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Effects of volume-matched once-weekly and thrice-weekly high-intensity interval training (HIIT) on body adiposity in adults with central obesity: Study protocol for a randomized controlled trial

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ABSTRACT

Objective: This study aims to examine the comparative effects of 75 min of volume-matched once-weekly and thrice-weekly high-intensity interval training (HIIT) on body adiposity in adults with central obesity.
Methods: This assessor-blinded, three-arm, randomized controlled trial will recruit 315 physically inactive adults with central obesity (aged ≥18 years, body mass index ≥23, waist circumference ≥90 cm for men and ≥80 cm for women). Participants will be randomly allocated to the once-weekly HIIT, thrice-weekly HIIT or usual care control group. Participants in the HIIT groups will receive weekly exercise training sessions for 16 weeks, prescribed either once or three times weekly. Each HIIT session will consist of a supervised program of four 4-min high-intensity intervals at 85%–95% peak heart rate (HR_{peak}) interspersed with 3-min active recovery intervals at 50%–70% HR_{peak}. Participants in the once-weekly HIIT group will perform the 25-min HIIT bout three times with a break between each 25-min HIIT bout. The usual care control group will receive bi-weekly health education classes. The outcome assessments will be conducted at baseline, 16 weeks (post-intervention) and 32 weeks (follow-up). The primary outcome will be total body adiposity assessed by dual-energy X-ray absorptiometry (DXA). The secondary outcome measures will include markers of cardiovascular and metabolic health (body composition, cardiorespiratory fitness, blood pressure, and blood lipids), mental health, cognitive performance, health-related quality of life, sleep quality, habitual physical activity, diet, medication, adverse events and adherence to the intervention.
Impact of the project: The findings from this study are expected to consolidate the therapeutic efficacy of HIIT for the management of central obesity and inform the comparative compliance, feasibility and suitability of once-weekly and thrice-weekly HIIT as exercise strategies to manage obesity. In particular, the present study is expected to provide a novel perspective on the utility of low-frequency HIIT (i.e., once-weekly) as an effective and sustainable exercise strategy to tackle the obesity pandemic. The anticipated findings will hold substantial translational value by informing public health policies and enhancing exercise compliance in the physically inactive obese population.
Trial registration: ClinicalTrials.gov (NCT04887454).

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1. Introduction

Obesity is a global public health priority with alarming prevalence and is one of the fastest growing diseases of the 21st century.[1] In 2019, excess body weight was responsible for over 160 million years of healthy life lost (disability-adjusted life years, DALYs) and over 5 million deaths.[2] Global obesity prevalence has tripled since 1975, rising from 4.6% to 14% between 1980 to 2019.[1] It is projected that by 2025, over a billion people will be obese globally.[3] Obesity is a chronic and multifactorial disease that substantially increases the risk of numerous non-communicable diseases (NCDs)[4] including cardiovascular diseases (CVD), cancers and mental health disorders, and even has a profound detrimental impact on the prognosis and mortality risk of COVID-19 infection.[4–13]

Notably, central obesity, characterized by the accumulation of adipose tissue at the abdominal region, has been shown to better inform the risk of excess adipose tissue on the development and prognosis of pathological conditions.[14–16] Excess abdominal adipose tissue is linked to insulin resistance, the precursor of type 2 diabetes mellitus, and more importantly, it creates an atherogenic pro-inflammatory environment via elevated levels of inflammatory markers such as *C*-reactive protein and interleukin 6.[17] This atherogenic environment contributes to the pathogenesis of atherosclerosis and greatly increases the risk of CVD.[18] Unsurprisingly, it has been well documented in the literature that abdominal adiposity is strongly and positively associated with mortality.[19,20] This observation is well illustrated by Zhang and colleagues,[21] who investigated the association between abdominal adiposity and mortality in the 16-year follow-up of over 44,000 women from the Nurses' Health Study cohort. In this study, the authors observed that women in the highest waist circumference quintile had a relative risk of 1.79, 1.99 and 1.63 for all-cause mortality, CVD mortality and cancer mortality, respectively. The increased risk of developing health complications associated with abdominal obesity highlights the specific concern for the accumulation of adipose tissue at the abdominal region, and underscores the need for an effective and adherable treatment strategy.

Integral to the management of obesity is lifestyle modification. In particular, the beneficial effects of physical activity on weight control and central adiposity are well established, and is considered as a cornerstone of obesity management.[22] Moreover, the robust improvements induced by exercise on cardiovascular health and cardiorespiratory fitness coupled with the substantial reductions in cardiovascular and all-cause mortality further accentuate the importance of exercise in managing obesity.[23] Notably, these improvements are not expected to be achievable via medications or dietary modifications alone.[24] Indeed, obesity management guidelines worldwide[25–28] unequivocally advocate for the use of physical activity and exercise as an essential component of a weight reduction program. In accordance with the physical activity recommendations of the World Health Organization (WHO),[29] obesity management guidelines from the American Heart Association (AHA),[25] American College of Cardiology (ACC),[25] The Obesity Society (TOS),[25] European Obesity Management Task Force[26] and others[27,28] all advocate for at least 150 min of moderate-intensity aerobic exercise a week, with further increases to 200–300 min a week being recommended to maintain weight loss or to minimize weight regain in the long term. Despite regular physical activity being a key component in the management of obesity and its resulting NCDs,[22] participation remains insufficient. Recent global estimates reported that in 2022, 27.5% of the global adult population were physically inactive and did not meet the recommended level of physical activity to protect their health.[30] Among the obese population, the phenomenon of physical inactivity is magnified.[31] Adults with obesity or central obesity were reported to be less likely to meet physical activity guidelines when compared to their normal weight or waist circumference counterparts.[31] This low compliance to physical activity and exercise training can be explained by 'lack of time', which is one of the most commonly cited barriers to engaging in regular exercise.[32,33] This suggests that time-efficient exercise strategies could help improve adherence to exercise regimens.

Emerging evidence suggests that high-intensity interval training (HIIT) represents an effective, enjoyable and feasible exercise strategy for the general population including those with obesity.[34–36] Specifically, there is evidence in the literature to substantiate the application of HIIT for reducing total body adiposity and visceral adiposity.[35] A meta-analysis by Wewege and colleagues reported that HIIT induced a within-group reduction of 1.7 kg in total body fat mass in overweight and obese adults and was comparable to moderate-intensity continuous training (MICT) despite having a lower time commitment.[35] These findings were corroborated in subsequent meta-analyses, which reported that HIIT induced a within-group reduction of 1.38 kg[37] and 2 kg[38] in total body fat mass. Although literature has validated the effectiveness of HIIT on improving adiposity, more evidence is needed to assess the optimal HIIT frequency to reduce adiposity while minimizing exercise time. Indeed, only a few studies have investigated the efficacy of low-frequency HIIT (i.e., once-weekly) on reducing adiposity.[35,38] In the meta-analysis by Wewege and colleagues, 12 out of the 13 included studies had a HIIT exercise frequency of three or more times a week.[35] Similarly, among the 39 studies included in the meta-analysis by Maillard and colleagues, all except two studies had a HIIT exercise frequency of three or more times a week.[38] As low-frequency HIIT further attenuates time commitment and increases feasibility as a result of reduced commute time and greater flexibility on the choice of day to exercise, overweight and obese individuals may perceive low-frequency HIIT as a more attractive and adherable exercise strategy. The significance of investigating the role of low-frequency HIIT in the management of obesity and pathological conditions is further highlighted by the growing interest in the 'weekend warrior' exercise pattern.[39] Individuals who concentrate their physical activity on 1 or 2 days of the week are termed 'weekend warriors' and have been shown to experience lower all-cause, CVD and cancer mortality than inactive individuals.[39,40] Intriguingly, the health benefits of HIIT performed in a 'weekend warrior' exercise pattern have not been elucidated. Consequently, it remains to be confirmed whether HIIT performed in a once-weekly exercise pattern against a more commonly adopted thrice-weekly exercise pattern, with matched exercise volumes benchmarked against the WHO vigorous-intensity physical activity recommendation, can elicit comparable improvements in physical and mental health and augment the management of pathological conditions. Accordingly, it is critical to investigate the efficacy of once-weekly HIIT on reducing total body adiposity in overweight and obese individuals, and its comparative effectiveness against the conventional thrice-weekly HIIT exercise frequency.

2. Methods

2.1. Study hypothesis and purpose

This study aims to examine the comparative effects of volume-matched once-weekly HIIT and thrice-weekly HIIT on total body adiposity in overweight adults with central obesity. We hypothesize that 16 weeks of once-weekly HIIT and thrice-weekly HIIT will reduce total body adiposity similarly in inactive, overweight adults with central obesity when compared with the usual care control group.

2.2. Study design and study setting

This study will be an assessor-blinded, three-arm, randomized controlled trial (ClinicalTrials.gov ID: NCT04887454). Eligible participants will be randomized to the thrice-weekly HIIT, once-weekly HIIT, or usual care control groups at a ratio of 1:1:1 (Fig. 1). The enrollment period began on September 1, 2021 and data collection is estimated to be completed by July 30, 2024. All outcome measures will be conducted at the Li Ka Shing Faculty of Medicine, The University of Hong Kong.

Outcome assessments will be measured at baseline, 16 weeks (post-intervention) and 32 weeks (follow-up). All assessments will be completed during two visits. The details of each visit are listed in Table 1. The HIIT intervention will be group-based and conducted on treadmills in the laboratory under supervision. The health education classes for the usual care control group will be conducted as group-based, face-to-face classes. The class sizes will be adjusted as needed to comply with any public health infection control measures. The present protocol adheres to the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and the Consensus on Exercise Reporting Template (CERT). 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 20–066). 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. The study will be promoted through a large-scale poster and leaflet mailing campaign at local community centers, universities, and housing estates. Responding individuals will be contacted via email or telephone and invited to attend the preliminary screening to confirm eligibility.

The inclusion and exclusion criteria are summarized in Table 2. Inclusion criteria include: (1) aged 18 years or above, (2) ethnic Chinese, (3) overweight (body mass index [BMI] ≥23 according to the classification adopted by the Department of Health of the Hong Kong SAR Government), and (4) centrally obese (waist circumference of ≥90 cm for men and ≥80 cm for women according to the classification adopted by the International Diabetes Federation [IDF] for Chinese ethnic group).[41] Males and females will be recruited to enhance the generalizability of the study findings.

Exclusion criteria include: (1) medical and somatic conditions that prevent brisk walking, (2) chronic diseases affecting mobility and motor function (e.g., neurological disease, musculoskeletal disorder, spinal cord injury, autoimmune diseases, arthritis, or Parkinson's disease), (3) chronic diseases affecting cardiorespiratory and metabolic health (e.g., cancers, cardio-/cerebrovascular diseases, heart disease, diabetes mellitus, pneumonia, chronic pulmonary diseases, nephritis, or nephrosis), (4) signs of cardiac arrhythmia indicated by aberrant electrocardiogram during graded VO_{2max} test, (5) regular moderate-to-vigorous intensity

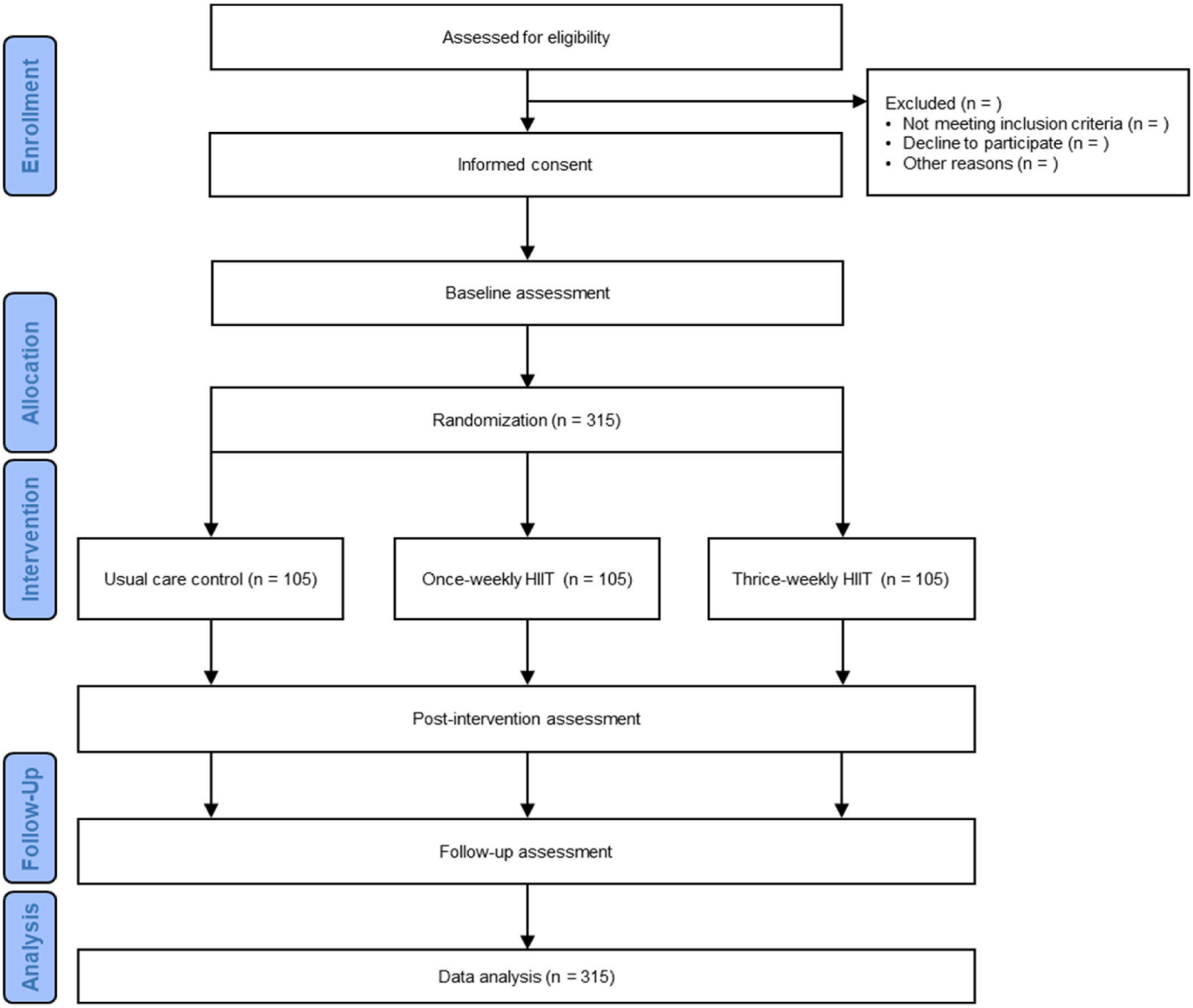

Fig. 1. Flow diagram for participant screening, randomization, assessments and interventions.

Table 1
Schedule of enrollment, assessments, and interventions.

	Enrollment	Baseline		Randomization	Intervention	Post-Intervention		Follow-Up	
	−2 months	−1 month		−1 week	0–16 weeks	4 months		8 months	
Enrollment									
Screening	✓								
Informed Consent	✓								
Allocation				✓					
Interventions									
HIIT *x*1/wk					✓				
HIIT *x*3/wk					✓				
Usual Care Control					✓				
Outcome Assessments									
		Day 1	Day 2			Day 1	Day 2	Day 1	Day 2
DXA and Body Mass[a]		✓				✓		✓	
MRI[a]		✓				✓		✓	
Waist and Hip Circumference[a]			✓				✓		✓
Blood Pressure[b]			✓				✓		✓
Venous Blood Collection[b]			✓				✓		✓
Medication Usage			✓				✓		✓
VO_{2max}		✓				✓		✓	
Quality of Life and Mental Health			✓				✓		✓
Sleep Quality			✓				✓		✓
Cognitive Assessment		✓				✓		✓	
Physical Activity and Dietary Intake		✓				✓		✓	
Adherence					✓				
Adverse Events					✓				

VO_{2max} will be measured at the end of the assessment visit. Prior to the testing, participants will be asked to avoid exercise, caffeine, and alcohol for 24 h.
[a] Participants will be asked to fast for at least 4 h, but will be allowed to drink water and take their usual medication. Participants will be asked to empty their bladder before scanning.
[b] Participants will be asked to fast for at least 8 h, but will be allowed to drink water.

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

Inclusion Criteria	Exclusion Criteria
1 Aged 18 years or above	1 Medical and somatic conditions that prevent brisk walking
2 Ethnic Chinese	2 Chronic diseases affecting mobility and motor function (e.g., neurological disease, musculoskeletal disorder, spinal cord injury, autoimmune disease, arthritis, or Parkinson's Disease)
3 Overweight, defined as BMI ≥23	3 Chronic diseases affecting cardiorespiratory and metabolic health (e.g., cancers, cardio-/cerebrovascular diseases, heart disease, diabetes mellitus, pneumonia, chronic pulmonary diseases, nephritis, or nephrosis)
4 Centrally obese, defined as waist circumference ≥80/90 cm for women/men	4 Signs of cardiac arrhythmia indicated by aberrant electrocardiography during graded VO_{2max} test
	5 Regular moderate-to-vigorous intensity exercise (≥150 min weekly)
	6 Daily smoking habit
	7 Excess alcohol consumption (daily ≥10 g for women and ≥20 g for men)
	8 Claustrophobia, body size limitation, metal implants, or pace makers that would preclude entry in the MRI machine
	9 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)

exercise (≥150 min weekly) in the past 3 months, (6) daily smoking habit, (7) excess alcohol consumption (daily ≥20 g for men and ≥10 g for women) in the past 3 months,[42] (8) claustrophobia or other conditions (e.g., body size limitations, metal implants, or pace makers) that preclude magnetic resonance imaging (MRI), and (9) 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) in the past 6 months. Research personnel will provide the participants with written and verbal information about the trial and the potential risks and benefits of the study participation. Written informed consent will be obtained before the commencement of the study.

2.3.2. *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 thrice-weekly HIIT, once-weekly HIIT, or usual care control groups at a ratio of 1:1:1. The randomized allocation sequence will be generated using a web-based randomization sequence generator. The randomized allocation sequence will be kept by an independent researcher, who will not interact with the participants 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.

2.3.3. *Blinding*

Due to the nature of exercise interventions, certified trainers and participants cannot be blinded to the assigned groups. Outcome assessors will be blinded to the group allocations at all assessment time points (baseline, post-intervention, and follow-up). Participants will be instructed not to disclose their group assignment during outcome measurements. Research personnel conducting the statistical and data analyses will also be blinded to the group allocations.

2.4. *Interventions*

Participants in the HIIT groups will receive weekly exercise training sessions for 16 weeks, prescribed once- or thrice-weekly. The aerobic training will be conducted on motorized treadmills (TF30XR, Matrix) and will be supervised by certified trainers. A warm-up and cool-down period will be included before and after each HIIT session, which will consist of a 5 to 10-min walk at an intensity of 50%–60% of the peak

heart rate (HR_{peak}). Each HIIT session will consist of four 4-min high-intensity intervals at 85%–95% HR_{peak} interspersed with 3-min active recovery intervals at 50%–70% HR_{peak}.[43] Participants in the once-weekly HIIT group will repeat the 25-min HIIT bout three times with a 15–30 min break between each 25-min HIIT bout.[44] Participants will be instructed to reach the target intensity within the initial 2-min and maintain the target intensity for the final 2-min of each high-intensity interval. The treadmill speed and incline will be determined individually to allow participants to exercise appropriately at the target intensity. Heart rate will be continuously monitored during the training using a Polar A300 monitor with an OH1 heart rate sensor.

Following the recommendations of Taylor and colleagues,[45] trainers will measure and record the average heart rate during the final 2-min of each high-intensity interval and at the final 30 s of each active recovery interval. The rating of perceived exertion (RPE) based on the 6–20 Borg scale for each 4-min high-intensity interval and at the final 30 s of each active recovery interval will be recorded by the trainers. The treadmill speed and incline will be recorded by the trainer at the final 1-min of each high-intensity interval. The first 4 weeks will be the familiarization period to allow participants to familiarize and adapt to the HIIT intervention (Table 3). Participants will be instructed to achieve at least 50% of the prescribed weekly HIIT volume by week 2, with the aim to gradually progress over the next 2 weeks to reach the prescribed weekly volume at week 4. To facilitate adaptation to the prescribed HIIT volume and to reduce the risk of injury in subsequent training sessions, participants will also be instructed to perform stretching and lower-body muscle-strengthening exercises.[46] After the 4-week familiarization period, participants will then perform the prescribed weekly HIIT sessions for the remaining 12 weeks of the intervention period (Fig. 2). Participants with difficulty adapting to the prescribed HIIT intervention will be allowed more time to reach the prescribed training volume, and their health and progress will be closely monitored for safety.

Participants in the usual care control group will receive a health education program for 16 weeks. Research personnel will deliver one 2.5-h health education class every 2 weeks to match the duration of the HIIT sessions. The content of the health education program will be based on the information provided by the Department of Health of the Hong Kong SAR Government and will include topics covering major health issues related to obesity (listed in Table 4). Health information provided to the usual care control group will also be made available to the participants in the HIIT groups in the form of leaflets/handouts.

Table 3
Targeted exercise volume in the familiarization period for the HIIT groups.

Weeks	Sessions	Targeted Exercise Volume
Week 1	1 (HIIT *x*1/wk) 1–3 (HIIT *x*3/wk)	Aerobic Training HIIT for 3 intervals x 4-min (HIIT *x*1/wk) or 1 interval x 4-min (HIIT *x*3/wk), interspersed with 3-min active recovery Lower-Body Muscle-Strengthening Bodyweight squats (3 sets x 8–12 repetitions [HIIT *x*1/wk] or 1 set x 8–12 repetitions [HIIT *x*3/wk], 1-min rest between sets) Bodyweight lunges (3 sets x 3–6 repetitions [HIIT *x*1/wk] or 1 set x 3–6 repetitions [HIIT *x*3/wk], 1-min rest between sets) Lateral band walk (3 sets x 10–15 repetitions [HIIT *x*1/wk] or 1 set x 10–15 repetitions [HIIT *x*3/wk], 1-min rest between sets) Stretching for major lower-body muscle groups
Week 2	2 (HIIT *x*1/wk) 4–6 (HIIT *x*3/wk)	Aerobic Training HIIT for 6 intervals x 4-min (HIIT *x*1/wk) or 2 intervals x 4-min (HIIT *x*3/wk), interspersed with 3-min active recovery Lower-Body Muscle-Strengthening Bodyweight squats (3 sets x 9–13 repetitions [HIIT *x*1/wk] or 1 set x 9–13 repetitions [HIIT *x*3/wk], 1-min rest between sets) Bodyweight lunges (3 sets x 4–7 repetitions [HIIT *x*1/wk] or 1 set x 4–7 repetitions [HIIT *x*3/wk], 1-min rest between sets) Lateral band walk (3 sets x 11–17 repetitions [HIIT *x*1/wk] or 1 set x 11–17 repetitions [HIIT *x*3/wk], 1-min rest between sets) Stretching for major lower-body muscle groups
Week 3	3 (HIIT *x*1/wk) 7–9 (HIIT *x*3/wk)	Aerobic Training HIIT for 9 intervals x 4-min (HIIT *x*1/wk) or 3 intervals x 4-min (HIIT *x*3/wk), interspersed with 3-min active recovery Lower-Body Muscle-Strengthening Bodyweight squats (3 sets x 10–14 repetitions [HIIT *x*1/wk] or 1 set x 10–14 repetitions [HIIT *x*3/wk], 1-min rest between sets) Bodyweight lunges (3 sets x 5–8 repetitions [HIIT *x*1/wk] or 1 set x 5–8 repetitions [HIIT *x*3/wk], 1-min rest between sets) Lateral band walk (3 sets x 12–19 repetitions [HIIT *x*1/wk] or 1 set x 12–19 repetitions [HIIT *x*3/wk], 1-min rest between sets) Stretching for major lower-body muscle groups
Week 4	4 (HIIT *x*1/wk) 10–12 (HIIT *x*3/wk)	Aerobic Training HIIT for 12 intervals x 4-min (HIIT *x*1/wk) or 4 intervals x 4-min (HIIT *x*3/wk), interspersed with 3-min active recovery Stretching for major lower-body muscle groups

2.5. Primary outcome measure

2.5.1. Total body adiposity

Total body fat mass will be measured using a whole-body dual-energy X-ray absorptiometry (DXA) scan. Participants will be asked to fast for 4 h before the scan, but will be allowed to drink water and take their usual medication. Participants will wear loose-fitting and minimal clothing containing no metallic materials, remove any external metallic objects, and empty their bladder prior to the measurement. Participants will be positioned on the DXA scanner (Horizon A, Hologic Inc., Bedford, MA, USA) by trained research personnel according to the recommended positioning and alignment of head, arms, hands, legs and feet based on the National Health and Nutrition Examination Survey (NHANES) method.[47] Scans will be analyzed using Hologic APEX Software (Version 5.6.0.5, Hologic Inc.) according to the manufacturer's recommendations for body composition analysis. Data will be extracted using an automated program.[48]

2.6. Secondary outcome measures

2.6.1. Body composition

Total body fat percentage, total body lean mass, appendicular lean mass, total body bone mineral content, and total body bone mineral density will be measured by a whole-body DXA scan.

2.6.2. Visceral adipose tissue and subcutaneous adipose tissue

The amount of abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) will be assessed on a 1.5 T and 3.0 T MRI scanner (SIGNA™ Explorer – 60 cm, General Electric Healthcare and SIGNA™ Premier – 70 cm, General Electric Healthcare). 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 the abdominal VAT and SAT volume between the above anatomical landmarks will be calculated. Image analysis will be conducted by 3D Slicer (http://www.slicer.org).[49] Segment Editor will be used to specify the SAT and VAT in the images. The threshold will be set at 150 (AU) which consistently includes the SAT and VAT and excludes the background. Smoothing will be used to remove small extrusions and fill small gaps in the images. Total volume of fat will be calculated based on a full 3D segmentation. Another segment will be generated for the identification of SAT. Level tracing will be used to identify SAT on slices

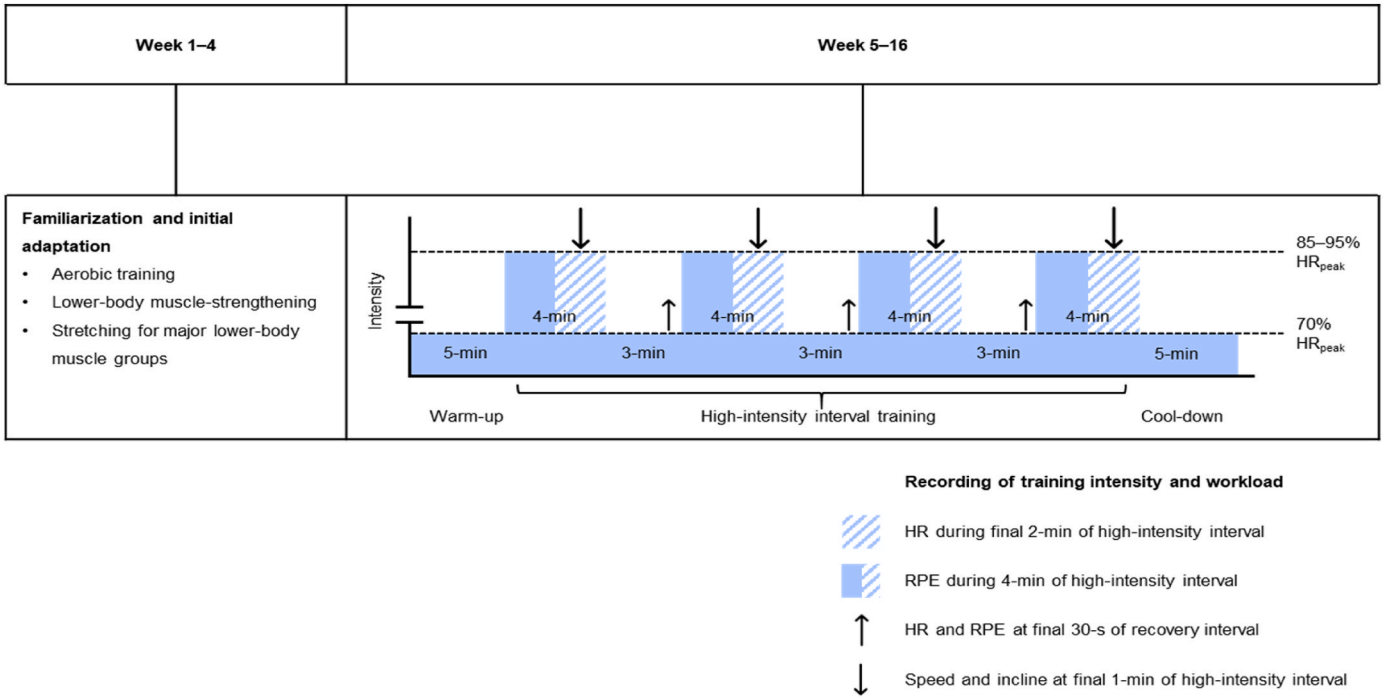

Fig. 2. Training protocol for the HIIT groups.

Table 4
Topics and contents of the health education classes.

Topics	Contents
Obesity & Metabolic Health	1 Obesity & central obesity
	2 Metabolic syndrome
	3 Cardiovascular diseases & cardiovascular fitness
Diet	4 Food pyramid & energy balance
Physical Activity	5 Physical activity recommendations & sedentary lifestyle
Musculoskeletal Health	6 Chronic pain & osteoporosis
Sleep	7 Sleep and obesity
	8 Overall course wrap-up

from each participant. Fill-between-slices will be applied to create complete 3D segmentation for SAT. Segment statistics will be used to calculate the volume of total adipose tissue, the volume of SAT and the volume of VAT. Processing and analysis of the MRI data will be performed by two assessors blinded to the group allocation. One research personnel will analyze the whole dataset of MRI images, while another research personnel will analyze a subset of the MRI images (20% of the overall images) to ensure the reliability of the results.[50] The intraclass correlation will be used to assess the degree of agreement of the VAT and SAT data between the two independent research personnel.

2.6.3. Body anthropometry

Participants will be asked to fast for 4 h before anthropometric measurements. A stadiometer (seca 213, seca) with a 205 cm limit will be used to measure body height. A calibrated electronic weighing scale (UC-321, A&D Medical) with a capacity of 0.05–150 kg and ±0.05 kg accuracy will be used to measure body weight. BMI will be determined by the equation: BMI (kg/m^2) = body mass (kg)/height^2 (m^2). Waist circumference will be measured on bare skin midway between the lowest rib and the superior border of the iliac crest using an inelastic measuring tape (seca 201, seca) to the nearest 0.1 cm. Waist circumference measurements will be performed at the end of normal expiration. Hip circumference will be measured around the widest portion of the buttocks. Circumference measurements will be repeated three times and the average values will be recorded.

2.6.4. Blood pressure

Blood pressure will be measured in the morning on the same day as the venous blood collection. Participants will be asked to refrain from exercising and consuming caffeine, alcohol and blood pressure medications before the measurement.[51] After 5–10 min of rest in a seated position with their back supported in a quiet environment, blood pressure will be measured in the upper arm oscillometrically using a digital blood pressure monitor (HEM-907, Omron). Systolic (SBP) and diastolic blood pressure (DBP) will be obtained using an appropriately sized cuff, with the lower end of the cuff placed 2–3 cm above the antecubital fossa and the arm supported at the heart level. Three measurements will be taken at 1-min intervals and the average value will be recorded.

2.6.5. Blood biomarkers

Participants will be asked to fast overnight for at least 8 h before the venous blood sampling performed by a certified phlebotomist.[52,53] Fresh blood samples will be sent to an accredited medical laboratory to measure fasting plasma glucose (FPG) and the cholesterol profile (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol and triglycerides). The remaining blood samples will be centrifuged at 4 °C and 3000 rpm for 10 min and then aliquoted and stored at −80 °C for subsequent analyses.

2.6.6. Medication usage

The frequency and dosage of medications for chronic health conditions will be recorded at the baseline, post-intervention, and follow-up assessments. Medications consumed will be converted into the lowest recommended dosage (LRD) units, as defined by the Prescribers' Digital Reference and presented as the weekly consumed LRD.[54]

2.6.7. Cardiorespiratory fitness

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 wireless 12-lead stress testing electrocardiogram (Quark T12x, COSMED) will be used to continuously measure and record VO_2, VCO_2, and heart rate,

respectively. Prior to the test, participants will be asked to avoid exercise, caffeine and alcohol for 24 h. We will adopt the modified Bruce protocol[55] because we expect physically inactive participants with central obesity to be deconditioned and have poor aerobic fitness. Exercise intensity will be continuously increased every 3-min until voluntary exhaustion. The RPE will be recorded at the end of every 3-min stage. The maximal RPE will be obtained when the participant reaches voluntary exhaustion. The maximal heart rate attained will be considered the HR_{peak}. Maximal oxygen consumption (VO_{2max}) will be determined from the highest rolling 30-s average.[56]

2.6.8. Adherence to the intervention

Adherence to the HIIT intervention will be reported according to the recommendations of Taylor and colleagues.[45] For the HIIT and control groups, adherence to attendance will be reported as the percentage of sessions attended out of the total sessions prescribed. The number and percentage of participants who meet the attendance criteria (defined as attending ≥70% of the prescribed sessions) will be reported as well. For the HIIT groups, adherence to intensity will be reported as the percentage of sessions meeting the intensity criteria (defined as the average training intensity at ≥85% HR_{peak} during the high-intensity intervals) compared with the sessions attended after the familiarization period (weeks 5–16). The adherence to duration will be reported as the percentage of sessions meeting the duration criteria (defined as completing ≥3 out of 4 and ≥ 9 out of 12 of the high-intensity intervals for the thrice-weekly and once-weekly HIIT groups, respectively) compared with the sessions attended after the familiarization period (weeks 5–16). To promote participant retention, participants who are absent from any intervention sessions will be contacted by our research personnel who will inquire after them and reinforce the health benefits of the intervention program. The reasons for dropout will be ascertained and reported.

2.6.9. Health-related quality of life

The validated Chinese version of the standard 12-Item Short Form Survey (SF-12) will be used to measure health-related quality of life.[57] The SF-12 is a 12-item questionnaire covering eight health domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Physical and mental health-related quality of life will be assessed using the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, respectively. The scores range from 0 to 100, with a higher score representing better physical and mental health-related quality of life.

2.6.10. Mental health

The Hospital Anxiety and Depression Scale (HADS) will be used to measure symptoms of anxiety and depression. The HADS is a 14-item questionnaire containing seven items in the depression subscale and seven items in the anxiety subscale, with each item scored on a four-point scale ranging from 0 to 3. The overall score in each subscale ranges from 0 to 21, with a higher score indicating greater psychological distress. The Chinese version of HADS has been validated in Hong Kong adults with excellent reliability (Cronbach's alpha: overall scale = 0.86, depression subscale = 0.82, anxiety subscale = 0.77), and is strongly correlated with the Hamilton Rating Scale for Depression ($r = 0.67$, $p < 0.001$) and Hamilton Rating Scale for Anxiety ($r = 0.63$, $p < 0.001$).[58]

The Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) will also be used to measure the severity of depression and anxiety symptoms, respectively. The PHQ-9 is a 9-item questionnaire measuring depression severity according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[59] Participants will be asked to rate how often each depressive symptom has occurred in the past 2 weeks, with each item evaluated on a severity scale ranging from 0 to 3. The total score ranges from 0 to 27 and the severity of depressive symptoms will be evaluated based on the following 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).[60] The GAD-7 is a 7-item questionnaire measuring anxiety severity according to the diagnostic criteria of DSM-IV.[59] Each item describes one anxiety disorder symptom and assesses the presence and severity of the symptom in the past 2 weeks, with each item scored on a scale from 0 to 3. The overall score ranges from 0 to 21 and the severity of anxiety symptoms will be evaluated based on the following cutoff scores: 0–4 indicates minimal anxiety, 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 with excellent reliability (Cronbach's alpha = 0.898).[61]

2.6.11. Sleep quality

The Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) will be used to measure sleep quality and perceived insomnia severity, respectively. The PSQI is a 19-item questionnaire measuring seven sleep components: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. Each component is scored from 0 (no sleep problem) to 3 (sleep impairment) yielding a total score ranging from 0 to 21, with a higher score indicating poorer sleep quality. The Chinese version of the PSQI has been validated in Hong Kong adults with excellent reliability (Cronbach's alpha = 0.82).[62] The ISI is a 7-item questionnaire assessing the following dimensions: severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. Each item is scored from 0 (no problem) to 4 (very severe problem) yielding a total score ranging from 0 to 28, with a higher score indicating greater perceived severity and impact of insomnia. The Chinese version of the ISI has been validated in Hong Kong older adults with excellent reliability (Cronbach's alpha = 0.81).[63]

Participants' sleep will also be recorded by 7-day actigraphy and 7-day sleep diary. Participants will be instructed to wear an ActiGraph device (GT9X Link, ActiGraph) on their non-dominant wrist for 24 h over 7 days to record their sleep. During the actigraphy monitoring period, participants will also be asked to record their perceived sleep pattern on a sleep diary form. Objectively estimated and subjectively reported 7-day averages of sleep parameters, including sleep onset latency, number of awakenings, wake time after sleep onset, total sleep time, average awaken time and sleep efficiency will be obtained from the actigraphy data and the sleep diary, respectively.

2.6.12. Cognitive performance

Cognitive performance will be assessed in objective tests in the following order: (1) Digit Span Forward task, (2) Digit Span Backward task, (3) Stroop task, and (4) Go/No-Go task. This cognitive assessment battery will be administered only at baseline and at the post-intervention timepoints. The Digit Span tasks will be administered in pencil-and-paper format by assessors, whereas the Stroop and Go/No-Go tasks will be administered by computer using E-Prime 3.0 (Version 3.0.3.80, Psychology Software Tools) and supervised by assessors. The assessors will provide standardized instructions to participants prior to each task.

Short-term and working memory will be measured using the forward and backward versions of the Digit Span task, respectively.[64] In each task, assessors will read out a sequence of numbers at a speed of ~1 digit per second. Participants will be asked to repeat each sequence in the same order in the forward task and in the reverse order in the backward task. Prior to each task, participants will receive one practice trial and then 14 trials for each task. Forward and backward testing will begin with a 3-digit and 2-digit sequence, respectively. For each task, list lengths will be adjusted adaptively by the 1:2 staircase rule to reflect

participant performance, i.e., a single correct response will increase the length of the subsequent list by one digit, and two consecutive incorrect responses will reduce the length of the subsequent list by one digit. The digits will be sampled randomly without replacement up to a list length of nine digits, with additional constraints that successive digits cannot occur in regular ascending or descending sequence (e.g., 1–2 or 2–1) or in ascending or descending odd or even pairs (e.g., 1–3 or 2–4), and single digit duplications can occur after participant's span surpasses nine digits. The longest list correctly reported on any of the 14 trials and the list length where 50% of lists would be correctly reported based on an estimation using psychophysical procedures will be recorded as the maximum length and mean span, respectively, with higher scores indicating better performance.

Attention will be measured using the Stroop task.[65] This task consists of three subtasks with different conditions that will be administered in the following order: (1) word condition, (2) color-patch condition, and (3) incongruent condition. The stimuli will be presented in the center of the screen. The stimuli in the word condition will consist of the names of colors in black ink ('green', 'red', 'yellow', 'blue') in a Traditional Chinese font (綠, 紅, 黃, 藍). The stimuli in the color-patch condition will consist of rectangles in green, red, yellow, or blue ink. The stimuli in the incongruent condition will also consist of the names of colors but presented in an inconsistent colored ink (e.g., the word 'blue' is in green ink). Participants will receive four practice trials and then nine blocks of four trials (36 experimental trials) for each condition. For each trial, participants will be asked to respond by indicating the name of the color (word condition), the color of the rectangle (color-patch condition), and the color of the ink instead of the name of the color (incongruent condition) by pressing keyboard buttons '1' (green), '2' (red), '3' (yellow), or '4' (blue). A central fixation cross will be presented for 500 m s before each stimulus, which will be visible until a keystroke is registered or after a deadline of 1500 m s after presentation. Trials will be separated by an inter-stimulus interval (ISI) lasting 500 m s with feedback on the correctness of the responses. The correctness of each response and the time to complete each condition will be recorded, with a lower error rate and a shorter time to complete each condition indicating better performance.

Response inhibition will be measured using the Go/No-Go task.[66] In this task, participants will wear headphones and will be presented with a white circle in the center of a black screen. For each trial, they will hear either one beep or two beeps. Participants will be asked to respond by clicking once on the white circle with the left mouse button if they hear one beep and not to click the mouse if they hear two beeps. The circle will remain on the screen until a left mouse button click is registered or after a deadline of 1000 m s after presentation. Participants will receive ten practice trials and then 100 experimental trials. Practice trials will be separated by an ISI lasting 1000 m s with feedback on the correctness of the responses. Experimental trials will be separated by an ISI lasting 500 m s, during which no feedback will be provided on the correctness of the responses. The proportion of No-Go trials will be 20%. The correctness of each response and the median response time for correct Go trials will be recorded, with a lower error rate and a shorter response time indicating better performance.

2.6.13. Monitoring habitual physical activity and dietary intake

Potential confounding factors include changes in habitual physical activity and diet. All participants will be instructed to refrain from any additional exercise sessions during the intervention period, but will be allowed to maintain their usual daily physical activities and dietary habits. Exercise sessions in addition to the intervention protocol will be recorded by the research personnel. General dietary recommendations from the Department of Health of the Hong Kong SAR government will be provided. We will use an ActiGraph device and a weighed food diary to monitor and record physical activity and diet, respectively. These instruments have been adopted in our previous studies.[67,68]

Participants will be instructed to wear the ActiGraph device (GT9X Link, ActiGraph) on their non-dominant wrist for 24 h over 7 consecutive days. The ActiGraph device is a three-axis accelerometer that objectively records daily physical activity. The ActiGraph data will undergo wear time validation to screen for non-wear time. The time spent performing vigorous-, moderate- and light-intensity activities will be obtained by analyzing the ActiGraph data using the ActiLife software (Version 6.13.4) provided by the manufacturer. A 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 the portable electronic weighing scales (KD-400, Tanita) to weigh all foods and fluids consumed over 3 consecutive days (including two weekdays and one weekend day). Daily diet will be analyzed using dietary analysis software (FoodWorks 10 Professional, Xyris). If food items are not listed in the dietary analysis software, we will consult a local dietitian to confirm the caloric and macronutrient content.

2.6.14. Adverse events

Adverse events will be assessed and recorded using a standardized checklist (Fig. 3). For the HIIT groups, trainers will inquire after participants weekly to ascertain any adverse events (e.g., fatigue, dizziness, headache, knee strain injury, or joint/muscle pain, etc.). Any training-related adverse events will be immediately followed up to see whether they are preventable (e.g., incorrect running technique or use of inappropriate running shoes). For the usual care control group, participants will be asked about their health and wellbeing in each bi-weekly session to ascertain any adverse events. In the case of a sustained or severe adverse event, the incident will be reported to the medical doctor attached to this project for further medical advice. In accordance with the principles of Good Clinical Practice (GCP) and the Consolidated Standards of Reporting Trials (CONSORT) Harms statement,[69] the reason, nature and severity of the adverse event, and the potential association with the intervention will be ascertained by the 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 intention-to-treat (ITT) analysis.

2.7. Statistical power and sample size consideration

No previous studies have directly compared the effectiveness of volume-matched once- and thrice-weekly HIIT on total body fat mass. According to a meta-analysis on the effects of HIIT on total body fat mass,[38] the within-group effect size of HIIT studies that employed running as the exercise modality was 0.34. However, this calculated effect size does not consider the comparison relative to a control group. Consistent with the literature, our previous study demonstrated that an 8-week thrice-weekly HIIT intervention resulted in a significant reduction in total body fat mass with a within-group effect size of 0.37 (Cohen's d), and a between-group effect size of 0.6 (Cohen's d) for the comparison between the HIIT group and the control group.[70] The sample size calculation in this study will adopt a stringent criterion of $\alpha = 0.01$ with a moderate effect size of 0.6 (Cohen's d) based on our previous study. Based on the aforementioned parameters, a sample size of 84 participants per group is required to achieve a 90% power to detect significant changes in total body fat mass. A total of 315 participants will be recruited after accounting for a 20% attrition rate.

2.8. Analytical approach and reporting

The study will consist of a 16-week intervention phase followed by a 16-week follow-up phase. The pre-specified primary endpoint is at 16 weeks (post-intervention) with the secondary endpoint at 32 weeks (follow-up). Generalized estimating equations (GEE) adjusted with baseline measurements will be used to assess the treatment effects.

Adverse Events Checklist

Falls	Abrasion / Laceration	Contusion / Hematoma
	Sprain / Strain	Dislocation
	Fracture	Other: _____
Cardiovascular	Lightheadedness / Dizziness	Angina / Chest tightness
	Shortness of breath	Arrhythmia
	Syncope	Orthopnea
	Hypotension	Myocardial Infarction
	Stroke / Transient Ischemic Attack	Other: _____
Musculoskeletal	Soreness / Cramp	Sprain / Strain
	Muscle pull / tear	Tendon / Ligament tear
	Joint trauma	Fracture
	Other: _____	
Health Care Use	Doctor visit	Hospitalization
	Death	Other: _____

Participant Study Code: _____

Adverse Event Date: _____

Describe the adverse event in detail (e.g., location of injury, duration of pain / discomfort)

_____

_____

_____

Fig. 3. Adverse events checklist.

Pairwise comparison will be performed using linear contrasts to estimate differences in the treatment effects between the groups at 16 and 32 weeks. Sensitivity analyses will be performed by adjusting for factors such as gender, age, BMI, socioeconomic status, adherence, physical activity and diet in the GEE model. If age is found to be a factor associated with the treatment effect, a subgroup analysis will be performed for age and participants will be categorized into (1) under 50, or (2) 50 or above. The ITT principle will be applied therefore all randomized participants will be included in the analysis. Missing observations will be handled by multiple imputation (MI). The statistical

analyses will be performed using SAS. 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 CONSORT. Secondary analyses will be performed based on adherence data to examine the dose-response relationship between HIIT adherence and other outcome variables.

2.9. Data management

2.9.1. Data entry

Double data entry will be performed to ensure data quality. A unique master study code will be used for each participant for anonymous data collection and entry, which ensures the personal information and identity of participants is strictly protected.

2.9.2. Data monitoring

The data management team will continuously monitor the collected data at the baseline, post-intervention, and follow-up assessment time points, and the trial progress will be reported to the investigators. The results will be fully disseminated in peer-reviewed scientific journals and conferences. Although we anticipate that any adverse events related to the exercise interventions will be minor, any unexpected severe adverse events that occur multiple times during the trial will be reported and the situation discussed with the medical doctor to determine if the trial should be terminated.

2.9.3. Security and back-up of data

All the study data will be stored separately from the participants' personal information. Hard copy and electronic data will be kept in lockable filing cabinets and encrypted hard disks, respectively. Participants' identity will be stored on encrypted hard disks kept in lockable filing cabinets. Only the research personnel of this project will have access to the lockable filing cabinets and the encrypted hard disks.

3. Discussion

The present study aims to compare the efficacy of volume-matched once-weekly HIIT versus thrice-weekly HIIT on total body adiposity in overweight adults with central obesity. The findings of this study are expected to further consolidate the therapeutic efficacy of HIIT for the management of central obesity. Moreover, the results will provide further insights into the comparative compliance and feasibility of once-weekly HIIT and thrice-weekly HIIT in inactive, overweight and centrally obese adults, and inform whether they are suitable as exercise strategies to manage obesity. In particular, the present study is expected to provide a novel perspective on the utility of a 'weekend warrior' low-frequency HIIT exercise pattern (i.e., once-weekly HIIT) as an effective and sustainable exercise strategy to tackle the obesity pandemic. These anticipated findings will hold substantial translational value, informing public health policies and enhancing exercise compliance in the physically inactive obese population.

3.1. Efficacy of once-weekly and thrice-weekly HIIT for reducing body adiposity

Consistent with the conclusions from meta-analyses on HIIT and adiposity,[35,38] we hypothesize that both once-weekly HIIT and thrice-weekly HIIT will significantly reduce total body adiposity in overweight and centrally obese adults. Encouraging evidence from the literature illustrates that a modest weight loss of 5%–10% will have a plethora of wide-ranging health benefits. These benefits range from improved CVD risk factors (e.g., cholesterol profile, triglyceride levels, and blood pressure) to improved comorbid conditions (e.g., metabolic dysfunction-associated steatohepatitis [MASH]) and mental health problems (e.g., depression).[71,72] It is clear that substantial reductions in fat mass can also deliver significant health benefits.[72] Nonetheless, modest reductions of 5%–10% have also been suggested to produce clinically meaningful improvements in health. However, longitudinal studies examining the health benefits accrued from a modest reduction in fat mass are lacking. In the meta-analysis by Wewege and colleagues,[35] HIIT performed using a running protocol induced a within-group reduction of 2.6 kg in adipose tissue. As noted by the authors, this 2.6 kg reduction in fat mass portrays a modest improvement in body composition, corresponds to a reduction of ~10% from baseline levels, and reaches a clinically meaningful threshold for fat loss. This highlights the efficacy of HIIT in reducing adiposity and its potential to confer health benefits by meeting clinically meaningful reductions in fat mass. Proposed mechanisms of HIIT on reducing adiposity include: (1) increased fat oxidation via increased mitochondrial capacity and density, (2) increased lipolysis via elevations in catecholamines, and (3) appetite suppression.[73] Intriguingly, despite robust evidence on the efficacy of moderate to high-frequency HIIT (i.e., three to five times a week) on reducing body fat, there is a paucity of evidence investigating the efficacy of low-frequency HIIT. Previously, our team has demonstrated that once-weekly HIIT performed for 8 weeks reduced body fat mass and waist circumference in overweight and obese males.[70] Hence, low-frequency HIIT may also be an efficacious exercise strategy to manage obesity. The present study expands upon the findings of our previous research and seeks to elucidate the comparative efficacy of various frequencies of HIIT on total body adiposity when the exercise volume is matched.

3.2. Adherence and sustainability of once-weekly and thrice-weekly HIIT

Conventionally, exercise guidelines recommend exercise on a moderate to high-frequency basis. As evident in the American College of Sports Medicine (ACSM) guidelines for exercise prescription,[74] vigorous aerobic exercise was recommended to be performed at least 3 days a week. Indeed, the most commonly prescribed exercise frequency of HIIT in the literature is moderate to high-frequency, which has been shown to be efficacious in managing adiposity. This observation is well illustrated by Wewege and colleagues and by Maillard and colleagues,[35,38] in which their efficacious findings on the beneficial effects of HIIT on adiposity were mainly derived from studies that employed a HIIT frequency of three or more times a week. Nevertheless, there are concerns over the practicality of adhering to a moderate to high-frequency HIIT program. As reported by Reljic and colleagues,[75] the pooled dropout rate across 67 HIIT interventions was 17.6% after adjusting for publication bias. Among the 67 HIIT interventions included in the meta-analysis, studies mainly implemented a thrice-weekly training frequency with an average intervention duration of ~9 weeks. The authors suggested that a greater time effort was associated with greater dropout rates. This emphasizes the importance of time-related factors in influencing participants' decision to discontinue exercise regimens. Thus, suggesting that higher frequency HIIT programs may negatively affect participants' exercise compliance. Unsurprisingly, similar findings were observed in our earlier work. A higher adherence was reported in once-weekly HIIT (64%) when compared to thrice-weekly HIIT (45%).[70] It is, therefore, reasonable to assume that low-frequency HIIT may improve exercise compliance in the obese population by further circumventing the perceived time-related barriers that are commonly cited for not participating in regular physical activity and dropping out from exercise programs.

To conclude, this study will provide evidence on the efficacy of exercise volume-matched once-weekly and thrice-weekly HIIT on adiposity. We expect this study to demonstrate the efficacy of once-weekly and thrice-weekly HIIT in reducing fat mass, with once-weekly HIIT inducing similar reductions to thrice-weekly HIIT.

4. Trial status

The study was prospectively registered at ClinicalTrials.gov

(NCT04887454) on May 14, 2021. The first participant was recruited on September 1, 2021 and the study is estimated to be completed by July 30, 2024.

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Ethics approval and consent to participate

This study has been approved by the Institutional Review Board (IRB) of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 20–066). Annual trial progress reports have been submitted to the IRB office for auditing the trial. Written informed consent will be obtained from all participants before enrollment in the study.

Credit author statement

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Declaration of competing interest

The authors declared no competing interests.

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