Effects of one-year once-weekly high-intensity interval training on body adiposity and liver fat in adults with central obesity: Study protocol for a randomized controlled trial

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ABSTRACT

Objective: This study aims to examine the effects of one-year, once-weekly high-intensity interval training (HIIT) on body adiposity and liver fat in adults with central obesity.
Methods: One-hundred and twenty adults aged 18—60 years with central obesity (body mass index ≥25, waist circumference ≥90 cm for men and ≥80 cm for women). This is an assessor-blinded randomized controlled trial. Participants will be randomly assigned to the HIIT group or the usual care control group. Each HIIT session will consist of 4 × 4-min bouts at 85%—95% maximal heart rate, interspersed with 3-min bouts at 50%—70% maximal heart rate. The HIIT group will complete one session per week for 12 months, whereas the usual care control group will receive health education. The primary outcomes of this study are total body adiposity and intrahepatic triglyceride content. The secondary outcomes include abdominal visceral adipose tissue, subcutaneous adipose tissue, body mass index, waist circumference, hip circumference, cardiorespiratory fitness, lean body mass, bone mineral density, blood pressure, fasting blood glucose, insulin, triglycerides, glycated hemoglobin, cholesterol profile, liver function enzymes, medications, adherence to exercise, adverse events, quality of life, and mental health. Outcome measure will be conducted at baseline, 12 months (post-intervention), and 24 months (one-year follow-up).
Impact of the project: This study will explore the benefits of long-term once-weekly HIIT with a follow-up period to assess its effectiveness, adherence, and sustainability. We expect this intervention will enhance the practical suitability of HIIT in inactive adults with central obesity, and provide insights on low-frequency HIIT as a novel exercise option for the management of patients with central obesity and liver fat.
Trial registration: ClinicalTrials.gov (NCT03912272) registered on 11 April 2019.

1. Introduction

Obesity has become a severe global pandemic, given its rapidly growing worldwide prevalence.[1] Obesity is associated with a significantly increased risk of all-cause mortality,[2] cardiovascular

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disease,[3] and mental health.[4–6] Individuals with obesity, particularly those with adipose tissue accumulation at the abdominal regional, are more susceptible to developing metabolic associated (non-alcoholic) fatty liver disease (MAFLD).[7] Paralleling the increasing worldwide prevalence of obesity, MAFLD is emerging as a global problem, with the prevalence estimated to be 24%. Up to 59% of people living with MAFLD will develop non-alcoholic steatohepatitis (NASH).[8] Furthermore, some patients with NASH will develop progressive and severe liver disease.[9]

The current guidelines for the management of patients with MAFLD recommend exercise as the first line treatment.[10] The American College of Sports Medicine (ACSM) recommends that adults should engage in moderate-intensity aerobic exercise for at least 30 min × 5 days weekly or vigorous-intensity aerobic exercise for at least 20 min × 3 days weekly.[11] However, the high weekly commitment of long-term exercise makes adherence challenging, especially for time-poor individuals. This is supported by a previous study that indicated a "lack of time" is the primary reason preventing people from engaging in regular physical activity.[12] For this reason, a sustainable and effective exercise strategy is needed. Furthermore, high-intensity interval training (HIIT) has gained in popularity due to its superior benefits on cardiorespiratory fitness[13] and lower time commitment compared to moderate-intensity continuous training (MICT). According to the ACSM's Worldwide Survey of Fitness Trends, HIIT was regarded as the top five fitness trend between 2014 and 2021.[14]

Taylor and colleagues demonstrated that three HIIT sessions weekly over 12 months induced a twofold reduction in liver fat compared with MICT,[15] although this was marginally non-significant (p = 0.077), likely due to the smaller sample size of the subanalysis (n = 42) in the original larger trial (n = 93).[16] In addition, Sabag and colleagues reported that performing low-volume HIIT (one 4-min session) 3 days weekly improved liver fat in inactive adults with obesity and type 2 diabetes.[17] Although the aforementioned studies showed that HIIT might be an effective approach for reducing liver fat, there have been few studies that have investigated the efficacy of low-frequency (e.g., once weekly) HIIT on liver fat reduction. A previous epidemiological study showed that physical activity patterns characterized by one or two sessions per week might be sufficient to reduce all-cause, cardiovascular disease, and cancer mortality risk.[18] Therefore, we speculate that a single session of high-intensity exercise weekly could provide adequate stimulus to build up long-lasting adaptations and health benefits. This premise is consistent with our previous results demonstrating that 8 weeks of once-weekly HIIT could induce improvements in total body adiposity.[19] However, the effectiveness and sustainability of long-term low-frequency HIIT on liver fat reduction is unknown.

2. Methods

2.1. Study hypothesis and purpose

This study aims to examine the effects of long-term once-weekly HIIT on total body adiposity and hepatic fat in adults with central obesity. We hypothesize that HIIT once weekly for 12 months will reduce total body fat and liver fat in inactive adults with central obesity compared with the usual care control group.

2.2. Study design and study setting

This study will be an assessor-blinded, two-arm, randomized controlled trial (ClinicalTrials.gov ID NCT03912272). Participants with central obesity will be randomized to either the HIIT group or usual care control group at a ratio of 1:1 (Fig. 1). The enrollment period began on 1 July 2019 and data collection is estimated to be completed by 30 July 2024. All outcome measures will be conducted in LKS Faculty of Medicine, The University of Hong Kong. All outcome assessments will be measured at baseline, 12 months (post-intervention), and 24 months (one-year follow-up). All assessments at baseline, post-intervention, and follow-up will involve three separate visits. The details of each visit are listed in Table 1. To promote participant retention and follow-up, a certificate of completion will be awarded to the participants who complete the follow-up assessments. For the participants who are absent from the intervention session, our research personnel will immediately contact them and reinforce the health benefits of the intervention program. Furthermore, the benefits of receiving the free-of-charge body comprehensive assessments (e.g., body scans and blood biomarkers analysis) serve as another form of incentive for participants to return for the post-intervention and follow-up assessments. The HIIT intervention will be conducted in an outdoor area or on treadmills in the laboratory. The health education classes for the usual care control group will be conducted in a small-group online format (i.e., four to ten participants/group). The participants will be instructed to behave as in the 12 months of the intervention during the 12-month follow-up period. The present protocol adheres to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).[20] The study protocol and consent forms have been approved by the Institutional Review Board (IRB) of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 18–098). Annual trial progress reports will be submitted to the IRB office for auditing the trial.

2.3. Participants

2.3.1. Eligibility

This study will recruit participants from the community and the university campus. We will promote the study through a large-scale poster and leaflet mailing campaign at local community centers, universities, and housing estates. The responding individuals will be contacted via email or telephone to confirm initial eligibility.

The inclusion and exclusion criteria are summarized in Table 2. Inclusion criteria include: 1) aged 18–60 years, 2) central obesity, defined as body mass index (BMI) ≥ 25 (obesity classification adopted by Department of Health, Hong Kong SAR Government) and waist circumference of ≥90 cm for men and ≥80 cm for women (central obesity according to the International Diabetes Federation's Chinese ethnic-specific criterion), 3) ethnic Chinese, 4) able to communicate in Cantonese, Mandarin, or English, and 5) willing to make lifestyle changes to treat their obesity (not including pharmacological or surgical treatments). Males and females across a broad age range will be recruited to enhance the generalizability of the study findings. Exclusion criteria include: 1) physically active (≥150 min moderate-intensity exercise or ≥ 75 min vigorous-intensity exercise weekly), 2) regular HIIT (≥ one session weekly) in the past 6 months, 3) medical history of chronic pulmonary or kidney disease, heart failure, cancer, or liver disease except MAFLD, 4) physical conditions that limit exercise participation (e.g., limb loss), 5) inability to ambulate at a high intensity due to chronic disease (e.g., chronic arthritis/osteoarthritis, neurological, musculoskeletal and autoimmune diseases), 6) daily smoking habit, 7) excess alcohol consumption (daily ≥30 g of alcohol for men and ≥20 g for women[21]) in the past 6 months, 8) surgery, therapy, or medication for obesity or weight loss in the past 6 months (e.g., gastric bypass, gastric band, sleeve gastrectomy, gastric reduction duodenal switch, or dietitian-prescribed dietary program), and 9) body size limitations, claustrophobia, or implants (e.g. metal
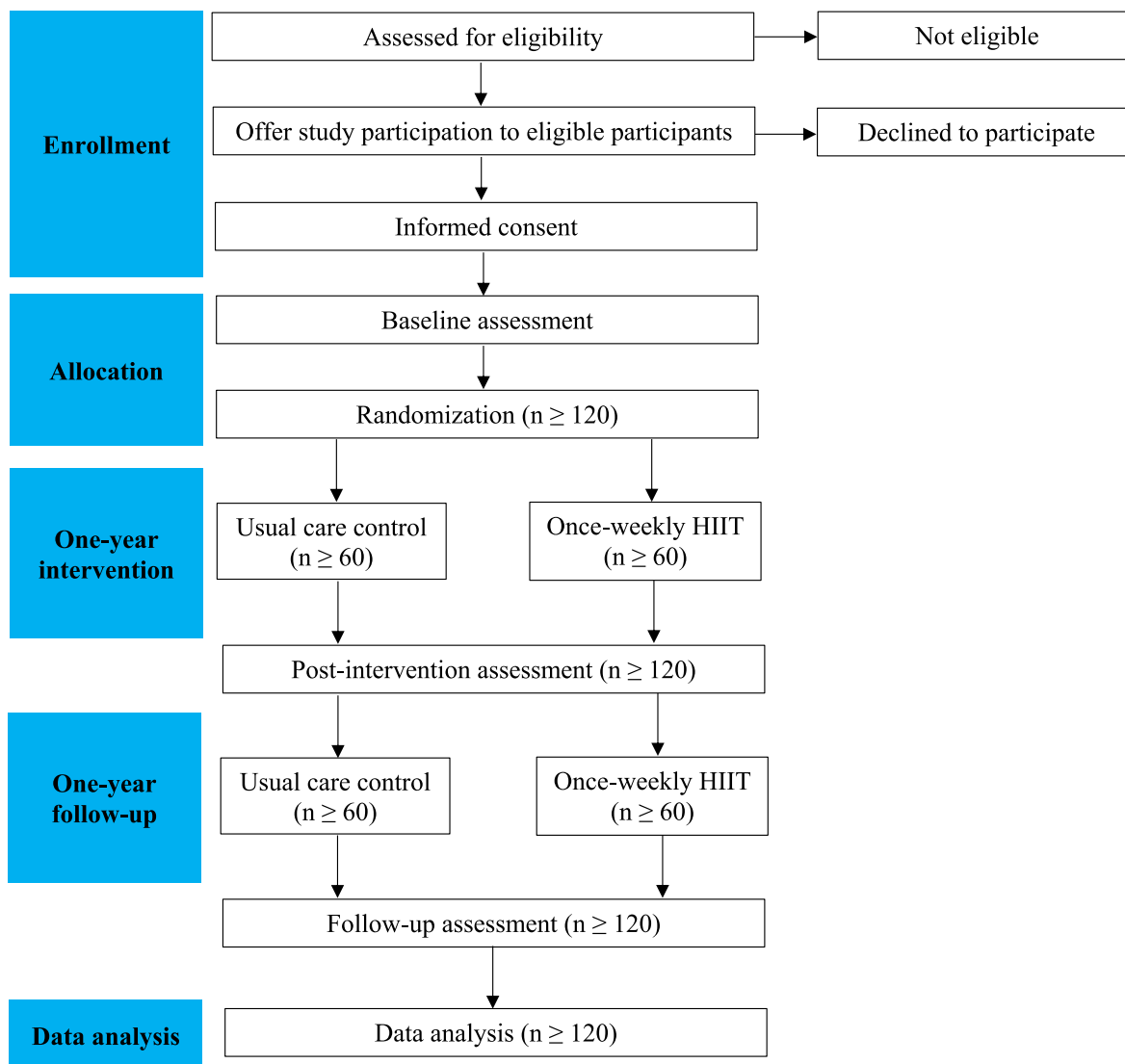
Fig. 1. Flow diagram for participant screening, randomization, and interventions.

implants or pace makers) that preclude magnetic resonance imaging (MRI) scanning. During the study period, participants identified to have major physical changes that considerably affect body composition and weight (e.g., receiving formal treatment for obesity or disease-induced weight loss) will be excluded from the study and handled by the intention to treat (ITT) analysis. Individuals who fulfill the abovementioned criteria will be invited for a preliminary visit to confirm their eligibility. Our research personnel will explain the potential risks to the participants and written informed consent will be obtained before the start of the study. Enrolled participants will receive written and verbal information on the study protocol.

2.3.2. Blinding
Because of nature of the exercise intervention, instructors and participants will not be blinded to the assigned groups. The outcome assessors at all assessment time points (i.e., baseline, post-intervention, and follow-up) will be blinded to the group allocation, and participants will be instructed not to disclose their group assignment during measurements/tests. Two full-time research

personnel will coordinate the overall project. All personnel involved in the data entry, outcome assessments, and outcome analyses will be blinded to the group allocation. The research personnel conducting the statistical analyses will also be blinded to the treatments, which will be identified by a number code.

2.3.3. Randomization: sequence generation and allocation concealment
Participants will be randomly assigned to the study groups after completion of the baseline assessments. Participants will be randomly assigned to either the usual care control group or HIIT intervention group on a 1:1 basis. A randomized allocation sequence will be generated on a computer. The computer-generated randomized allocation sequence will be kept by an independent researcher, who will not interact with the participants during recruitment to avoid potential allocation bias. Research personnel will contact the independent researcher to retrieve the next allocation sequence, which will be kept in sealed opaque envelopes.

Table 1
Schedule of enrollment, intervention, and assessments.

	Enrollment	Baseline		Randomization	Intervention	Post-intervention		Follow-up	
	−3 months	−1 to 2 months		- 1 to 2 weeks	0−12 months	12 months		24 months	
Enrollment									
Eligibility screen	✓								
Informed consent	✓								
Allocation				✓					
Interventions									
HIIT × 1/wk					✓				
Usual care control					✓				
Outcome assessments									
		Day 1 or 2	Day 3			Day 1 or 2	Day 3	Day 1 or 2	Day 3
MRS and MRI scan[a]		✓				✓		✓	
DXA and body mass[a]		✓				✓		✓	
VO$_{2peak}$		✓				✓		✓	
Blood pressure			✓				✓		✓
Blood collection[b]			✓				✓		✓
Waist and hip circumference[b]			✓				✓		✓
Medication usage		✓				✓		✓	
Adherence to exercise					✓				
Quality of life and mental health		✓				✓		✓	
Sleep quality and quantity		✓				✓		✓	
Physical activity and dietary intake			✓			✓		✓	
Adverse events					✓				

VO$_{2peak}$ will be measured at the end of the assessment visit (day 1 or 2). Prior to the testing, participants will be asked to avoid exercise, caffeine, alcohol, and tobacco for 24 h and food for 1 h.

[a] MRS, MRI, and DXA scans will be conducted on the same day (day 1 or 2). Prior to the scans, participants will be asked to fast for at least 4 h, but will be allowed to drink water and take their usual medications. Participants will be asked to evacuate their bowels and bladder before scanning.

[b] Participants will be asked to fast for at least 10 h.

Table 2
Inclusion and exclusion criteria for participation in the study.

Inclusion criteria	Exclusion criteria
1. Aged 18−60 years 2. Central obesity, defined as BMI ≥25 and waist circumference of ≥90/80 cm for men/women 3. Ethnic Chinese 4. Cantonese, Mandarin, or English speaking	1. Physically active (≥150 min moderate-intensity exercise weekly or ≥ 75 min vigorous-intensity exercise weekly) 2. Regular HIIT (≥ one session weekly) 3. Medical history: a. Chronic pulmonary disease 　　b. Kidney disease 　　c. Heart failure and coronary artery disease 　　d. Cancer 　　e. Liver disease except for MAFLD 4. Somatic conditions that limit exercise participation (e.g., limb loss) 5. Inability to ambulate at a high intensity due to chronic disease 6. Smoking habit 7. Excessive alcohol consumption (20 g daily/140 g weekly for men and 10 g daily/70 g weekly for women)[21] 8. Surgery, therapy, or medication for obesity or weight loss (e.g., gastric bypass, gastric band, sleeve gastrectomy, gastric reduction duodenal switch, or dietitian-prescribed dietary program) 9. Body size limitation, claustrophobia or metal implants, which precludes entry in the MRI machine

2.4. Interventions

Participants in the HIIT group will receive one 35-min HIIT session weekly for 12 months. The HIIT training will be supervised by a certified athletic/fitness trainer in an open field setting or on treadmills (TF30XR, Matrix) in the research center. A warm-up and cool-down period consisting of a 5-min walk or brisk walk at 70% intensity of the maximal heart rate (HRmax) will be included before and after each session, respectively. Each HIIT session will consist of four 4-min high-intensity bouts at 85%−95% HRmax interspersed with three 3-min active recovery bouts at 50%−70% HRmax. The treadmill speed will be manually increased during the last 10 s of the recovery bouts. Participants will be instructed to reach the target heart rate zone in the first minute of the high-intensity bouts. This 4 × 4-min HIIT protocol has been shown to be well-tolerated, safe, and effective in improving cardiorespiratory fitness among the population with lifestyle-induced cardiometabolic disease.[22] Heart rate will be continuously monitored

during the training using a Polar A300 with an OH1 heart rate monitor. The average heart rate during the high-intensity bouts and the lowest heart rate during the active recovery bouts will be recorded. The first six sessions will be used to familiarize the participants to the HIIT intervention (Table 3). During these sessions, participants will be asked to perform stretching exercises targeting major muscle groups and muscle strengthening and conditioning for lower-limb muscles to reduce the risk of injury during the subsequent training sessions. In the first six sessions, participants will also receive aerobic training progressing from moderate-to-high-intensity at gradually increasing exercise volume to allow them to adapt to the prescribed HIIT volume. If participants have difficulty in adapting or progressing to the designated HIIT intervention, they will be allowed more time to reach the prescribed volume. We will closely monitor the progress and health of any slow-progressing participants. Data from participant(s) with sustained difficulty in adapting to the prescribed HIIT (>6 weeks) will be recorded and analyzed separately in a per protocol analysis to

Table 3
Targeted exercise volume in the familiarization period of the HIIT group.

Sessions	Targeted exercise volume
1	Static stretching for major muscle groups
	<u>Lower limb muscle training</u>
	Squat (2 sets × 15 repetitions, 1-min rest between sets, with bodyweight)
	Calf raise (2 sets × 15 repetitions, 1-min rest between sets, with bodyweight)
	<u>Aerobic training</u>
	Moderate-intensity interval walking for 2 bouts × 4 min, interspersed with a 3-min rest
	Static stretching for major muscle groups
2	Static stretching for major muscle groups
	<u>Lower limb muscle training</u>
	Squat (2 sets × 15 repetitions, 1-min rest between sets, with bodyweight)
	Calf raise (2 sets × 15 repetitions, 1-min rest between sets, with bodyweight)
	Lunge (2 sets × 15 repetitions, 1-min rest between sets, with bodyweight)
	<u>Aerobic training</u>
	Moderate-intensity interval walking for 3 bouts × 4 min, interspersed with a 3-min rest
	Static stretching for major muscle groups
3	Static stretching for major muscle groups
	<u>Aerobic training</u>
	Moderate-intensity interval walking for 4 bouts × 4 min, interspersed with a 3-min rest
	Static stretching for major muscle groups
4	Static stretching for major muscle groups
	<u>Lower limb muscle training</u>
	Squat (2 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	Calf raise (2 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	Lunge (2 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	<u>Aerobic training</u>
	High-intensity training for 1 bout × 4 min
	Static stretching for major muscle groups
5	Static stretching for major muscle groups
	<u>Lower limb muscle training</u>
	Squat (3 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	Calf raise (3 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	Lunge (3 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	<u>Aerobic training</u>
	HIIT for 2 bouts × 4 min, interspersed with a 3-min rest
	Static stretching for major muscle groups
6	Static stretching for major muscle groups
	<u>Lower limb muscle training</u>
	Squat (3 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	Calf raise (3 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	Lunge (3 sets × 20 repetitions, 1-min rest between sets, with bodyweight)
	<u>Aerobic training</u>
	HIIT for 3 bouts × 4 min, interspersed with a 3-min rest
	Static stretching for major muscle groups

identify the reasons. After the first six sessions in the familiarization period, participants will perform the prescribed weekly HIIT session for the remainder of the intervention period (Fig. 2).

Participants in the usual care control group will receive 12 months of a health education program in small groups conducted online by research personnel. To match the duration of the HIIT
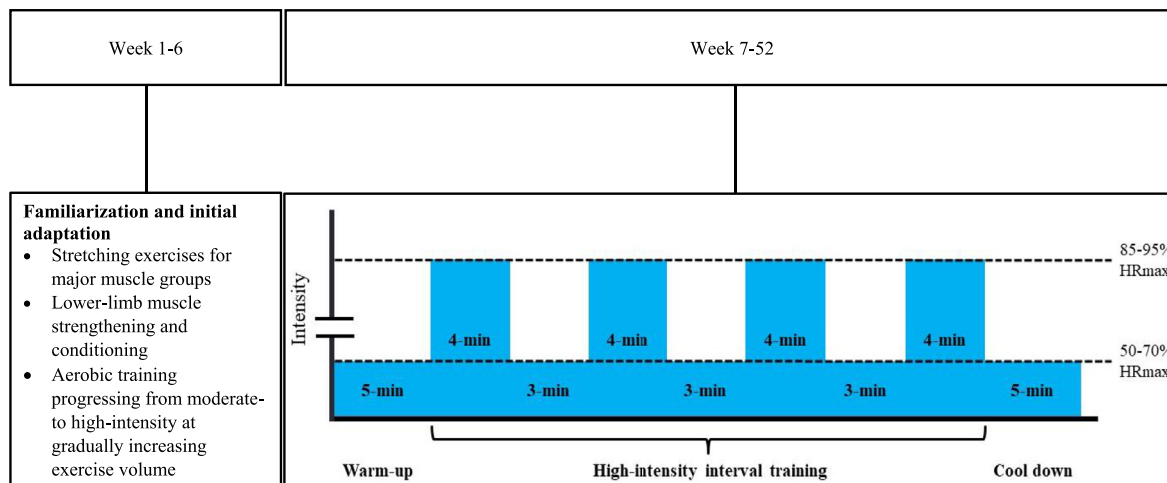

Fig. 2. Training protocol in the HIIT group.

interventions, we will deliver one 70-min health education class every 2 weeks. The topics will cover major health issues related to obesity (topics are listed in Table 4). The health education program is based on the information provided by the Department of Health of the Hong Kong SAR Government. Health information will also be provided to participants in the HIIT group in the form of leaflets/handouts throughout the intervention period.

To ensure adherence to the study, participants will be encouraged to attend ≥70% of classes, and a reminder will be sent via telephone to participants absent from a session. All participants will be instructed to maintain their normal daily physical activity and dietary habits throughout the study.

2.5. Primary outcome measures

2.5.1. Intrahepatic triglycerides

We will perform ^{1}H-MR spectroscopy (^{1}H-MRS) to measure intrahepatic triglyceride (IHTG) content. Before the scan, participants will be asked to fast for at least 4 h, but will be allowed to drink water and take their usual medications. Participants will also be asked to evacuate their bowels and bladder before scanning. Participants will be positioned in the 1.5-T scanner (SIGNA™ Explorer − 60 cm, General Electric Healthcare) by a trained MRI radiographer. An initial free-breathing and multiplanar localizer scan will be performed prior to the MRI scan. A $3 \times 3 \times 3$ cm^3 voxel will be manually placed at the right lobe of the liver (Couinaud lobe segment V-VIII), avoiding bile ducts, large vessels, focal lesions, and liver edges during the MRS scan.[23] After 5 min of the free-breathing scan, spectra will be obtained using the single-voxel point-resolved spectroscopy (PRESS) sequence. Spectral data will be exported as a raw dataset (p-file) for spectral analysis. The raw data will be analyzed using the open-source Spectroscopic Imaging, Visualization, and Computing (SIVIC) software package. Water and methylene peak amplitudes will be used to calculate the IHTG content using the following equation[24]:

$$IHTG \ content = \frac{methylene \ peak}{methylene \ peak + water \ peak} \times 100\%$$

An IHTG content of >5% will be used to indicate MAFLD.[25] The use of ^{1}H-MRS for the diagnosis of hepatic steatosis is highly reproducible and correlates to detection by liver biopsy (linear correlation coefficient of 0.644, p < 0.001[26]), and is considered the gold standard for non-invasive detection of low levels of liver fat.[27]

2.5.2. Total body adiposity

Total body fat mass in grams will be measured using a whole-body dual-energy X-ray absorptiometry (DXA). Before the scan, participants will be asked to fast for at least 4 h, but will be allowed to drink water and take their usual medications. Participants will also be asked to evacuate their bowels and bladder before scanning. Participants will be positioned in the DXA scanner (Horizon, Hologic Inc., Waltham, USA) by trained research personnel. The typical coefficient of variation of the DXA scanner for the detection of fat mass is 1.4% from duplicate analyses.[28]

2.6. Secondary outcome measures

2.6.1. Visceral adipose tissue and subcutaneous adipose tissue at the abdominal region

The amount of abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) will be assessed on a 1.5-T whole-body scanner (SIGNA™ Explorer − 60 cm, General Electric Healthcare) and analyzed by sliceOmatic 5.0 (Tomovision) medical imaging analysis software. A breath-hold localizer scan will be performed prior to the MRI scan. The T1-weighted in-phase and out-of-phase images will be obtained by fast spoiled gradient-echo sequences during suspended end expiration. The VAT and SAT areas between the thoracic diaphragm and the upper border of the first sacral vertebra will be marked on each transverse image, and abdominal VAT and SAT volume will be calculated using the morphology and region growing function. The MRI data processing

Table 4
Topic and content of the health education.

Topic	Subtopic
Obesity and metabolic health	Obesity
	Central obesity
	Hypertension
	Blood lipids
	Diabetes
	Metabolic syndrome
	Cardiovascular disease and cardiovascular fitness
	Liver health
Diet	Food pyramid
	Food energy
	Saturated and unsaturated fat, high and low cholesterol foods, and glycemic index
	Common misconception of diet
Musculoskeletal health	Osteoporosis
	Osteoarthritis and gout
	Musculoskeletal problems due to obesity
	Low back pain
	Knee joint pain
	Stretching
	Myofascial release
Physical activity	Current physical activity recommendations and sedentary lifestyle
	Walking posture
Mental health	Mental health (depression and anxiety)
	Mental health (mental well-being)
	Sleep and insomnia
	Management of stress
Overall course wrap up	

and analysis will be performed by two assessors blinded to the group allocation. One research personnel will analyze the whole dataset of MRI images, whereas the other research personnel will analyze a subset of the MRI images (i.e., 20% of the overall images) to ensure the reliability of the results. The intraclass correlation will be used to test the degree of agreement of the VAT and SAT data between the two independent research personnel.

2.6.2. Body anthropometry

Participant will fast for at least 10 h before body measurements on the same day as venous blood collection. The BMI will be determined by the equation: BMI (kg/m^2) = body mass/height.[2] A calibrated electronic digital weighing scale (UC321, A&D Medical) with a capacity of 0.05−150 kg and ±0.05 kg accuracy will be used to weigh the participants. A stadiometer (Seca 213, SECA) with a 205 cm limit will be used to measure body height. For waist circumference measurement, assessors will kneel to the right side of the participants and palpate the lowest rib and top of the iliac crest. A horizontal line will be drawn on the bare skin at midway between the lowest rib and the superior border of the iliac crest (practice from World Health Organization[29]) and at the superior border of the iliac crest (practice from United States National Institutes of Health).[30] For hip circumference measurement, an anatomical circumference measuring tape (seca201, SECA) to the nearest 0.1 cm will be applied on the drawn horizontal lines. All three measurements will be repeated three times and the average values will be recorded for the analysis. Measurement will be performed at the end of normal expiration.

2.6.3. Cardiorespiratory fitness test

A graded exercise test to voluntary exhaustion will be conducted on a calibrated motor-driven treadmill (T150 DE LC MED, COSMED). A gas analysis system (Quark CPET, COSMED) and heart rate monitor (OH1, polar) will be used to continuously measure and record VO_2, VCO_2, and heart rate, respectively. We will use the modified Bruce protocol in this test,[31] as we expect physically inactive participants with central obesity will have poor aerobic fitness. Before commencing the test, participants will spend 2 min in a standing rest state to measure resting pulmonary gas exchange. During the test, exercise intensity will be continuously increased every 3 min until voluntary exhaustion. The rate of perceived exertion (RPE) scale (ranging from 6 to 20) will be recorded in the standing rest test and at the end of every 3-min stage. The maximal RPE value is obtained when the participant reaches voluntary exhaustion. The maximal oxygen consumption (VO_{2peak}) will be determined from the highest rolling 30-s averages during the test.[32] The maximal attainable heart rate will be considered as the HRmax.

2.6.4. Blood pressure

Blood pressure will be measured in the morning on the same day as the venous blood collection. Participants will fast overnight for at least 10 h and refrain from consuming caffeine, alcohol, and blood pressure drugs before the assessments. After 10 min of seated rest, blood pressure will be measured in the left arm using an aneroid sphygmomanometer (KJ-106, Accumed). Systolic and diastolic blood pressure and mean arterial pressure will be obtained using an appropriately sized cuff placed over the brachial artery region with the arm supported at the heart level. Three measurements will be taken at 1-min intervals and the average value will be recorded for the analysis.

2.6.5. Blood biomarkers

Participants will fast overnight for at least 10 h, avoid strenuous exercise 48 h before venous blood sample collection. Participants

will sit in a quiet environment for 10 min before blood collection from an antecubital vein in the forearm by a certified phlebotomist. Fresh blood samples will be sent to an accredited medical laboratory to measure fasting glucose, insulin, triglycerides, glycated hemoglobin, cholesterol profile (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and total cholesterol), and liver function enzymes (alanine aminotransferase and aspartate aminotransferase). The remaining blood samples will be centrifuged and stored at −80 °C for subsequent analyses. In addition, fasting glucose and insulin values will be used to evaluate insulin resistance using the homeostasis model assessment 2 (HOMA2) calculator (https://www.dtu.ox.ac.uk/homacalculator/).

2.6.6. Appendicular lean body mass and bone mineral content

Appendicular lean body mass and bone mineral content will be determined using whole-body DXA. Given that acute food and fluid intake are likely to alter the total mass and lean mass, participants will be asked to fast for at least 4 h and evacuate their bowels and bladder before entering the scanner.[33] All metallic artifacts will be eliminated to ensure accurate measurement of bone mineral content. Participants will be positioned in the DXA scanner (Explorer S/N 91075, Hologic Inc., Waltham, USA) by trained research personnel. The typical coefficients of variation of the DXA scanner is 0.4% for lean mass and 1.0% for bone mass from duplicate analyses.

2.6.7. Medication usage

The frequency and dosage of medications for cardiometabolic conditions will be recorded at baseline, post-intervention, and follow-up assessments. The data will be presented as the total number of lowest recommended dose (LRD), as defined by Prescribers Digital Reference (https://www.pdr.net/).

2.6.8. Attendance and adherence

The session attendance and adherence to HIIT will be reported according to the recommendations of Taylor and colleagues.[34] The attendance data will be reported as the proportion of sessions attended. Adherence to the intensity (i.e., proportion of sessions meeting the prescribed intensity) and duration (i.e., number of high-intensity bouts completed) of the training will also be reported. The reasons for dropout will be ascertained and reported. Secondary analysis will be performed based on the attendance and adherence data to examine the dose-response relationship between HIIT and other outcome variables.

2.6.9. Quality of life and mental health

The validated Chinese version Standard 12-Item Short Form Survey (SF-12) will be used to measure health-related quality of life.[35] This 12-item questionnaire assesses physical functioning, emotional and mental health, bodily pain, general health, vitality, and social functioning. A higher overall score indicates a better quality of life. The Chinese-Cantonese version of the Hospital Anxiety and Depression Scale (HADS)[36] will be used to evaluate mood level. This instrument is designed to measure depression and anxiety in non-psychiatric settings. The 14-item scale has seven items in the depression subscale and seven in the anxiety subscale. The overall score in each subscale ranges from 0 to 21, with a higher score indicating higher psychological distress. The Chinese-Cantonese version of HADS has been validated in Hong Kong Chinses adults[36] with excellent reliability (Cronbach's alpha: overall scale = 0.86, depression subscale = 0.82, anxiety subscale = 0.77), and has close correlations with the Hamilton Rating of Depression (r = 0.67, p < 0.001) and Hamilton Rating of Anxiety (r = 0.63, p < 0.001). The Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) scale will be used as supplementary assessments to measure the

occurrence and severity of depression and anxiety, respectively. The PHQ-9 instrument is a 9-item questionnaire measuring a heterogeneous spectrum of symptoms of major depressive disorder derived from the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[37] The questionnaire asks participants how often they were bothered by each depressive symptom in the past 2 weeks: "not at all" (score 0), "several days" (score 1), "more than half the days" (score 2), and "nearly every day" (score 3). The severity of depressive symptoms is categorized according to the suggested overall cutoff scores: 0–4 indicates minimal depression, 5–9 indicates mild depression, 10–14 indicates moderate depression, 15–19 indicates moderately severe depression, and ≥20 indicates severe depression. The Chinese version of PHQ-9 has been validated in Hong Kong adults with excellent reliability (Cronbach's alpha: 0.82).[38] The GAD-7 instrument is a 7-item questionnaire modified from the diagnostic criteria of DSM-IV for screening generalized anxiety disorder and severity.[39] Each item describes one anxiety disorder symptom and assesses the frequency of the symptom over the past 2 weeks. The response options and scoring methods are similar to PHQ-9. The severity of GAD-7 is evaluated based on the suggested cutoff scores: 5–9 indicates mild anxiety, 10–14 indicates moderate anxiety, and ≥15 indicates severe anxiety. The Chinese version of GAD-7 has been validated in general hospital outpatients[40] with a Cronbach's alpha of 0.898.

2.6.10. Sleep quality and quantity

The Chinese version of the Pittsburgh Sleep Quality Index (PSQI) will be used to measure sleep quality and quantity. It consists of 19 items measuring seven sleep components: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component is scored from 0 to 3 ("0" representing no sleep problem to "3" indicating sleep impairment), with scores added together to yield the "global score" ranging from 0 to 21. The Chinese version of PSQI has been demonstrated to have a satisfactory test-retest reliability of 0.85 in insomniac and general populations.[41]

2.6.11. Monitoring of physical activity and dietary intake

Potential confounding factors in this project include changes in physical activity and diet. We will assess these factors as secondary outcome measures. All participants will be instructed to refrain from any additional exercise sessions during the 1-year intervention period, but will be allowed to maintain their usual daily physical activities and dietary habits. Exercise sessions in addition to the prescribed HIIT session will be recorded by the HIIT coaches. We will provide general dietary recommendations based on the accessible resources from the Department of Health of the Hong Kong SAR Government. We will use an actigraph, the International Physical Activity Questionnaires Short From (IPAQ-SF), and a weighed food diary to monitor and record physical activity and diet. These instruments have been adopted in our previous studies.[42,43] Actigraph activity monitor (wGT3X-BT, Actigraph, USA) is a three-axis accelerometer that objectively records daily physical movement/activity. Participants will be instructed to wear the actigraph device on the non-dominant wrist for 24 h over 7 consecutive days during each assessment period. The time spent engaged in very vigorous, vigorous, moderate, and light-intensity activities will be obtained by analyzing the motion data recorded on the actigraph using ActiLifeV6.11.7 provided by the manufacturer. The 3-day weighed food diary will be used to determine the daily caloric intake and the relative proportions of macronutrients (carbohydrates, fats, and proteins). Participants will be given written and verbal instructions on how to use portable electronic weighing scales to weigh all foods and fluids consumed over 3 consecutive days (including two weekdays and one weekend) during each assessment period. Daily diet will be analyzed using dietary analysis software (Food Processor, ESHA). If the food items are not listed in the dietary analysis software, we will confirm the caloric and macronutrient contents with a local dietitian.

2.6.12. Adverse events

Adverse events will be recorded as a secondary outcome. For the HIIT group, coaches will question participants after each HIIT class to ascertain any adverse events (such as fatigue, dizziness, headaches, knee strain injury, and joint/muscle pain, etc.). Any training-related adverse events will be immediately followed up to see whether they are preventable, such as incorrect running technique or inappropriate running shoes. Research personnel will contact participants in the HIIT and control groups monthly to ask if they have experienced any health problem, such as injuries not related to HIIT. Research personnel will obtain all the necessary information to complete the adverse event documentation. In the case of a sustained or severe adverse event, the incident will be reported to the medical doctor attached to this project, specializing in sports medicine, for further medical advice. In accordance with the principles of Good Clinical Practice and CONSORT reporting of harms,[44,45] the reason, nature and severity of the adverse event, and the potential association with the intervention will be ascertained by our research personnel and ratified by the medical doctor. Participants with sustained adverse events or serious adverse events affecting his/her daily life will be advised to withdraw from the study. Participants withdrawn from the intervention due to a serious adverse event will be included in the ITT analyses.

2.7. Statistical power and sample size considerations

We will recruit a minimum of 120 participants according to the sample size estimate based on an $\alpha = 0.05$ and statistical power of 90%. This sample size will be adequate for obtaining a significant total body fat mass reduction according to the calculated Cohen's d of 0.34 for total body fat mass based on our preliminary data on the standardized mean difference (SMD) post-intervention relative to baseline in the once-weekly HIIT arm compared to the control arm.[46,47] Our calculated effect size is slightly smaller than that reported by Wewege et al. (fat mass SMD of 0.44 after HIIT)[48] and Batacan et al. (percent body fat SMD of 0.40 after HIIT),[49] which is probably attributed to our lower exercise frequency. Our estimated sample size takes into account an attrition rate of 20%. A previous study reported dropout rates of 13%–19% in 5- to 16-week HIIT programs.[48] Notably, our proposed sample size retains a power of 75% to detect a reduction of 1.4 kg total body fat mass, assuming a standard deviation of 4 kg based on the observations reported by Wewege et al.,[48] at a very high attrition rate of 40%. A reduction of 1.4 kg equates to an 8% reduction in total body fat mass in our examined participants, which exceeds the suggested clinically meaningful value of 5%.[50] Notably, our proposed sample size has adequate statistical power to also detect a significant reduction of 1.5% in intrahepatic triglycerides measured by ^{1}H-MRS (the other primary outcome measure in this study), as our adopted effect size is comparable to the observed effect sizes (0.3–0.4) after 12 weeks of HIIT in MAFLD patients.[51,52] Given the >5% cutoff threshold of intrahepatic triglycerides for defining MAFLD, a 1.5% reduction equates to a 30% change due to HIIT in an individual with 5% intrahepatic triglycerides. As data on fat reduction examined by DXA after long-term low-frequency HIIT is lacking, our sample size estimation is based on our preliminary total body fat mass data measured by bio-impedance analysis (BIA). Given that BIA has been shown to underestimate the magnitude of fat mass change induced by lifestyle interventions compared to DXA,[28] we expect the actual

statistical power of using DXA in this project would be higher. This further ensures the adequacy of our proposed sample size for achieving robust statistical power.

2.8. Analytical approach and reporting

Generalized estimating equations (GEE) will be used to assess the treatment effects with baseline measurements used as covariates to control for potential confounding factors. Pairwise comparison will be performed with linear contrasts to estimate differences in the treatment effects between groups at 12 and 24 months. Secondary analysis will be performed after adjusting for factors such as gender, age, presence of MAFLD, hypertension, adherence, etc. For handling dropouts, we will invite all participants to post-intervention and follow-up assessments even if they have withdrawn from the study.[53] We will use ITT to allow all randomized participants to be included in the analysis. Missing observations will not be replaced, as GEE can accommodate missing values using a natural missingness mechanism.[54] The statistical analyses will be performed using commercially available statistical software. The significance level will be set at P < 0.05 and 95% confidence intervals will accompany all estimates. Data will be reported according to the guidelines of consolidated standards of reporting trials (CONSORT).[55]

2.9. Data management

2.9.1. Data entry
Data will be double entered to ensure data quality and accuracy. Data entry will be separately performed by two independent researchers in a blinded manner. The personal information and identity of participants will be strictly protected. Each participant will be assigned a unique master study number, which corresponds to the anonymously collected data.

2.9.2. Data monitoring
The data management team will continuously monitor the collected data biweekly and report the study's progress to the investigators. The results will be fully disseminated in peer-reviewed scientific journals and conferences. We expect any possible adverse events related to exercise interventions in this study will be minor. However, if any unexpected severe adverse events occur multiple times during the trial, our investigators will discuss the situation with the medical doctor to consider termination of the trial.

2.9.3. Security and back-up of data
All the study data will be stored separately from the participants' personal information. Participant identity will be stored on encrypted hard disks kept in a locked cabinet. Only the research personnel of this project will be able to access the locked cabinet and the encrypted hard disks.

3. Discussion

In the present study, we will investigate the effects of long-term low-frequency HIIT in adults with central obesity. We expect our data will support the use of once-weekly HIIT to reduce liver fat and total body adiposity. Furthermore, our findings are expected to enhance the practical suitability of HIIT as a regular exercise modality in inactive adults with central obesity.

3.1. Effectiveness of low-frequency HIIT for liver fat and total body fat mass

In this study, we hypothesize that low-frequency HIIT will induce long-term improvements on body fat. Previously, our preliminary data demonstrated that low-frequency HIIT for 8 weeks induced improvements in body fat mass and waist circumference in the absence of changes to body weight in overweight or obese males.[19] The present study is expected to extend our understanding of long-term low-frequency HIIT for the management of patients with obesity. Although this project targets adults with central obesity, we expect a large portion of our participants will have MAFLD, as it is strongly associated with central obesity and general obesity.[7] A 10-year historical cohort study evaluating the impact of different lifestyle factors and exercise at least once weekly in MAFLD patients showed a reduction in MAFLD in Asian men.[56] This encouraging evidence suggests that HIIT once weekly shows promise as an effective therapeutic exercise modality for managing MAFLD. We anticipate our participants with mild steatosis (IHTG: 5%—33%)[57] will show remission from MAFLD after the 1-year low-frequency HIIT intervention.

3.2. Adherence and sustainability of low-frequency HIIT

According to the ACSM guidelines for exercise prescription, vigorous aerobic exercise should be performed at least 3 days per week.[11] These guidelines are consistent with a systematic review and meta-analysis of HIIT for patients with lifestyle-induced cardiometabolic disease that showed a 4×4-min protocol (i.e., work = 4 intervals $\times$ 4 min at 85%—95% HRmax; rest = 3 intervals $\times$ 3 min at 70% HRmax) for at least 3 days weekly resulted in an almost double improvement of VO_{2max} and was more enjoyable than moderate-intensity continuous training.[13] Practically speaking, frequent exercise may compromise adherence to regular exercise due to the considerable time commitment, as "lack of time" was the most commonly cited reason for people not participating in exercise.[12] Our preliminary study observed the adherence to the exercise program was relatively higher in the 8-week once-weekly HIIT group (93.1%, 7.4 out of 8 sessions) compared to the twice weekly (86.1%, 14 out of 16 sessions) and thrice weekly (89.2%, 21.3 out of 24 sessions) groups.[19] Long-term adherence to the exercise program is important for sustaining fat loss and preventing bodyweight regain after the intervention.[58] A long-term trial is needed to confirm the adherence and sustainability of low-frequency HIIT in inactive populations with central obesity. Meanwhile, maintenance of the low-attrition and adherence in the usual care control group is one of the potential challenges in the present study.

Furthermore, it is worth noting that the current trial will be conducted during the COVID-19 pandemic. Pandemic-related social and demographic factors such as stay-at-home and work-from-home orders or changes in income and occupation could affect habitual physical activities.[59] As changes in physical activity and diet are potential confounding factors in this project, if we observe more than 20% of participants (i.e., the assumed attrition rate in this study) change their habitual lifestyles due to pandemic-related reasons, we will re-adjust the sample size to maintain the planned statistical power in the present study. In addition, mounting evidence revealed that obesity is highly associated with different psychiatric outcomes, such as depression,[4] anxiety,[5] and insomnia.[6] We anticipated that our participants with central obesity might experience greater psychological distress, given that the mental health burden was drastically increased in Hong Kong during the COVID-19 pandemic.[60] Therefore, psychological assessments (i.e., depression, anxiety, and sleep) will be included in the secondary outcomes to investigate the effect of low-frequency HIIT on psychological conditions in our participants with central obesity.

In conclusion, this study will provide evidence on the effects of the long-term low-frequency HIIT and the follow-up will assess its

effectiveness, safety, adherence, and sustainability. We expect this intervention will enhance the practical suitability of low-frequency HIIT in inactive adults with central obesity and represent a new exercise modality for the management of central obesity and liver fat.

Trial status

The study was prospectively registered at ClinicalTrials.gov (NCT03912272) on 11 April 2019. The first participant was recruited on 16 July 2019 and the trial is estimated to be completed by 30 July 2024.

Author statement

Edwin Chin: Data curation; Formal analysis; Writing - original draft; Writing - review & editing.

Chit-Kay Leung: Data curation; Writing - review & editing.

Danny Yu: Data curation; Writing - review & editing.

Angus Yu: Data curation; Formal analysis; Writing - review & editing.

Joshua Bernal: Data curation; Writing - review & editing.

Christopher Lai: Methodology; Software; Writing - review & editing.

Derwin Chan: Funding acquisition; Methodology; Investigation; Writing - review & editing.

Heidi Ngai: Funding acquisition; Methodology; Investigation; Writing - review & editing.

Patrick Yung: Funding acquisition; Methodology; Investigation; Writing - review & editing.

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Daniel Fong: Funding acquisition; Methodology; Investigation; Formal analysis; Writing - review & editing.

Shelley Keating: Funding acquisition; Methodology; Investigation; Software; Writing - review & editing.

Jeff Coombes: Funding acquisition; Methodology; Investigation; Writing - review & editing.

Parco Siu: Conceptualization; Funding acquisition; Methodology; Investigation; Project administration; Supervision; Formal analysis; Writing - original draft; Writing - review & editing.

Ethics approval and consent to participate

This study has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 18−098). Written and verbal informed consent will be obtained from all participants before enrollment in the study.

Declaration of competing interest

The authors declare no competing interests.

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