) - measured using ^{1}H-MRS
- Liver polyunsaturated lipid index (%) - measured using ^{1}H-MRS
- Total hepatic lipid composition (%) - measured using ^{1}H-MRS
- Liver inflammation - measured using MRI
- Visceral adipose tissue - measured using MRI
- Subcutaneous abdominal adipose tissue - measured using MRI
- Body mass and body fat percentage
- Blood pressure
- Aerobic fitness (peak oxygen uptake)
- Circulating metabolic biomarkers (fasted blood sample)
    - Liver enzymes
    - Glucose
    - Insulin
    - Lipids
    - HbA1c
    - HOMA-IR (surrogate marker of peripheral insulin resistance)
    - ADIPO-IR (surrogate marker of adipose tissue insulin resistance)
    - Inflammatory proteins
    - Hepatokines
- Objectively measured sedentary time & physical activity assessed via the GENEactiv physical activity monitor
- Energy and macronutrient intake (two weekdays and one weekend day)

10. TRIAL PARTICIPANTS

Overall description of trial participants

The participants we are seeking to recruit are inactive and obese men, with clinically elevated liver fat, with or without T2DM/prediabetes. The inclusion and exclusion criteria can be found overleaf.

Recruitment strategy

Recruitment will target individuals within multiple settings: hospital clinics, primary care, community weight management services, research databases (UHL & NUH NHS Hospital Trusts, Loughborough University), the community, internet and local media.

Hospital clinics

Within relevant diabetes, liver disease and bariatric surgery clinics across Leicester and Nottingham, study posters will be displayed, and clinicians may identify participants and distribute Participant Information Leaflets and Participant Information Sheets.

General practice and primary care

Across Leicestershire and Nottinghamshire, GP surgeries will be contacted to request support with recruitment for this study. If willing, they will be asked to identify potential participants and circulate Invitation Letters and Participant Information Sheets. Access to GP surgeries will be supported by the CRN and regional CCGs. Other primary care centres (dental practices, opticians, community pharmacies) within Nottingham University Hospitals NHS Trust and University Hospitals Leicester NHS Trust will also be asked to display advertisement materials (study poster) and provide Participant Information Leaflets.

Community weight management services

The study will be advertised by providers of Tier 2 (lifestyle intervention) and 3 (specialist weight management programs) weight management services within Leicestershire, Nottinghamshire and Derbyshire. Session leaders will identify potential participants via databases or during clinical contacts and provide copies of Participant Information Leaflets / Sheets. The study will also be advertised via poster at service facilities.

Research databases

Eligible individuals who have previously taken part in research studies and whom have consented to be contacted about future research studies will be contacted. Investigators involved in this study have access to databases of such individuals across the NIHR Nottingham BRC, NIHR Leicester BRC and Loughborough University. Potential participants will either be posted a Participant Information Leaflet or

contacted via telephone – depending on the preference of the investigator who is responsible for curating the participant database.

Community and internet

Participants will be recruited from the general public through various routes:

- *Commercial weight management programmes:* session leaders from local weight loss programs will advertise the study to their cohorts by mentioning the study at meetings and providing copies of Participant Information Leaflets / Sheets.
- *Websites:* the study will be advertised on University (Loughborough, Nottingham and Leicester) and Hospital Trust (Nottingham, Leicester) websites where links to investigator contact details and electronic versions of study information resources will be provided. Anyone interested in taking part will subsequently be able to contact the research team.
- *Local media:* the research team will liaise with University (Loughborough, Nottingham and Leicester) public relations teams to advertise the study within the community. Advertisements routes may include press releases (website, radio, newspaper) where investigator's contact details will be provided for anyone who may be interested in taking part after hearing about the study.
- *Study posters:* will be displayed in hospital trusts, university and local community (where permitted).

Inclusion criteria

- Men
- ≥ 30 - ≤ 75 years of age
- Body mass index ≥ 27 - ≤ 45 kg/m^2 (or ≥ 23 to 45 45 kg/m^2 if south Asian)
- Waist circumference ≥ 94 cm (or ≥ 90 cm if south Asian)
- Clinically elevated liver fat (≥ 5.56% assessed via ^{1}H-MRS)[17]
- Participant is willing and able to give informed consent to participate
- Participant can communicate effectively in English
- Participant is able to meet the time demands of the study

Additional criteria for participants without T2DM

- HbA1c < 6%

Additional criteria for participants with T2DM/prediabetes

- Diagnosed T2DM or prediabetes

- Treatment via lifestyle or metformin only within the last 6 months
- HbA1c 6.0 – 10%
- Willingness to enter Part B of the study and be randomised to exercise training or control
- Able to meet the time and physical demands encompassed within the exercise training intervention

Exclusion criteria

- Contraindications to magnetic resonance procedures
- Contraindications to exercise training
- Participating in regular purposeful exercise training of vigorous intensity – frequency ≥ 3 sessions per week and intensity ≥6.0 metabolic equivalents (METs)
- Weight instability or planned/ on-going dietary intervention
- Unable to communicate sufficiently in English
- Co-morbidity that the research team determine to be a contraindication to involvement
- Current smoker
- Uncontrolled hypertension - systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg

Additional criteria for participants with T2DM/prediabetes

- Taking additional oral anti-diabetic medications to metformin e.g. SGLT2i, GLP-1RA, DPP4 inhibitors, TZDs within the last 6 months
- Taking insulin

11. STUDY PROCEDURES

Verbal eligibility check

Prior to commencing the study, participants will be contacted via telephone and an initial verbal eligibility check will take place (approx. 30 min conversation). Following this, potentially eligible participants will be invited to visit the Sir Peter Mansfield Imaging Centre for study assessment visitone.

Within 72 hours of each visit to a research site (assessment visits and supervised training sessions), participants will be contacted via telephone by a member of the research team and a verbal COVID-19 symptom screening questionnaire will be administered. As per site guidelines, the questionnaire will be site-specific to Leicester and Nottingham sites. Furthermore, the COVID-19 symptom screening questionnaire will be further completed by participants upon arrival at each study site visit to further screen for symptoms.

Assessment visit 1 - Sir Peter Mansfield Imaging Centre (University of Nottingham)

Informed consent

Before any study related procedure can take place, the participant must sign and date the most recent approved version of the Informed Consent Form. Before consent is obtained the responsible individual will ensure that the participant fully understands all aspects of the study. It will also be clearly stated that the participant is free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give the reason for withdrawal. If a participant withdraws from the study but does not withdraw their consent, then data already obtained may be used for the study. If a participant has withdrawn due to an adverse event, a healthcare professional will follow up as appropriate.

The consent form will be signed and dated based up on an informed decision. The consent process will be performed by someone who has received consent training, has been authorised by the Chief Investigator, and is named on the delegation of authority log. The original signed form will be retained at the study site and copy will be given to the participant. A third copy will be posted to the participant's GP.

Questionnaires

Participants will complete several pen and paper based questionnaires to assess their eligibility to participate in the study and to provide baseline study data. These will include the following:

- Physical Activity Readiness Questionnaire - to determine participants' readiness to exercise and/or contraindications
- Loughborough University Health Screen Questionnaire – to obtain an overview of participants' medical history, current medications and family history of disease
- Sir Peter Mansfield Imagining Centre Magnetic Resonance Safety Screening Form – to assess potential contraindications to MRI

- Demographics & contact details – to determine participants' date of birth, ethnicity and postal address

Anthropometry, blood pressure and finger prick blood test

Height, body mass and waist circumference will be measured using standard techniques and body mass index (BMI) will be calculated. Body fat percentage will be estimated using bioelectrical impedance analysis. Blood pressure will be assessed using an automated monitor after participants have sat quietly for 10 minutes (average of three measurements). A finger prick blood test will be taken to check preliminary eligibility (HbA1c, glucose, lipids) using a point-of-care device.

Magnetic resonance imaging (MRI)

MRI data will be acquired using a 3T Philips Ingenia MRI scanner. Liver fat quality indices and total intrahepatocellular liver fat fractions will be determined using ^{1}H-MRS via the quantification of individual lipid group peaks. Liver inflammation, visceral adipose tissue and subcutaneous abdominal adipose tissue will be measured via MRI. The techniques used to measure these outcomes have been validated and published previously [13,18,19].

Familiarisation with weighed food records and physical activity monitors

Participants will be provided with a wrist worn (watch-like) physical activity monitor (GENEactiv) that they will wear 24 h/day for the next seven days. Participants will also be shown how to keep an accurate weighed food record and will be provided with food scales and diary to facilitate a three-day record within the next seven days (two week and one weekend day).

After this session, MRI scans will be assessed to examine whether or not participants have an amount of liver fat that if high enough for inclusion in the study (> 5.56%). If liver fat is less than this then participants will not be permitted to participate. If liver fat is equal to or greater than this level, then participants will be invited to attend study assessment visit two.

Assessment visit 2 - Leicester General Hospital (Leicester Diabetes Centre) or Queens Medical Centre Hospital (NIHR Nottingham BRC)

Fasting blood sample

Participants will be asked to attend the second study assessment visit having not eaten since the prior evening. These visits will therefore occur in the morning (before 10:30). At the start of this visit participants will provide a fasting venepuncture blood sample (50 mL blood) after having sat down for 10 minutes. This sample will be collected from an antecubital vein by an individual trained and experienced in phlebotomy. One blood bottle will be sent to hospital pathology labs for the analysis of glycated haemoglobin. The remaining samples will be processed immediately and stored until the end of the trial within -80^{o}C freezers at the research sites. Following the last participants visit, samples will

be transported to Loughborough University (at -80ºC) by a commercial courier. Samples will then be analysed in batch for:

- Lipids
- C-reactive protein
- Liver enzymes
- Glucose
- Insulin
- Nonesterifed fatty acids
- Hepatokines
- Inflammatory proteins
- Genotype (gene variants linked to NAFLD)

Medical evaluation and aerobic fitness

A healthcare professional will take a full medical history from participants in order to identify any factors that may prohibit individuals from completing the study. Blood pressure will be measured, and a 12 lead ECG and a physical examination* will also be performed. Finally, a symptom limited progressive treadmill exercise test will be undertaken on a treadmill. This test will require participants to exercise at increasingly harder intensities until volitional exhaustion. A clinical professional will monitor participants' blood pressure and ECG during this test which will be terminated if clinically indicated.

* The physical examination is optional and dependent on findings from Medical History and 12 Lead ECG. It is to be performed by individuals qualified to do physical examinations.

Randomisation

After visit two, participants entering Part B of the study will be randomised (1:1) to condition (exercise training or control). Randomisation will be performed by the trial statistician (Dr Ghazala Waheed) (see section 13 for additional details). The involvement of participants who are only completing Part A of the study will end at this point.

Six week intervention

Participants randomised to control will receive no interventions during the six-week intervention phase. During this time, control participants will be asked to not change any aspects of their lifestyles. Ahead of week five, participants will be posted a physical activity monitor to wear continuously during week five and six. Participants will also complete weighed food diaries during week five (two weekdays and one weekend day).

Participants randomised to exercise training will complete four exercise training sessions per week during the six-week intervention. Each week, at least one session will be supervised by the research team whilst the remaining sessions will consist of participants undertaking brisk walking on their own. All exercise sessions will be composed of continuous moderate-intensity exercise and last 35 - 50 minutes in duration (depending on intervention week). The specific details relating to these training sessions can be seen in section 12 (Table 2).

Assessment visit 3 (post-intervention) - Sir Peter Mansfield Imaging Centre (University of Nottingham)

The assessments undertaken at visit three will be a repeat of those completed during visit one.

Assessment visit 4 (post-intervention) - Leicester General Hospital (Leicester Diabetes Centre) or Queens Medical Centre Hospital (NIHR Nottingham BRC)

The assessments undertaken at visit four will be a repeat of those completed during visit two except that a medical examination will not be performed.

12. TREATMENT OF TRIAL PARTICIPANTS

Overview of procedures

This study will consist of two parts (A and B) and will include two discrete groups of participants.

1. Obese men with NAFLD – will complete Part A only
2. Obese men with NAFLD and T2DM/prediabetes – will complete Part A and B

Table 1 provides an overview of the procedures that participants will undertake as part of this study.

Table 1: summary of trial procedures for study participants

Visit	Duration	Procedure(s)
Study Part A – all participants		
Telephone interview	30 min	Verbal eligibility check against inclusion / exclusion criteria
Assessment visit 1 (SPMIC)	2 h	Informed consent, study questionnaires, anthropometry, blood pressure, finger prick test, MRI scan
Assessment visit 2 (QMC or LGH)	2 h	Fasting blood sample, medical examination, peak oxygen uptake test
Study Part B – obese men with NAFLD & T2DM/prediabetes only		
3-20 **Exercise training** (supervised sessions at QMC, LGH or Loughborough University)	1 h per session	Heart rate, RPE
Assessment visit 3 (SPMIC)	2 h	Study questionnaires, anthropometry, blood pressure, MRI
Assessment visit 4 (QMC or LGH)	2 h	Fasting blood sample, peak oxygen uptake test

RPE - ratings of perceived exertion, MRI magnetic resonance imaging, HbA1c – glycated haemoglobin, SPMIC – Sir Peter Mansfield Imaging Centre, QMC – Queens Medical Centre Hospital, LGH - Leicester General Hospital

At the beginning of the study, all potential participants will complete a telephone interview to verbally assess eligibility for the study (age, sex, activity status, smoking status, habitual alcohol intake,

understanding of English, medical history, medication use, contraindications to the study procedures, willingness and ability to undertake six weeks exercise training). Participants who are potentially eligible will then be invited to attend the Sir Peter Mansfield Imaging Centre located on the University of Nottingham campus for the first study assessment visit.

Prior to each visit to a study site (including assessment visits and supervised training sessions) participants will be contacted via telephone by a member of the research team within 72 hours of their visit to complete a site-specific COVID-19 symptom screening questionnaire. Upon arrival at the study site, participants will verbally complete the COVID-19 symptom screening questionnaire again with a member of the research team.

Before participants' first study visit, they will be asked to consume a normal diet i.e. no unusual feasting or energy restriction, in the prior 24 h. No alcohol or high caffeine containing foods will be permitted during this time. Participants will also be asked to attend the research centre in the morning having not eaten since the prior evening (after 22:00). At this initial visit, a member of the research team will check participants' understanding of the study and written informed consent will be obtained. Participants will then complete additional screening and eligibility assessments as detailed in section 11. Before leaving the research centre, participants will have a physical activity monitor attached to them (watch like device) that they will wear for the next seven days. They will also be provided with food weighing scales and a food diary to assist them in providing a three-day weighed food record (two week and one weekend day) within the subsequent seven days.

After study assessment visit one, the research team will contact participants by telephone to inform them whether or not they have sufficiently high liver fat to permit their inclusion in the study. If so, study assessment visit two will be arranged. If participants do not meet the inclusion criteria, they will be asked to post back the food diary and physical activity monitor using a prepaid envelope already provided. These individuals will take no further part in the study.

Participants' second assessment visit will take place at the Queens Medical Centre Hospital (Nottingham) or the Leicester General Hospital (depending on preference). Ahead of this visit, they will be asked to consume a 'normal diet' in the 24 h beforehand. No alcohol or high caffeine containing foods will be permitted during this time. Participants will also be asked to attend the research centre in the morning having not eaten since the prior evening (after 22:00). Participants will bring their physical activity monitor and food diary with them to this visit. During this visit participants will undertake all of the assessments outlined in section 11. The completion of this visit will mark the end of procedures for participants who are only completing Part A of the study (obese men with NAFLD). In due course, a

member of the study team will contact these individuals via telephone in order to discuss the provision of feedback in relation to their results.

Participants progressing to Part B of the study (obese men with NAFLD and T2DM/prediabetes) will then be randomised to exercise training or control for six weeks. Participants will be made aware of their group assignment via telephone. Control participants will undergo no interventions and will be asked not to alter any aspect of their lifestyle during the next six weeks. Ahead of week five, control participants will receive a physical activity monitor and food diary in the post to enable them to record their habitual physical activity and food intake during weeks five and six. After the intervention phase has ended, control participants will complete two additional study assessment visits (visits three and four) to obtain post-intervention measurements. These visits will be a repeat of assessment visits one and two (excluding the pre-exercise screening in visit two).

Participants randomised to the exercise training group will complete 24 exercise training sessions (35 to 50 min of moderate-intensity exercise) during the six-week intervention. Four training sessions will be completed each week, with at least one of these sessions being supervised by the study team. Participants will have the option to undergo these sessions at Loughborough University (National Centre of Sport and Exercise Medicine), Nottingham (Queens Medical Centre Hospital) or Leicester (Leicester General Hospital) depending on preference. The remainder of the sessions each week to be completed by participants will be unsupervised sessions of brisk walking which will be recorded via a heart rate monitor and watch. Participants will be supported after each unsupervised session via a telephone call from a member of the research team and the intensity and duration of the session will be recorded from the watch. Participants in the exercise group will wear a wrist-worn movement sensor throughout the entire training phase and will complete weighed food diaries (two week and one weekend day) in the fifth and sixth weeks of training.

Exercise training

The exercise training program in Part B of this study is based upon joint guidelines published by the European Association for the Study of Liver Disease (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO); which state that individuals with NAFLD should aim to complete 150 to 200 min per week of exercise [20]. Participants will therefore complete four, 50 min exercise training sessions each week. Each training session will be composed of moderate-intensity continuous exercise at a target intensity that will be determined using a combination of age-predicted maximum heart rate (70-75%) and RPE (13-14).

During each week of exercise training, participants will complete four exercise training sessions, of which at least one of these sessions will be a supervised training sessions. The duration of exercise training will progress from week one to week six to support participants' completion of the programme (Table 2).

Supervised exercise training sessions will include a 10-minute warm-up and five min cool down at a self-selected light intensity (RPE 11 – 'fairly light'). All supervised training sessions will take place on a treadmill (walking or jogging); however, a cycle ergometer will be available for participants to use should they feel discomfort with prolonged upright exercise. Supervised training sessions will occur Monday to Friday.

Participants will undertake the non-supervised training sessions in their habitual environment e.g. local park. In these sessions, participants will undertake brisk walking at an intensity corresponding to 70-75% of maximum age-predicted heart rate and/or an RPE of 13-14. The intensity and duration of sessions will be monitored using a heart rate monitor and accompanying watch.

Table 2: overview of the supervised & unsupervised moderate-intensity continuous exercise training sessions

	Supervised exercise sessions			**Unsupervised exercise sessions**	
Training Week	**Warm up duration (min)**	**Cool down duration (min)**	**Main body duration (min)**	**Brisk walking session duration (min)**	**Total weekly exercise duration (min)**
1	10	5	20	45	150
2	10	5	25	45	165
3	10	5	30	45	180
4	10	5	30	50	185
5	10	5	35	50	200
6	10	5	35	50	200

NB: four exercise training sessions will be completed each week, of which at least one session will be a supervised exercise training session and the remainder will be an unsupervised session.

Given funding limitations, control participants will not be offered the exercise intervention at the end of the study. Instead, the research team will offer to provide support to participants wishing to become more active beginning with a discussion of their physical activity and fitness data obtained from the study.

Remuneration and expenses

Participants will not be paid for their participation in Part A or B of this study. Travel expenses will be provided for participants

13. SAFETY REPORTING

Definitions

Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether or not considered related to the study.

Adverse Reaction (AR)

All untoward and unintended responses related to the study.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions. There are no expected ARs in this study.

Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or

- Is a congenital anomaly/birth defect.
- Other important medical events*

  *Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Expected Serious Adverse Events/Reactions

This study is a non-invasive lifestyle related study and therefore no SAE/Rs are expected.

Suspected Unexpected Serious Adverse Reactions

This study is a non-invasive lifestyle related study and therefore no SUSARs are expected.

Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by investigators or reported by the participant, whether or not attributed to study, will be recorded on the CRF. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

Reporting Procedures for Serious Adverse Events

All SAEs must be reported to the Sponsor within one working day of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&D Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The Chief

Investigator will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the Chief Investigator shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceding 12 months.

14. STATISTICS

Description of statistical methods

Descriptive statistics will be calculated to outline the characteristics of the study sample. Normality of data will be assessed using histograms and box plots, while further analysis of skewness and kurtosis will be conducted if normality is not clear from the histograms and box plots. Depending on the distribution of data, participant characteristics will be reported as mean (SD) or median (IQR) and number (percentage) for continuous variables and for categorical variables respectively.

For part A of the study, data will be checked for parametric assumptions. Independent samples t-tests will used to analyse differences in continuous variables between study groups (obese men with NAFLD and obese men with NAFLD and T2DM in part A of the study). To examine factors associated with NAFLD and T2DM, univariate logistic regression models will be performed with NAFLD and T2DM (diabetic individuals with NAFLD vs. non-diabetic individuals with NAFLD) as the dependent variable. All variables significantly associated with NAFLD and T2DM in univariate logistic regression analyses will be included in multivariate logistic regression analysis.

For part B of the study, baseline descriptive statistics will be summarised by treatment arm (Intervention vs control). Data will be checked for parametric assumptions. For the primary outcome, change in hepatic saturated lipid index (%) from baseline to six weeks due to moderate-intensity exercise training in men with NAFLD and T2DM/prediabetes, treatment arms will be compared using linear regression modelling. The analysis will include a binary indicator for randomisation group as the explanatory variable, terms for the stratification category (ethnicity) and adjustments for the baseline measure of the outcome (hepatic saturated lipid index).

Complete case analysis will be utilised for the primary analysis. Intention to treat will be carried out as sensitivity analysis, using multiple imputation for missing values. Secondary outcomes will be analysed using similar methods as the main analysis, with an appropriate model selected dependent on the distribution of the outcome.

The assumptions associated with each model will be assessed and where these are not met alternative models or parameterisations will be considered. A value of $P<0.05$ will be considered statistically significant for all analyses. Statistical analyses of the baseline data and all future analysis will be carried out using STATA version 15.

The Number of Participants

The sample size for the research outlined in this protocol was undertaken by a statistician in the Leicester Clinical Trials Unit. The sample size calculations were informed by data published in a previous study which validated the method for measuring hepatic fat quality via ^{1}H-MRS[16].

Part A of this research (cross-sectional analyses) was powered (80%) to detect a difference in the liver saturated fat indices of 0.5 between men with NAFLD with T2DM versus non-diabetic men with NAFLD (alpha 5%, SD 0.4 in each group). 28 participants are needed to provide adequate statistical power for this analysis (14 in each group). Based on the same data, the power calculation showed that 24 participants are needed for Part B of the outlined research (RCT). This is inflated to 26 to allow for expected drop-out (10%).

Please note that the baseline data for all participants entering Part B of this research will be used in Part A and therefore the cross-sectional analyses will include data from 26 men with NAFLD & T2DM and 14 non-diabetic men with NAFLD.

Procedure for dealing with missing and spurious data

Missing data will be replaced using multiple imputation or another appropriate method. In Part B, participants completing less than 85% of all training sessions will not be included in the final analysis.

15. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

Beyond the study team, direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

16. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Loughborough University as sponsor operate a risk-based audit programme to which this study will be subject. The research team will be responsible for all elements of study management on an on-going basis. A documented monitoring log and audit trail will be maintained throughout the lifetime of the study. The CI and PIs will oversee the set-up and conduct of study procedures at each site. All source data and study documents will be made available for Sponsor monitoring, and any external audits and inspections as appropriate, for example by the Research Ethics Committee.

It is acknowledged that accidental protocol deviations can happen at any time; however, thorough training of research staff and appropriate utilisation of SOPs will limit the likelihood of deviations occurring. One-off protocol deviations will be documented on the relevant forms and the Chief Investigator will be notified. Frequent protocol deviations will be escalated to the TSC and appropriate actions considered.

17. CODE OF PRACTICE AND REGULATIONS

Ethics

Approval from Loughborough University (sponsor), a Local Research Ethics Committee (REC), the Health Research Authority (HRA), University of Nottingham, University Hospitals of Leicester NHS Trust R&D and Nottingham University Hospitals Trust R & D will be sought prior to the commencement of the research. This will ensure that all ethical and indemnity issues are dealt with appropriately. The research protocol, Participant Invitation Letter, Informed Consent Form, Participant Information Sheet and any proposed advertising material will be submitted to the sponsor, main REC, and host institutions for approval. All formal correspondence with NHS REC and host institutions will be retained. The Chief Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. The Chief Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the International Conference on Harmonisation Guidelines for Good Clinical Practice (IHC-GCP).

Participants will be free to withdraw at any time from the study without giving a reason and without their legal rights being affected. We do not anticipate any harm, discomfort or risk to anyparticipant enrolled in this study. The overall care and comfort of the participant will be considered paramount at all times during the study.

Sponsor Standard Operating Procedures

All relevant SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines.

Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

Approvals

Once Sponsor authorisation has been confirmed, the protocol, Informed Consent Form, Participant

Information Letter, Participant Information Sheet, GP correspondence documents and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (HRA), and the host institution for written approval.

Once Sponsor authorisation has been confirmed, the Chief Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

The Chief Investigator will formally notify NHS REC and host institutions of study end once the trial is closed.

Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. Participants will be identified only by initials and a participant's ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. Direct access to all documents will be granted where appropriate to authorised representatives from the sponsor, host institution and the regulatory authorities for monitoring, audits and inspections. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to doso.

Other Ethical Considerations

In this study, it is possible that the study team may identify various health issues during the process of screening and trial assessments. As examples, magnetic resonance imaging may identify liver masses, or ECG traces may identify abnormal heart electrical rhythms. In these instances, the study team will immediately inform the participant and provide written notification. If the participant consents, this information will also be shared with their GP so that appropriate follow-up can occur.

18. DATA HANDLING AND RECORD KEEPING

All data collected will be kept strictly confidential and in accordance with the Data Protection Act 1998. The research staff will ensure that the participants' anonymity is maintained. On all study-specific documents, other than the signed consent form and enrolment log, the participant will be identified by initials and/or a participant ID number, not by name.

All research data will be kept in a secure location accessible only by named members of the research team during the active phase of the study and until the data have been analysed. It will then be archived for five years after the end of the trial and subsequently destroyed.

Direct access to information gathered in this study will only be available to individuals who have been granted access. The sponsor, host institution and regulatory authorities can permit trial related monitoring, audits and inspections.

All study documentation containing identifiable patient data will be managed in accordance with ICH-GCP, Research Governance Framework for Health and Social Care and the Data Protection Act. Information will only be obtained from the patient if necessary for the study.

All electronic data will be stored on secure university (Loughborough University) or hospital (NUH / UHL) network drives, to which only the relevant study staff have access, which is granted by the Chief Investigator. All study documents and data will be kept for 5 years. Paper copies of the CRFs will be stored in locked cabinets at research sites.

19. STUDY GOVERNANCE

PPI Involvement Group: the NIHR Leicester BRC has an established diabetes PPI group who frequently provide support for research projects led by researchers within the Diabetes Research Centre (University of Leicester) and Loughborough University (School of Sport, Exercise and Health Sciences). Members of this group reviewed the research outlined in this protocol before the project underwent peer review by Diabetes UK and have supported the development of study materials for this proposal (e.g. Participant Information Sheet, Informed Consent Form, Case Report Forms). Two individuals from this group will become members of the TSC to help facilitate the smooth and timely conduct of the research.

Trial steering committee (TSC)

A TSC will provide oversight of this study with meetings convened every other month in the first 12 months of the study and quarterly thereafter. Membership of this committee will comprise the CI, PIs, Co-investigators and PPI representatives.

Data safety monitoring committee

There will be no data safety monitoring committee for this study. All data safety matters will be dealt with immediately by the Chief Investigator and reviewed by the study team at TSCmeetings.

Access to the final study dataset

The Chief Investigator will hold the master copy of the final study dataset. All co-investigators may be permitted access to this file as deemed necessary by the Chief Investigator.

20. FINANCE AND INSURANCE

This research will be funded by Diabetes UK (Early Career Small Grant – Dr James King) and the NIHR Nottingham and Leicester BRCs. All costs due to be incurred within this research project are detailed below. Please note that this study will additionally be supported by the established infrastructure within the NIHR Leicester and Nottingham BRCs (costs not identified here). Support will include a Post-Doctoral Research Associate (0.5 WTE), PhD student and Administrator who will form the basis of the study team. Medical support for clinical procedures will also be provided by clinical research fellows and cardiac nurses employed within the BRCs.

Table 2: itemised research study costings

	Cost of procedure	**Funder**
Imaging procedures	£16,500	Diabetes UK - £13,000 Nottm BRC - £3,500
HbA1c (hospital labs)	£480	Nottm BRC - £480
In-house blood analysis	£5,712	Diabetes UK - £1,500 Leicester BRC - £4,212
Participant travel	£1,062 (est. maximum amount)	Leicester BRC - £1,062
Investigator travel	£1,170 (est. maximum amount)	Diabetes UK - £500 Leicester BRC - £670
Total cost	**£24,924**	

Sponsorship for this study will be provided by Loughborough University. Loughborough University will therefore provide indemnity to meet the potential legal liabilities of the sponsor for harm to participants arising from the management of the research; and for harm to participants arising from the design of the research. If a patient is harmed due to negligence this would be covered by the NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them

21. PUBLICATION / DISSEMINATION POLICY

At the end of this study the data will be tabulated and analysed statistically. These data will then be written up within a final report that will be submitted by the Chief Investigator to the primary study sponsor (Diabetes UK) within six months of study completion. Within one year after the end of the study, the Chief Investigator will also submit a final report to REC outlining the results and any publications/abstracts. All investigators identified on this document will be acknowledged on the final report to Diabetes UK and REC. It will be made clear in the PIS that this final report will subsequently be made available to participants after the study and individual feedback will be available in the desired format e.g. verbally or in writing.

It is envisaged that results from this study will be published in relevant peer-reviewed scientific journals and will also be submitted for conference presentations. The TSC will oversee the development of manuscripts and abstracts; and the list / order of authors shall be decided at the point of submission. The guidelines outlined by the scientific journal in question shall be used to determine the criteria for authorship for each manuscript on a case-by-case basis. In all presentations and publications, all funders will be appropriately acknowledged (Diabetes UK, NIHR Nottingham and Leicester Biomedical Research Centres).

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