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Personalising Activity to Target Peak Hyperglycaemia and Prevent Cardiovascular Disease in People with Type 2 Diabetes: A Protocol for A Randomised Controlled Trial

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Personalising Activity to Target Peak Hyperglycaemia and Prevent Cardiovascular Disease in People with Type 2 Diabetes: A Protocol for A Randomised Controlled Trial

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ABSTRACT

Introduction: The benefits of physical activity for glycaemic control in type 2 diabetes (T2D) are well-known. However, whether established glycaemic and cardiovascular benefits can be maximised by exercising at a certain time of day is unknown. Given postprandial glucose peaks contribute to worsening glycated haemoglobin (HbA1c) and cardiovascular risk factors, and that exercise immediately lowers blood glucose, prescribing exercise at a specific time of day to attenuate peak hyperglycaemia may improve glycaemic control and reduce the burden of cardiovascular disease in people with T2D.

Methods and analysis: Individuals with T2D (N=54, aged 40-75 years, body mass index 27-40 kg/m^2) will be recruited and randomly allocated (1:1), stratified for sex and insulin, to one of three groups: i) exercise at time of peak hyperglycaemia (ExPeak, personalised), ii) exercise not at time of peak hyperglycaemia (NonPeak), or iii) waitlist control (WLC, standard-care). The trial will be five months, comprising an eight-week intervention and three-month follow up. Primary outcome is the change in HbA1c pre- to post-intervention. Secondary outcomes include vascular function (endothelial function and arterial stiffness), metabolic control (blood lipids and inflammation) and body composition (anthropometrics and dual-energy x-ray absorptiometry [DEXA]). Tertiary outcomes will examine adherence.

Ethics and dissemination: The joint UOW and ISLHD Ethics Committee approved protocol (2019/ETH09856) prospectively registered ACTRN12620000547943. Study results will be published as peer-reviewed articles, presented at national/international conferences and media reports. Findings will impart new knowledge to the scientific community, general public, and practitioners, regarding the benefits of personalising exercise timing in people with T2D.

Abstract word count: 249

Trial registration number: ACTRN12620000547943

Keywords: T2D, exercise, timing, adherence, peak hyperglycaemia, cardiovascular risk

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Article Summary: Strengths and Limitations of this Study

- This is the first randomised controlled trial to determine the effects of personalising exercise to attenuate peak hyperglycaemia, on long-term glycaemic control, cardiovascular risk, and exercise adherence in people with T2D.
- This study will be conducted in free-living conditions, with contact/delivery of the intervention for the first eight weeks mirroring standard-care, thus increasing real-world applicability of the proposed exercise prescription.
- Due to the COVID-19 pandemic, this study will be a combination of remote and local data collection methods. For participants who are unable to attend the university for in-lab assessments due to COVID-19 restrictions, dried blood spot testing kits will be used (to measure glycaemic control, inflammation, and blood lipids), or HbA1c will be reported from the most recent routine blood test, and vascular/DEXA measurements will be excluded.

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INTRODUCTION

Approximately 463 million adults are living with type 2 diabetes (T2D) and this number is expected to increase to 700 million by 2045 [1]. Individuals with T2D have a twofold greater risk of developing atherosclerotic cardiovascular disease (CVD; e.g., myocardial infarction, stroke, etc.) and CVD accounts for ~70% of deaths in T2D patients [2]. T2D is characterised by elevated fasting and postprandial blood glucose levels [3]. Large excursions in blood glucose, especially during the postprandial period (i.e., postprandial hyperglycaemia) cause oxidative stress, inflammation, and endothelial dysfunction, which mechanistically links impaired glucose regulation with the development of CVD in people with T2D [4, 5]. Acute and chronic exercise training improve blood glucose regulation and reduce cardiovascular risk factors. The benefits of exercise training on glycaemic control are largely attributed to the accumulated effects of individual exercise sessions [6, 7] increasing contraction- and insulin-mediated glucose uptake [7, 8] consistently and overtime. The current guidelines for physical activity recommend adults accumulate ~150-300 min of moderate intensity aerobic activity throughout the week to improve or maintain health [9], including glycaemic control (i.e., glycated haemoglobin [HbA1c]) in people with T2D [10]. However, mounting evidence [11–15] indicates that exercise timing (e.g., pre- vs post-meal, or morning vs afternoon) influences glycaemic responses, yet there are no consistent guidelines on exercise timing in any current physical activity recommendations globally.

Multiple systematic reviews have recently examined the effects of exercise timing on measures of glycaemic control in people with T2D and suggest the best time to exercise is within the first few hours after a meal [11–13]. However, performing exercise at different times of the day (i.e., morning vs afternoon) has also shown to influence glycaemic responses [14, 15]. For example, Savikj et al. (2019) recently demonstrated that two weeks of high intensity interval training (HIIT; three days/week) performed in the afternoon improved 24 h glucose concentration by -0.6 mmol/L more than HIIT in the morning [14], whereas a separate study by Teo et al. (2019) found no significant differences in any glycaemic outcomes (HbA1c, fasting or postprandial glucose) after 12 weeks of exercise (three days/week) performed in the morning vs afternoon [15]. Given the inconsistent findings and broad recommendations in the current literature (i.e., exercise timing relative to time of day or meal consumption), a more personalised approach may be needed to target CVD and for practitioners to prescribe exercise timing for people with T2D. Postprandial

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hyperglycaemia is linked to CVD and timing exercise to specifically target the largest postprandial excursion (i.e., peak hyperglycaemia) of the day may lead to greater glycaemic benefits and reduced cardiovascular risk.

It is unknown if prescribing daily exercise at a specific time of day, to attenuate peak hyperglycaemia, will lead to greater improvements in HbA1c compared to the current physical activity guidelines of accumulating ~150-300 min/week at any time. Further, the vascular effects of exercising specifically to attenuate peak hyperglycaemia are unknown. The endothelium is a key regulator of vascular homeostasis and endothelial function is an early risk factor for CVD [16, 17]. Hyperglycaemia increases production of reactive oxygen species [18] and the resulting oxidative stress reduces vascular homeostasis (i.e., by increasing vasoconstriction and decreasing vasodilation) which can lead to endothelial dysfunction and CVD over time. A longer-term intervention of daily exercise is now warranted to garner a better understanding of exercise timing on glycaemic control and to examine whether exercising at the time of peak hyperglycaemia improves HbA1c and reduces cardiovascular risk factors.

The aim of this trial is to determine whether exercising to attenuate peak hyperglycaemia (exercise beginning ~30 min before peak hyperglycaemia) improves glycaemic control (HbA1c and 24 h mean, fasting and postprandial glucose) and reduces cardiovascular risk factors (including lipids, c-reactive protein, vascular function), more than exercising not at time of peak hyperglycaemia (exercise ~90 min after peak hyperglycaemia) or at any time of the day (no prescribed exercise time i.e., physical activity guidelines) in people with T2D. The efficacy, feasibility, and adherence to prescribing an exercise time will also be explored during a three-month follow-up. Given that postprandial hyperglycaemia is associated with worsening HbA1c [19] and endothelial dysfunction [20] in T2D, we hypothesise that exercising to attenuate peak hyperglycaemia will lead to the greatest improvements in glycaemic control, which in turn will improve vascular function and reduce cardiovascular risk.

METHODS

A single centre randomised controlled trial will be conducted at the University of Wollongong, Australia from July 2019 to December 2022 (Figure 1). Participants will be recruited

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through online advertising using a clinical trials recruitment company (Trial Facts). A medical screening questionnaire and informed consent will be obtained from all participants prior to participation. Data will be collected and stored in RedCap data management software.

Participants

Inclusion criteria:

- Physician diagnosed T2D (registration with the National Diabetes Services Scheme)
- HbA1c between 6.5-9.0%
- Aged between 40 and 75 years
- BMI between 27-40 kg/m^2
- Diabetes treated with lifestyle, oral medications and/or intermediate/long-acting insulin
- Stable weight for previous 3 months (± 4 kg)
- Stable medications for previous 3 months
- Able to speak and understand English

Exclusion criteria:

- Any absolute contraindications to exercise (i.e., musculoskeletal/joint injury, etc.)
- Presence or history of CVD, kidney or liver disease
- Diagnosed diabetes complications i.e., neuropathy, retinopathy etc.
- Diabetes treated with short acting insulin
- Uncontrolled hypertension (>160/90 mmHg)
- >150-300 min exercise/week (per Godin leisure time physical activity questionnaire)

Study Design

Fifty-four (N=54) males and females (aged 40-75 years, BMI 27-40 kg/m^2) will be recruited and randomised to one of three groups for eight weeks: i) exercise at time of peak hyperglycaemia (ExPeak), ii) exercise not at time of peak hyperglycaemia (NonPeak) or, iii) waitlist control (WLC). Participants allocated to the WLC group will be re-randomised to the ExPeak or NonPeak intervention group following the waitlist period. During the eight-week intervention (Phase 1), all groups will be prescribed ~150 min/week of physical activity as per the current guidelines. The intervention groups will be prescribed daily exercise at a specific time. During the exercise

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intervention, participants will have five telehealth consults with an accredited exercise physiologist, in line with Australia's Medicare health plan for people with diabetes. An automatic computer-generated random number table will be used to perform random allocation of participants (1:1 ratio), stratified for sex and exogenous insulin usage. A sealed envelope system will be used to blind researchers from group allocations. Allocations will be sealed in an opaque envelope (by a person independent to the clinical trial) until a participant is enrolled and needing to commence the intervention.

Participants will undergo a three-month follow-up (Phase 2) where adherence to exercising at a prescribed time (with minimal contact from the research team) will be assessed. During Phase 2, participants in the ExPeak group will be advised to continue exercising daily at their time of peak hyperglycaemia and participants in the NonPeak group will be advised to exercise in accordance with the World Health Organization 2020 guidelines for physical activity i.e., accumulate ~150-300 min of physical activity per week at any time of day [9], thus becoming the control group.

[INSERT STUDY DESIGN FIGURE HERE]

Interventions

All exercise sessions will be performed in a free-living setting (home-based) for the duration of this trial. Participants in the ExPeak and NonPeak groups will be prescribed ~22 min of daily moderate-intensity physical activity (aerobic exercise e.g., walking, cycling, swimming, etc.) for eight weeks, to align with the physical activity guidelines of accumulating at least 150 min of aerobic activity per week. The pre-intervention Continuous Glucose Monitoring (CGM) data (*outlined below*) will be used to determine time of peak hyperglycaemia. The ExPeak group will begin exercising ~30 min before their peak hyperglycaemia typically occurs and the NonPeak group will begin exercising ~90 min after their peak hyperglycaemia typically occurs. Participants in the control groups will exercise in accordance with the physical activity guidelines [9]. Exercise intensity will be determined using the Borg Scale to indicate Rate of Perceived Exertion, which uses numbered categories from 6-20 (i.e., no exertion at all to maximal exertion) to gauge how hard a person 'feels' they are working [21]. Daily exercise should be completed as one continuous bout but may be accumulated over a 30 min period depending on individual needs (ideally

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accumulated in bouts of >10 min, interspersed with short periods of rest). Participants will have two phone consults and five telehealth video consults with an accredited exercise physiologist on alternate weeks throughout the eight-week exercise intervention, in addition to maintaining standard care treatment with health care professionals and habitual medication and diet.

Experimental Protocol

The intervention period will be five months in total, with the eight-week intervention (Phase 1) commencing after two weeks of pre-intervention monitoring, and the three-month follow-up (Phase 2) commencing after two weeks of post-intervention monitoring. Pre- and post-assessments will be conducted at the University of Wollongong to evaluate glycaemic and metabolic control, vascular function, and body composition (Figure 2). Participants will be instructed to abstain from physical activity for >24 h and to fast for ~10 h before each in-lab assessment.

A two-week monitoring period will be conducted pre-intervention, midway through, post-intervention and after the three-month follow-up. Participants in the WLC group will have two additional weeks of baseline monitoring before the waitlist period commences. Participants will maintain normal daily activity and dietary patterns during each monitoring period, except for the midpoint assessment where they will continue to follow intervention protocol. During the three-month follow-up, participants will complete three short surveys (one at the end of each month, seven questions each) to assess adherence to the exercise prescription but will otherwise have no formal contact with the research team (Figure 2). Other than the prescribed exercise, participants will be asked to maintain normal dietary habits and medication usage throughout the study period.

[INSERT PROTOCOL TIMELINE FIGURE HERE]

Determination of Peak Hyperglycaemia

The 'Glucose Pattern Insights' report (automatically generated via LibreView software), for the two-week pre-intervention CGM (Freestyle Libre, Abbott), will be used to determine the average time that peak hyperglycaemia occurs for each participant (Figure 3). Trained researchers will verify time of peak hyperglycaemia by analysing the raw CGM data using the following methods: After the CGM data is cleaned and separated into full days (i.e., >24 h of uninterrupted data),

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maximum glucose and the time it occurs will be calculated for each day of the two-week monitoring period. The average time of day that peak hyperglycaemia occurs will be then determined for each participant —if peak hyperglycaemia occurs at the same time of day (or within ~30 min) on five or more occasions over the 14 d CGM period, that time of day will be identified as the time of peak hyperglycaemia. Alternatively, time of peak hyperglycaemia will be calculated as an average from 14 days of continuous glucose measurements. Time of peak hyperglycaemia will be re-assessed following the waitlist period for participants initially randomised to the WLC group and again in the ExPeak group for the three-month follow up.

[INSERT GLUCOSE PATTERN INSIGHT EXAMPLE HERE]

Outcome Measures

The primary outcome is the change in HbA1c following the eight-week intervention. Secondary outcome measures will examine additional indices of glycaemic control (via CGM derived variables [e.g., 24 h mean, area under the curve, glycaemic variability, time in range etc.] and a mixed meal tolerance test [MMTT]), vascular function (endothelial function and arterial stiffness), metabolic control (blood lipids and inflammation) and body composition (BMI, total and regional fat, and fat-free mass). Tertiary outcome measures will focus on the efficacy, feasibility, and adherence to exercise prescription (accelerometer and surveys). Apart from the mid-intervention assessment, participants will resume normal daily living (not exercise at their prescribed time) to assess training effects.

Glycaemic Control

The primary outcome of glycaemic control will be assessed by measuring HbA1c. A finger prick blood sample will be collected using a HbA1c (~2 µL) specific test disc and immediately analysed with the Cobas b 101 System (Roche Diagnostics).

Secondary glycaemic outcomes will also be assessed with CGM and a MMTT (low glycaemic index, Glucerna©). From each two-week CGM, we will calculate mean 24 h glucose, 24 h and 3 h postprandial area under the curve (AUC) and incremental area under the curve (iAUC) calculated using the trapezoid method [22], hyperglycaemia (time spent ≥10 mmol/L), glycaemic variability

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(mean amplitude of glycaemic variability [MAGE]) and nocturnal glucose profiles. We will also calculate mean glucose total AUC and iAUC for 2 h following the MMTT. The MMTT will begin after an overnight fast (>10 h), and blood glucose will be measured with the CGM and finger pricks (0, 15, 30, 60, 90 and 120 min) following drink consumption.

Metabolic Control

Metabolic control will be assessed by measuring blood lipids (triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein) and inflammation (CRP). Finger prick blood samples will be collected via lipid (~19 µL) or inflammation (~12 µL) specific test discs and immediately analysed with the Cobas b 101 System.

Body Composition

Waist to hip ratio, height, and weight will be measured to the nearest 0.1 cm and 0.1 kg, respectively, using standard scales, a stadiometer and measuring tape. Total and regional fat and fat-free mass will be measured by dual-energy x-ray absorptiometry ([DEXA], MedixDR Whole Body DEXA, SYD, AU).

Vascular Function

Endothelial function will be assessed by measuring endothelium-dependent flow-mediated dilation (FMD). This technique uses ultrasound imaging (Terason uSmart® 3300) of the brachial artery. Following 10-15 min of laying supine (at rest), a longitudinal section of the brachial artery, 2-3 cm above the antecubital fossa, will be imaged using B-mode ultrasound imaging (insonation angle of 60°). A blood pressure cuff placed around the forearm, 1-2 cm below the olecranon process, will then be rapidly inflated to ~60 mmHg above resting systolic blood pressure for 5 min. Brachial artery diameter and blood flow velocity will be recorded for 1 min before cuff inflation (baseline), ~30 s prior to cuff release (ischemic stimulus), and 3 min following cuff release (recovery) [23, 24]. The ~5 min recording will then be analysed with custom-designed edge-detection and wall-tracking software (Cardiovascular Suite, Quipu, Italy) which reduces user bias and increases accuracy. FMD will be reported as an absolute change in artery diameter (absolute FMD = $\text{postocclusion}_{\text{mean diameter}} - \text{preocclusion}_{\text{mean diameter}}$), and a relative change in artery diameter

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from baseline [%FMD = 100 × (absolute FMD/preocclusion$_{\text{mean diameter}}$)]. Allometric scaling will be used to account for potential confounders from baseline diameter [24, 25].

Blood flow (mL/min) will be measured using non-invasive Doppler from the cross-sectional area and blood velocity [velocity × π × (diameter2/4) × 60]. Shear rate (s-1) will then be determined from the diameter and velocity measures (four times velocity/diameter) [26]. Shear rate area under the curve (SR_{AUC}) will automatically be calculated from the diameter and velocity measures from the time of cuff release to peak dilation of the artery. Antegrade and retrograde mean blood velocities will be used to calculate baseline antegrade and retrograde shear rates (four times mean baseline antegrade or retrograde velocity ÷ mean baseline diameter), and the mean blood flow to mean arterial pressure ratio will be used to measure vascular conductance (mL/min/mmHg) [23, 24].

Central arterial stiffness will be assessed via pulse wave analysis (PWA) and pulse wave velocity (PWV) measurements (SphygmoCor® XCEL System, AtCor Medical). PWA will be used to measure central blood pressure. A brachial blood pressure cuff will be inflated and the central aortic pressure waveform, derived from pulsations at the brachial artery, will be recorded for 5 s and then automatically analysed through the SphygmoCor software. Key parameters of central blood pressure and arterial stiffness will be determined from the aortic waveform including systolic pressure, diastolic pressure, pulse pressure, aortic pressure, augmentation index and mean arterial pressure. PWV will be measured by holding a tonometer on the carotid artery for 10-15 s, while a femoral blood pressure cuff is automatically inflated. Once fully inflated, the femoral cuff and carotid tonometer will simultaneously record a 10 s capture of the carotid and femoral pressure waveforms. PWV will then be calculated by dividing the carotid-femoral distance by the pulse transit time; the carotid-femoral distance will be calculated by subtracting the proximal distance (distance between the carotid artery and sternal notch) from the distal distance (distance between the sternal notch and proximal edge of the femoral cuff) [PWV (m/s) = (distal – proximal$_{\text{distance}}$)/transit time] [27]. Measurements will be performed in duplicate. A third measurement will be taken if the difference between the two PWV values is >0.5 m/s and the average of the three values will be used.

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An automatic blood pressure monitor (Oscar2 Ambulatory Blood Pressure Monitor with SphygmoCor interfacing, SunTech Medical) will also be used to continuously assess blood pressure and pulse wave analyses every hour for 24 hours. We will report 24 h blood pressure as an average of 24 measurements.

Diet and Physical Activity Monitoring

Participants will complete a 7 d diet record during each two-week monitoring period. Food diaries will be analysed (using FoodWorks10 Nutrition Software) to confirm macronutrient composition and total energy intake are consistent throughout the study period. Physical activity will be monitored during the same 7 d period using an accelerometer (ActiGraph Bluetooth® Smart wGT3X-BT), worn around the waist during wake hours. Physical activity and sedentary time will be compared between groups at each timepoint during wake hours. The accelerometers will also be used to confirm exercise intensity and compliance to the exercise prescription. A heart rate monitor (Polar H7 Bluetooth® Heart Rate Monitor) will be worn during the midpoint monitoring period on the same days as the accelerometer, only during the exercise sessions, to assess exercise intensity.

Adherence and Lifestyle Questionnaires

Participants will complete a quality of life (SF-36) survey and a self-regulatory efficacy and physical activity questionnaire during each two-week monitoring period. Participants will also complete three surveys during the follow-up period, one at the end of each month that is specific to their exercise group, to assess adherence to exercise prescription between the ExPeak and control groups. Surveys will include questions on known perceived facilitators and barriers to filling the exercise prescription and, in turn, support or aggravation of intervention efficacy. Such factors will include the availability of nearby green and open spaces (e.g. beaches, parks) [28] and levels of felt safety to exercise outdoors during the day and evening hours [29].

Remote Participants

Participants who cannot attend the university (e.g., due to COVID-19 restrictions) for in-lab assessments will receive a home-based testing kit (via mail) which includes: a dried blood spot test kit (ZRT Laboratory kit for measurement of HbA1c, lipids, CRP, and insulin), CGM,

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accelerometer and Glucerna MMTT drink. Instructions will be provided and followed-up via a phone or video call. All other study protocols will be the same, however data for the DEXA and vascular assessments will not be available.

Patient and Public Involvement

No patient involved.

Statistical Analysis

Sample size

Sample size was calculated based on a previous study investigating the effect of exercise timing in people with T2D, where they reported a difference of -0.6 mmol/L in 24 h blood glucose between exercise performed in the morning vs afternoon [14]. To detect a clinically meaningful change in HbA1c between groups, with a moderate effect size of 0.2, statistical power of 80%, and an alpha level of 0.05 (two-sided), a total of ~54 participants is required for this trial. The power calculation is based on the change in HbA1c from a previous trial in our lab in people with T2D [30]. To account for an expected 15% drop-out rate, 63 participants will be recruited.

Statistics

This study will be reported according to the CONSORT 2010 Statement and the CONSERVE 2021 Statement for randomised controlled trials. Descriptive statistics will be assessed (means, standard deviation and frequencies), and histograms, Q-Q plots and the Shapiro-Wilk test will be used to identify outliers and test for normality. Linear mixed models (with time x intervention, and main effect of time) will be used to assess differences between groups, for primary (HbA1c) and secondary (CGM, MMTT, vascular function, metabolic control, and body composition) outcomes. Tertiary outcomes (e.g., adherence to the exercise prescription) will be analysed from the accelerometer and follow-up surveys (Qualtrics^{XM}). Attention to treat analyses will be performed for primary analyses (Phase 1) and per protocol analyses will be undertaken for secondary and tertiary outcomes (Phase 2). Data with skewed distribution will be log-transformed or square-rooted prior to the statistical analysis. For the three-month follow-up, intention to treat analysis will be used and missing data will not be imputed.

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DISCUSSION

The primary objective of this trial is to determine if strategically timing exercise, to reduce daily peak hyperglycaemia, will improve glycaemic control and lower cardiovascular risk factors in people with T2D. This is the first study to investigate whether prescribing exercise that is personalised to target daily peak hyperglycaemia, using CGM, can improve cardiovascular risk factors in T2D. Based on evidence from prior research [11, 31–33], it is hypothesised that strategically timing daily exercise to attenuate peak hyperglycaemia will improve glycaemic control (HbA1c), and the reduction in peak glycemia will improve vascular function (endothelial function and arterial stiffness), blood lipids and CRP, more than exercising not at peak hyperglycaemia or control standard-care (i.e., physical activity guidelines).

Recent evidence suggests exercise timing may be important to offset circadian rhythms [14] and to target postprandial hyperglycaemia [11] in T2D. However, there are no recommendations for exercise timing in the current physical activity guidelines (i.e., physical activity can be accumulated at any time throughout the week). Further, adherence to the current recommendations is notoriously poor. Regardless of the effectiveness for an intervention to improve diabetes management, findings will only be translatable if patients comply with and adopt to the treatment over the long-term. Therefore, adherence to prescribed daily exercise time (i.e., creating more of a habit) will be assessed for three months following the eight-week intervention. Exercising at the time of peak hyperglycaemia may improve self-efficacy to the exercise prescription, as results from the CGM data (pre/mid/post eight-week intervention) will allow participants to see the direct impact of exercise on blood glucose levels. Use of CGM in this trial not only offers the distinct advantage of determining time of peak hyperglycaemia, but will also allow us to examine any changes in daily glycaemic patterns, such as glycaemic variability, which are more closely related to cardiovascular risk than HbA1c [34]. If strategically timing exercise to attenuate peak hyperglycaemia improves long-term glycaemic control (HbA1c), reduces cardiovascular risk (endothelial dysfunction and arterial stiffness), and improves exercise adherence then this may be an alternative recommendation for physical activity prescription in people with T2D.

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Due to the COVID-19 pandemic, the vascular (endothelial function, arterial stiffness, 24 h blood pressure) and body composition (DEXA) measures will be unavailable for participants who are unable to attend the university due to COVID restrictions. Blood spot testing kits will be provided to assess HbA1c, blood lipids and inflammation.

were optional (from August-December 2020). Participants were also given the option to submit blood samples via dried blood spot testing kits (to assess HbA1c, blood lipids and inflammation), rather than having a blood sample collected at the university. All participants enrolled after December 2020 will be required to attend face-to-face assessments unless prohibited due to further COVID-19 restrictions.

ETHICS AND DISSEMINATION

This research has been reviewed and approved by the University of Wollongong Human Research Ethics Committee (2019/ETH09856). This trial was prospectively registered at the Australian New Zealand Clinical Trials Registry (ACTRN12619001049167). Participants will remain anonymous, and all collected data will be de-identified and coded. An alpha-numerical code (stored on a password protected central spreadsheet) will be allocated to each participant and used for identification on all subsequent paperwork. All results from the study will be published as peer-reviewed articles in international journals, presented at international conferences and promoted through social media. Changes to the protocol due to COVID-19 will be reported according to the CONSERVE 2021 Statement [35].

COMPETING INTERESTS

The authors have no conflicts of interest to disclose.

Data can be made available on request.

AUTHOR CONTRIBUTIONS

CRC drafted the manuscript. MEF, CRC, BMR, and TAB conceived and contributed to the design of the study and plan for analysis. MEF and CRC will conduct the study, collect data, and analyse data. MEF, CRC and TAB will analyse and interpret the data. All authors reviewed and approved the final manuscript.

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FIGURES

Figure 1. Study Design and Flow Chart. Eligible participants will be randomised (N=54) to one of three groups: i) exercise at peak hyperglycaemia (ExPeak; N=18), ii) exercise after peak hyperglycaemia (NonPeak; N=18), or iii) waitlist control (WLC; N=18). Participants randomised to WLC will be re-randomised to ExPeak or NonPeak after the waitlist period. Following the eight-week intervention (Phase 1), the ExPeak (N=27) group will continue to exercise at peak hyperglycaemia, whereas the NonPeak (N=27) group will become the control (CTL; N=27) group for the three-month follow-up (Phase 2). Participants in the WLC and CTL groups will receive standard care advice to exercise in accordance with the World Health Organization physical activity guidelines.

Figure 2. TIMELINE OF STUDY PROTOCOL. Participants randomised to the waitlist control (WLC) group will undergo measures before and after an eight-week waitlist control period. Then are randomised to one of two intervention groups for eight weeks: i) exercise at peak hyperglycaemia ([ExPeak] ExRx: begin exercise ~30 min before peak hyperglycaemia) or ii) exercise after peak hyperglycaemia ([NonPeak] ExRx: begin exercise ~90 min after peak hyperglycaemia). All groups undergo pre-intervention CGM to measure time of peak hyperglycemia prior to interventions. **PHASE 1. Eight-week intervention:** Both intervention groups will perform ~22 min of daily exercise at their prescribed time. Participants will receive two phone consults and five telehealth video consults (via zoom or skype) with an Accredited Exercise Physiologist. **PHASE 2. Three-month follow-up:** The ExPeak group will continue to exercise for ~22 min/day at peak hyperglycaemia and the NonPeak group will exercise according

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to the physical activity guidelines. Three adherence surveys will be conducted (at the end of each month), but no formal contact. **Free Living Assessments:** 14 d CGM, 2 h MMTT, 7 d ActiGraph activity monitoring, 7 d HR monitoring (midpoint only; Polar Bluetooth HR monitor worn on same days as ActiGraph, only during prescribed exercise), 7 d diet record, quality of life survey, and self-regulatory efficacy and physical activity questionnaire. **In-Lab Assessments:** i) blood sample HbA1c, CRP, and blood lipids (TG, TC, HDL, and LDL); ii) vascular measures FMD and arterial stiffness via PWV/PWA; and iii) anthropometrics (height and weight) and body composition DEXA.

Abbreviations: waitlist control, WLC; exercise at peak hyperglycaemia (intervention group), ExPeak; exercise after peak (intervention group), NonPeak; exercise prescription, ExRx; accredited exercise physiologist, AEP; continuous glucose monitoring, CGM; mixed meal tolerance test, MMTT; heart rate, HR; glycated hemoglobin, HbA1c; c-reactive protein, CRP; triglyceride, TG; total cholesterol, TC; high-density lipoprotein, HDL; low-density lipoprotein, LDL; flow-mediated dilation, FMD; pulse wave velocity, PWV; pulse wave analysis, PWA; and dual-r-ray absorptiometry, DEXA.

Figure 3. Example 'Glucose Pattern Insights' Report, via LibreView, of a 24 h blood glucose curve averaged from 14 days of continuous glucose measurements.

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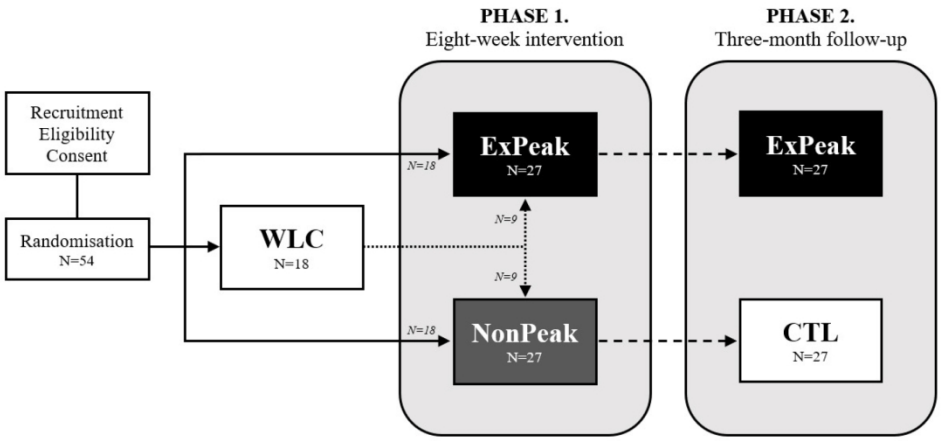

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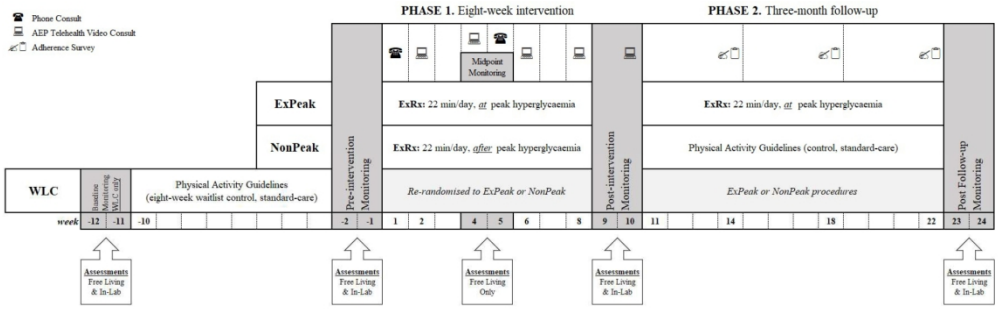

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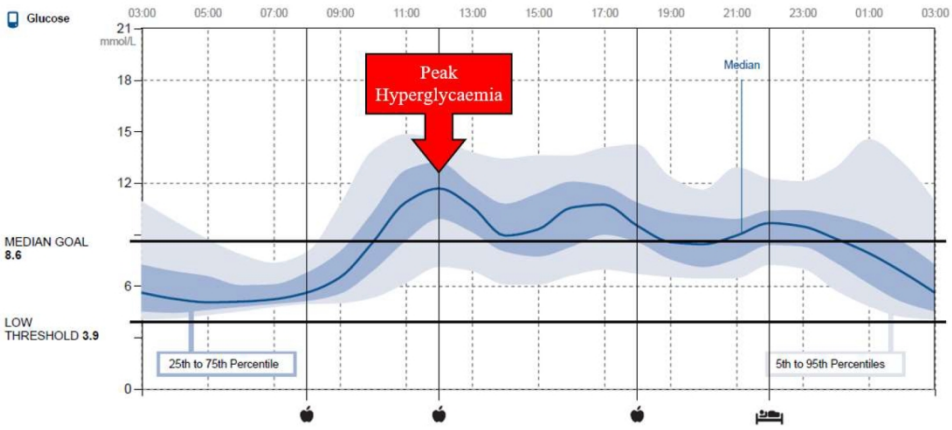

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871x414mm (57 x 57 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

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		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14

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Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	1
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	1
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6

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Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	2
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	22
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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Personalising Activity to Target Peak Hyperglycaemia and Improve Cardiometabolic Health in People with Type 2 Diabetes: A Protocol for A Randomised Controlled Trial

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Secondary Subject Heading:	Cardiovascular medicine, Sports and exercise medicine
Keywords:	Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Hypertension < CARDIOLOGY, CLINICAL PHYSIOLOGY, COMPLEMENTARY MEDICINE, Physiology < NATURAL SCIENCE DISCIPLINES, SPORTS MEDICINE

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Personalising Activity to Target Peak Hyperglycaemia and Improve Cardiometabolic Health in People with Type 2 Diabetes: A Protocol for A Randomised Controlled Trial

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Word count: 4029

Protocol version 1 September 2021

Trial Sponsor: University of Wollongong research-services@uow.edu.au

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ABSTRACT

Introduction: The benefits of physical activity for glycaemic control in type 2 diabetes (T2D) are well-known. However, whether established glycaemic and cardiovascular benefits can be maximised by exercising at a certain time of day is unknown. Given postprandial glucose peaks contribute to worsening glycated haemoglobin (HbA1c) and cardiovascular risk factors, and that exercise immediately lowers blood glucose, prescribing exercise at a specific time of day to attenuate peak hyperglycaemia may improve glycaemic control and reduce the burden of cardiovascular disease in people with T2D.

Methods and analysis: A single centre randomised controlled trial will be conducted by the University of Wollongong, Australia. Individuals with T2D (N=70, aged 40-75 years, body mass index 27-40 kg/m^2) will be recruited and randomly allocated (1:1), stratified for sex and insulin, to one of three groups: i) exercise at time of peak hyperglycaemia (ExPeak, personalised), ii) exercise not at time of peak hyperglycaemia (NonPeak), or iii) waitlist control (WLC, standard-care). The trial will be five months, comprising an eight-week intervention and three-month follow up. Primary outcome is the change in HbA1c pre- to post-intervention. Secondary outcomes include vascular function (endothelial function and arterial stiffness), metabolic control (blood lipids and inflammation) and body composition (anthropometrics and dual-energy x-ray absorptiometry [DEXA]). Tertiary outcomes will examine adherence.

Ethics and dissemination: The joint UOW and ISLHD Ethics Committee approved protocol (2019/ETH09856) prospectively registered at the Australian New Zealand Clinical Trials Registry. Study results will be published as peer-reviewed articles, presented at national/international conferences and media reports. Findings will impart new knowledge to the scientific community, general public, and practitioners, regarding the benefits of personalising exercise timing in people with T2D.

Abstract word count: 271

Trial registration number: ACTRN12619001049167

Keywords: T2D, exercise, timing, adherence, peak hyperglycaemia, cardiovascular risk

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Strengths and Limitations of this Study

- This is the first randomised controlled trial to examine the effect of personalising exercise timing to attenuate peak hyperglycaemia on cardiometabolic and vascular outcomes in type 2 diabetes.
- This study will employ a variety of data collection methods (in-lab and free-living) to measure changes in cardiovascular and metabolic health, physical activity and behaviour change.
- Recruitment of participants across Australia (urban and rural) with remote delivery is both a strength in diversity and inclusion and a limitation given the reliance on dried blood spot home collection, and vascular/body composition measures will not be availible for those unable to attend the university visits.
    - Related, a strength was adapting to COVID-19 whilst retaining high-quality study design and data collection with strong external validity

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INTRODUCTION

Approximately 463 million adults are living with type 2 diabetes (T2D) and this number is expected to increase to 700 million by 2045 [1]. Individuals with T2D have a twofold greater risk of developing atherosclerotic cardiovascular disease (CVD; e.g., myocardial infarction, stroke, etc.) and CVD accounts for ~70% of deaths in T2D patients [2]. T2D is characterised by elevated fasting and postprandial blood glucose levels [3]. Large excursions in blood glucose, especially during the postprandial period (i.e., postprandial hyperglycaemia) cause oxidative stress, inflammation, and endothelial dysfunction, which mechanistically links impaired glucose regulation with the development of CVD in people with T2D [4, 5]. Acute and chronic exercise training improve blood glucose regulation and reduce cardiovascular risk factors. The benefits of exercise training on glycaemic control are largely attributed to the accumulated effects of individual exercise sessions [6, 7] increasing contraction- and insulin-mediated glucose uptake [7, 8] consistently and overtime. The current guidelines for physical activity recommend adults accumulate ~150-300 min of moderate intensity aerobic activity throughout the week to improve or maintain health [9], including glycaemic control (i.e., glycated haemoglobin [HbA1c]) in people with T2D [10]. However, mounting evidence [11–15] indicates that exercise timing (e.g., pre- vs post-meal, or morning vs afternoon) influences glycaemic responses, yet there are no consistent guidelines on exercise timing in any current physical activity recommendations globally.

Multiple systematic reviews have recently examined the effects of exercise timing on measures of glycaemic control in people with T2D and suggest the best time to exercise is within the first few hours after a meal [11–13]. However, performing exercise at different times of the day (i.e., morning vs afternoon) has also shown to influence glycaemic responses [14, 15]. For example, Savikj et al. (2019) recently demonstrated that two weeks of high intensity interval training (HIIT; three days/week) performed in the afternoon improved 24 h glucose concentration by -0.6 mmol/L more than HIIT in the morning [14], whereas a separate study by Teo et al. (2019) found no significant differences in any glycaemic outcomes (HbA1c, fasting or postprandial glucose) after 12 weeks of exercise (three days/week) performed in the morning vs afternoon [15]. Given the inconsistent findings and broad recommendations in the current literature (i.e., exercise timing relative to time of day or meal consumption), a more personalised approach may be needed to

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target CVD and for practitioners to prescribe exercise timing for people with T2D. Postprandial hyperglycaemia is linked to CVD and timing exercise to specifically target the largest postprandial excursion (i.e., peak hyperglycaemia) of the day may lead to greater glycaemic benefits and reduced cardiovascular risk.

It is unknown if prescribing daily exercise at a specific time of day, to attenuate peak hyperglycaemia, will lead to greater improvements in HbA1c compared to the current physical activity guidelines of accumulating ~150-300 min/week at any time. Further, the vascular effects of exercising specifically to attenuate peak hyperglycaemia are unknown. The endothelium is a key regulator of vascular homeostasis and endothelial function is an early risk factor for CVD [16, 17]. Hyperglycaemia increases production of reactive oxygen species [18] and the resulting oxidative stress reduces vascular homeostasis (i.e., by increasing vasoconstriction and decreasing vasodilation) which can lead to endothelial dysfunction and CVD over time. A longer-term intervention of daily exercise is now warranted to garner a better understanding of exercise timing on glycaemic control and to examine whether exercising at the time of peak hyperglycaemia improves HbA1c and reduces cardiovascular risk factors.

The aim of this trial is to determine whether exercising to attenuate peak hyperglycaemia (exercise beginning ~30 min before peak hyperglycaemia) improves glycaemic control (HbA1c and 24 h mean, fasting and postprandial glucose) and reduces cardiovascular risk factors (including lipids, c-reactive protein, vascular function), more than exercising not at time of peak hyperglycaemia (exercise ~90 min after peak hyperglycaemia) or at any time of the day (no prescribed exercise time i.e., physical activity guidelines) in people with T2D. The efficacy, feasibility, and adherence to prescribing an exercise time will also be explored during a three-month follow-up. Given that postprandial hyperglycaemia is associated with worsening HbA1c [19] and endothelial dysfunction [20] in T2D, we hypothesise that exercising to attenuate peak hyperglycaemia will lead to the greatest improvements in glycaemic control, which in turn will improve vascular function and reduce cardiovascular risk.

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METHODS

A single centre randomised controlled trial will be conducted at the University of Wollongong, Australia from July 2019 to December 2022 (Figure 1). Participants will be recruited through online advertising using a clinical trials recruitment company (Trial Facts). A medical screening questionnaire and informed consent will be obtained from all participants prior to participation. Study data will be collected and managed using the secure online REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Wollongong, Australia [21, 22].

Participants

Inclusion criteria:

- Physician diagnosed T2D (registration with the National Diabetes Services Scheme)
- HbA1c between 6.5-9.0%
- Aged between 40 and 75 years
- BMI between 27-40 kg/m^2
- Diabetes treated with lifestyle, oral medications and/or intermediate/long-acting insulin
- Stable weight for previous 3 months (± 4 kg)
- Stable medications for previous 3 months
- Able to speak and understand English

Exclusion criteria:

- Any absolute contraindications to exercise (i.e., musculoskeletal/joint injury, etc.)
- Presence or history of CVD, kidney or liver disease
- Diagnosed diabetes complications i.e., neuropathy, retinopathy etc.
- Diabetes treated with short acting insulin
- Uncontrolled hypertension (>160/90 mmHg)
- >150 min of moderate to vigorous intensity exercise/week (per Godin leisure time physical activity questionnaire)

Study Design

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Seventy males and females (aged 40-75 years, BMI 27-40 kg/m^2) will be recruited and randomised to one of three groups for eight weeks: i) exercise at time of peak hyperglycaemia (ExPeak), ii) exercise not at time of peak hyperglycaemia (NonPeak) or, iii) waitlist control (WLC). Participants allocated to the WLC group will be re-randomised to the ExPeak or NonPeak intervention group following the waitlist period. During the eight-week intervention (Phase 1), all groups will be prescribed ~150 min/week of physical activity as per the current guidelines. The intervention groups will be prescribed daily exercise at a specific time. During the exercise intervention, participants will have five telehealth consults with an accredited exercise physiologist, in line with Australia's Medicare health plan for people with diabetes. An automatic computer-generated random number table will be used to perform random allocation of participants (1:1 ratio), stratified for sex and exogenous insulin usage. A sealed envelope system will be used to blind researchers from group allocations. Allocations will be sealed in an opaque envelope (by a person independent to the clinical trial) until a participant is enrolled and needing to commence the intervention.

Participants will undergo a three-month follow-up (Phase 2) where adherence to exercising at a prescribed time (with minimal contact from the research team) will be assessed. During Phase 2, participants in the ExPeak group will be advised to continue exercising daily at their time of peak hyperglycaemia and participants in the NonPeak group will be advised to exercise in accordance with the World Health Organization 2020 guidelines for physical activity i.e., accumulate ~150-300 min of physical activity per week at any time of day [9], thus becoming the control group.

[INSERT STUDY DESIGN FIGURE HERE]

Interventions

All exercise sessions will be performed in a free-living setting (home-based) for the duration of this trial. Participants in the ExPeak and NonPeak groups will be prescribed ~22 min of daily moderate-intensity physical activity (aerobic exercise e.g., walking, cycling, swimming, etc.) for eight weeks, to align with the physical activity guidelines of accumulating at least 150 min of aerobic activity per week. The pre-intervention Continuous Glucose Monitoring (CGM) data (*outlined below*) will be used to determine time of peak hyperglycaemia. The ExPeak group will

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begin exercising ~30 min before their peak hyperglycaemia typically occurs and the NonPeak group will begin exercising ~90 min after their peak hyperglycaemia typically occurs. Participants in the control groups will exercise in accordance with the physical activity guidelines [9]. Exercise intensity will be determined using the Borg Scale to indicate Rate of Perceived Exertion, which uses numbered categories from 6-20 (i.e., no exertion at all to maximal exertion) to gauge how hard a person 'feels' they are working [23]. Daily exercise should be completed as one continuous bout but may be accumulated over a 30 min period depending on individual needs (ideally accumulated in bouts of >10 min, interspersed with short periods of rest). Participants will have two phone consults and five telehealth video consults with an accredited exercise physiologist on alternate weeks throughout the eight-week exercise intervention, in addition to maintaining standard care treatment with health care professionals and habitual medication and diet.

Experimental Protocol

The intervention period will be five months in total, with the eight-week intervention (Phase 1) commencing after two weeks of pre-intervention monitoring, and the three-month follow-up (Phase 2) commencing after two weeks of post-intervention monitoring. Pre- and post-assessments will be conducted at the University of Wollongong to evaluate glycaemic and metabolic control, vascular function, and body composition (Figure 2). Participants will be instructed to abstain from physical activity for >24 h and to fast for ~10 h before each in-lab assessment.

A two-week monitoring period will be conducted pre-intervention, midway through, post-intervention and after the three-month follow-up. Participants in the WLC group will have two additional weeks of baseline monitoring before the waitlist period commences. Participants will maintain normal daily activity and dietary patterns during each monitoring period, except for the midpoint assessment where they will continue to follow intervention protocol. During the three-month follow-up, participants will complete three short surveys (one at the end of each month, seven questions each) to assess adherence to the exercise prescription but will otherwise have no formal contact with the research team (Figure 2). Other than the prescribed exercise, participants will be asked to maintain normal dietary habits and medication usage throughout the study period.

[INSERT PROTOCOL TIMELINE FIGURE HERE]

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Determination of Peak Hyperglycaemia

The 'Glucose Pattern Insights' report (automatically generated via LibreView software), for the two-week pre-intervention CGM (Freestyle Libre, Abbott), will be used to determine the average time that peak hyperglycaemia occurs for each participant (Figure 3). Trained researchers will verify time of peak hyperglycaemia by analysing the raw CGM data using the following methods: After the CGM data is cleaned and separated into full days (i.e., >24 h of uninterrupted data), maximum glucose and the time it occurs will be calculated for each day of the two-week monitoring period. The average time of day that peak hyperglycaemia occurs will be then determined for each participant —if peak hyperglycaemia occurs at the same time of day (or within ~30 min) on five or more occasions over the 14 d CGM period, that time of day will be identified as the time of peak hyperglycaemia. Alternatively, time of peak hyperglycaemia will be calculated as an average from 14 days of continuous glucose measurements. Time of peak hyperglycaemia will be re-assessed following the waitlist period for participants initially randomised to the WLC group and again in the ExPeak group for the three-month follow up.

[INSERT GLUCOSE PATTERN INSIGHT EXAMPLE HERE]

Outcome Measures

The primary outcome is the change in HbA1c following the eight-week intervention. Secondary outcome measures will examine additional indices of glycaemic control (via CGM derived variables [including 24 h mean, area under the curve, glycaemic variability, time in range etc.] and a mixed meal tolerance test [MMTT]), vascular function (endothelial function and arterial stiffness), metabolic control (blood lipids and inflammation) and body composition (BMI, total and regional fat, and fat-free mass). Tertiary outcome measures will focus on the efficacy, feasibility, and adherence to exercise prescription (accelerometer and surveys). Apart from the mid-intervention assessment, participants will resume normal daily living (not exercise at their prescribed time) to assess training effects.

Glycaemic Control

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The primary outcome of glycaemic control will be assessed by measuring HbA1c. A finger prick blood sample will be collected using a HbA1c (~2 µL) specific test disc and immediately analysed with the Cobas b 101 System (Roche Diagnostics).

Secondary glycaemic outcomes will also be assessed with CGM and a MMTT (low glycaemic index, Glucerna©). From each two-week CGM, we will calculate mean 24 h glucose, 24 h and 3 h postprandial area under the curve (AUC) and incremental area under the curve (iAUC) calculated using the trapezoid method [24], hyperglycaemia (time spent ≥10 mmol/L), glycaemic variability (mean amplitude of glycaemic variability [MAGE]) and nocturnal glucose profiles. We will also calculate mean glucose, total AUC and iAUC for 2 h following the MMTT. The MMTT will begin after an overnight fast (>10 h), and blood glucose will be measured with the CGM and finger pricks (0, 15, 30, 60, 90 and 120 min) following drink consumption.

Metabolic Control

Metabolic control will be assessed by measuring blood lipids (triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein) and inflammation (CRP). Finger prick blood samples will be collected via lipid (~19 µL) or inflammation (~12 µL) specific test discs and immediately analysed with the Cobas b 101 System.

Body Composition

Waist to hip ratio, height, and weight will be measured to the nearest 0.1 cm and 0.1 kg, respectively, using standard scales, a stadiometer and measuring tape. Total and regional fat and fat-free mass will be measured by dual-energy x-ray absorptiometry ([DEXA], MedixDR Whole Body DEXA, SYD, AU).

Vascular Function

Endothelial function will be assessed by measuring endothelium-dependent flow-mediated dilation (FMD). This technique uses ultrasound imaging (Terason uSmart® 3300) of the brachial artery. Following 10-15 min of laying supine (at rest), a longitudinal section of the brachial artery, 2-3 cm above the antecubital fossa, will be imaged using B-mode ultrasound imaging (insonation angle of 60°). A blood pressure cuff placed around the forearm, 1-2 cm below the olecranon

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process, will then be rapidly inflated to ~60 mmHg above resting systolic blood pressure for 5 min. Brachial artery diameter and blood flow velocity will be recorded for 1 min before cuff inflation (baseline), ~30 s prior to cuff release (ischemic stimulus), and 3 min following cuff release (recovery) [25, 26]. The ~5 min recording will then be analysed with custom-designed edge-detection and wall-tracking software (Cardiovascular Suite, Quipu, Italy) which reduces user bias and increases accuracy. FMD will be reported as an absolute change in artery diameter (absolute FMD = $\text{postocclusion}_{\text{mean diameter}} - \text{preocclusion}_{\text{mean diameter}}$), and a relative change in artery diameter from baseline [%FMD = 100 × (absolute FMD/$\text{preocclusion}_{\text{mean diameter}}$)]. Allometric scaling will be used to account for potential confounders from baseline diameter [26, 27].

Blood flow (mL/min) will be measured using non-invasive Doppler from the cross-sectional area and blood velocity [velocity × π × (diameter2/4) × 60]. Shear rate (s-1) will then be determined from the diameter and velocity measures (four times velocity/diameter) [28]. Shear rate area under the curve (SR_{AUC}) will automatically be calculated from the diameter and velocity measures from the time of cuff release to peak dilation of the artery. Antegrade and retrograde mean blood velocities will be used to calculate baseline antegrade and retrograde shear rates (four times mean baseline antegrade or retrograde velocity ÷ mean baseline diameter), and the mean blood flow to mean arterial pressure ratio will be used to measure vascular conductance (mL/min/mmHg) [25, 26].

Central arterial stiffness will be assessed via pulse wave analysis (PWA) and pulse wave velocity (PWV) measurements (SphygmoCor® XCEL System, AtCor Medical). PWA will be used to measure central blood pressure. A brachial blood pressure cuff will be inflated and the central aortic pressure waveform, derived from pulsations at the brachial artery, will be recorded for 5 s and then automatically analysed through the SphygmoCor software. Key parameters of central blood pressure and arterial stiffness will be determined from the aortic waveform including systolic pressure, diastolic pressure, pulse pressure, aortic pressure, augmentation index and mean arterial pressure. PWV will be measured by holding a tonometer on the carotid artery for 10-15 s, while a femoral blood pressure cuff is automatically inflated. Once fully inflated, the femoral cuff and carotid tonometer will simultaneously record a 10 s capture of the carotid and femoral pressure waveforms. PWV will then be calculated by dividing the carotid-femoral distance by the pulse

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transit time; the carotid-femoral distance will be calculated by subtracting the proximal distance (distance between the carotid artery and sternal notch) from the distal distance (distance between the sternal notch and proximal edge of the femoral cuff) [PWV (m/s) = (distal – $proximal_{distance}$)/transit time] [29]. Measurements will be performed in duplicate. A third measurement will be taken if the difference between the two PWV values is >0.5 m/s and the average of the three values will be used.

An automatic blood pressure monitor (Oscar2 Ambulatory Blood Pressure Monitor with SphygmoCor interfacing, SunTech Medical) will also be used to continuously assess blood pressure and pulse wave analyses every hour for 24 hours. We will report 24 h blood pressure as an average of 24 measurements.

Diet and Physical Activity Monitoring

Participants will complete a 7 d diet record during each two-week monitoring period. Food diaries will be analysed (using FoodWorks10 Nutrition Software) to confirm macronutrient composition and total energy intake are consistent throughout the study period. Physical activity will be monitored during the same 7 d period using an accelerometer (ActiGraph Bluetooth® Smart wGT3X-BT), worn around the waist during wake hours. Physical activity and sedentary time will be compared between groups at each timepoint during wake hours. The accelerometers will also be used to confirm exercise intensity and compliance to the exercise prescription. A heart rate monitor (Polar H7 Bluetooth® Heart Rate Monitor) will be worn during the midpoint monitoring period on the same days as the accelerometer, only during the exercise sessions, to assess exercise intensity.

Adherence and Lifestyle Questionnaires

Participants will complete a quality of life (SF-36) survey and a self-regulatory efficacy and physical activity questionnaire during each two-week monitoring period. Participants will also complete three surveys during the follow-up period, one at the end of each month that is specific to their exercise group, to assess adherence to exercise prescription between the ExPeak and control groups. Surveys will include questions on known perceived facilitators and barriers to filling the exercise prescription and, in turn, support or aggravation of intervention efficacy. Such

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factors will include the availability of nearby green and open spaces (e.g. beaches, parks) [30] and levels of felt safety to exercise outdoors during the day and evening hours [31].

Remote Participants

Participants who cannot attend the university (e.g., due to COVID-19 restrictions) for in-lab assessments will receive a home-based testing kit (via mail) which includes: a dried blood spot test kit (ZRT Laboratory kit for measurement of HbA1c, lipids, CRP, and insulin), CGM, accelerometer and Glucerna MMTT drink. Instructions will be provided and followed-up via a phone or video call. All other study protocols will be the same, however data for the DEXA and vascular assessments will not be available.

Statistical Analysis

Sample size

Sample size was calculated based on a previous study investigating the effect of exercise timing in people with T2D, where they reported a difference of -0.6 mmol/L in 24 h blood glucose between exercise performed in the morning vs afternoon [14]. To detect a clinically meaningful change in HbA1c between groups, with a moderate effect size of 0.2, statistical power of 80%, and an alpha level of 0.05 (two-sided), a total of ~54 participants (27 per intervention group) is required for this trial. The power calculation is based on the change in HbA1c from a previous trial in our lab in people with T2D [32]. To account for an expected 30% drop-out rate, 70 participants will be recruited.

Statistics

This study will be reported according to the CONSORT 2010 Statement and the CONSERVE 2021 Statement for randomised controlled trials. Descriptive statistics will be assessed (means, standard deviation and frequencies), and histograms, Q-Q plots and the Shapiro-Wilk test will be used to identify outliers and test for normality. Linear mixed models (with time x intervention, and main effect of time) will be used to assess differences between groups, for primary (HbA1c) and secondary (CGM, MMTT, vascular function, metabolic control, and body composition) outcomes. Tertiary outcomes (e.g., adherence to the exercise prescription) will be analysed from the accelerometer and follow-up surveys (Qualtrics^{XM}). Attention to treat analyses will be performed

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for primary analyses (Phase 1) and per protocol analyses will be undertaken for secondary and tertiary outcomes (Phase 2). Data with skewed distribution will be log-transformed or square-rooted prior to the statistical analysis. For the three-month follow-up, intention to treat analysis will be used and missing data will not be imputed.

Patient and Public Involvement

No patient involved.

ETHICS AND DISSEMINATION

This research has been reviewed and approved by the University of Wollongong Human Research Ethics Committee (2019/ETH09856). This trial was prospectively registered at the Australian New Zealand Clinical Trials Registry (ACTRN12619001049167). Participants will remain anonymous, and all collected data will be de-identified and coded. An alpha-numerical code (stored on a password protected central spreadsheet) will be allocated to each participant and used for identification on all subsequent paperwork. All results from the study will be published as peer-reviewed articles in international journals, presented at international conferences and promoted through social media. Changes to the protocol due to COVID-19 will be reported according to the CONSERVE 2021 Statement [33].

DISCUSSION

The primary objective of this trial is to determine if strategically timing exercise, to reduce daily peak hyperglycaemia, will improve glycaemic control and lower cardiovascular risk factors in people with T2D. This is the first study to investigate whether prescribing exercise that is personalised to target daily peak hyperglycaemia, using CGM, can improve cardiovascular risk factors in T2D. Based on evidence from prior research [11, 34–36], it is hypothesised that strategically timing daily exercise to attenuate peak hyperglycaemia will improve glycaemic control (HbA1c), and the reduction in peak glycemia will improve vascular function (endothelial function and arterial stiffness), blood lipids and CRP, more than exercising not at peak hyperglycaemia or control standard-care (i.e., physical activity guidelines).

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Recent evidence suggests exercise timing may be important to offset circadian rhythms [14] and to target postprandial hyperglycaemia [11] in T2D. However, there are no recommendations for exercise timing in the current physical activity guidelines (i.e., physical activity can be accumulated at any time throughout the week). Further, adherence to the current recommendations is notoriously poor. Regardless of the effectiveness for an intervention to improve diabetes management, findings will only be translatable if patients comply with and adopt to the treatment over the long-term. Therefore, adherence to prescribed daily exercise time (i.e., creating more of a habit) will be assessed for three months following the eight-week intervention. Exercising at the time of peak hyperglycaemia may improve self-efficacy to the exercise prescription, as results from the CGM data (pre/mid/post eight-week intervention) will allow participants to see the direct impact of exercise on blood glucose levels. Use of CGM in this trial not only offers the distinct advantage of determining time of peak hyperglycaemia, but will also allow us to examine any changes in daily glycaemic patterns, such as glycaemic variability, which are more closely related to cardiovascular risk than HbA1c [37]. If strategically timing exercise to attenuate peak hyperglycaemia improves long-term glycaemic control (HbA1c), reduces cardiovascular risk (endothelial dysfunction and arterial stiffness), and improves exercise adherence then this may be an alternative recommendation for physical activity prescription in people with T2D.

Strengths and Limitations

This is the first randomised controlled trial to examine the effects of personalising exercise timing to attenuate peak hyperglycaemia (determined via continuous glucose monitoring technology) on cardiometabolic and vascular health outcomes in individuals with type 2 diabetes. This study will be conducted in free-living conditions, with exercise performed at home and contact/delivery of *Phase 1* (8-week exercise intervention) mirroring standard-care (five telehealth calls with an exercise physiologist), while *Phase 2* (3-month follow-up) will assess adherence to the exercise prescription (with minimal contact from the research team); thus informing us of the real-world applicability of the proposed exercise prescription. In addition, this study will utilise a variety of data collection methods (in-lab and free-living) to objectively measure cardiometabolic health, vascular function, physical activity, and behaviour change across the trial. Due to the COVID-19 pandemic remote participants from across rural and urban Australia will be included, allowing for a wider range of individuals to be recruited while adhering to the COVID-19 restrictions. However,

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this is also a limitation as the vascular and body composition measures will be excluded for those who cannot attend university assessments, and dried blood spot testing kits will be used rather than the gold-standard plasma measurement of HbA1c. Finally, a limitation of the waitlist control group is the potential overestimation of intervention effects and bias in favour of the treatment group. Nevertheless, inclusion of the waitlist control group will provide insight on the cause-effect relationship between the intervention and subsequent health outcomes/behaviour changes, as these participants will follow a delayed-start design (i.e., will receive treatment following the waitlist period), thus allowing for direct comparisons to be made under various conditions with reduced error variance and not withholding treatment to individuals.

COMPETING INTERESTS

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

CRC drafted the manuscript. MEF, CRC, BMR, and TAB conceived and contributed to the design of the study and plan for analysis. MEF and CRC will conduct the study, collect data, and analyse data. MEF, CRC and TAB will analyse and interpret the data. All authors reviewed and approved the final manuscript.

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FIGURES

Figure 1. Study Design and Flow Chart. Eligible participants will be randomised (N=54) to one of three groups: i) exercise at peak hyperglycaemia (ExPeak; N=18), ii) exercise after peak hyperglycaemia (NonPeak; N=18), or iii) waitlist control (WLC; N=18). Participants randomised

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to WLC will be re-randomised to ExPeak or NonPeak after the waitlist period. Following the eight-week intervention (Phase 1), the ExPeak (N=27) group will continue to exercise at peak hyperglycaemia, whereas the NonPeak (N=27) group will become the control (CTL; N=27) group for the three-month follow-up (Phase 2). Participants in the WLC and CTL groups will receive standard care advice to exercise in accordance with the World Health Organization physical activity guidelines.

Figure 2. TIMELINE OF STUDY PROTOCOL. Participants randomised to the waitlist control (WLC) group will undergo measures before and after an eight-week waitlist control period. Then are randomised to one of two intervention groups for eight weeks: i) exercise at peak hyperglycaemia ([ExPeak] ExRx: begin exercise ~30 min before peak hyperglycaemia) or ii) exercise after peak hyperglycaemia ([NonPeak] ExRx: begin exercise ~90 min after peak hyperglycaemia). All groups undergo pre-intervention CGM to measure time of peak hyperglycemia prior to interventions. **PHASE 1. Eight-week intervention:** Both intervention groups will perform ~22 min of daily exercise at their prescribed time. Participants will receive two phone consults and five telehealth video consults (via zoom or skype) with an Accredited Exercise Physiologist. **PHASE 2. Three-month follow-up:** The ExPeak group will continue to exercise for ~22 min/day at peak hyperglycaemia and the NonPeak group will exercise according to the physical activity guidelines. Three adherence surveys will be conducted (at the end of each month), but no formal contact. **Free Living Assessments:** 14 d CGM, 2 h MMTT, 7 d ActiGraph activity monitoring, 7 d HR monitoring (midpoint only; Polar Bluetooth HR monitor worn on same days as ActiGraph, only during prescribed exercise), 7 d diet record, quality of life survey, and self-regulatory efficacy and physical activity questionnaire. **In-Lab Assessments:** i) blood sample HbA1c, CRP, and blood lipids (TG, TC, HDL, and LDL); ii) vascular measures FMD and arterial stiffness via PWV/PWA; and iii) anthropometrics (height and weight) and body composition DEXA.

Abbreviations: waitlist control, WLC; exercise at peak hyperglycaemia (intervention group), ExPeak; exercise after peak (intervention group), NonPeak; exercise prescription, ExRx; accredited exercise physiologist, AEP; continuous glucose monitoring, CGM; mixed meal tolerance test, MMTT; heart rate, HR; glycated hemoglobin, HbA1c; c-reactive protein, CRP; triglyceride, TG; total cholesterol, TC; high-density lipoprotein, HDL; low-density lipoprotein,

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LDL; flow-mediated dilation, FMD; pulse wave velocity, PWV; pulse wave analysis, PWA; and dual-r-ray absorptiometry, DEXA.

Figure 3. Example 'Glucose Pattern Insights' Report, via LibreView, of a 24 h blood glucose curve averaged from 14 days of continuous glucose measurements.

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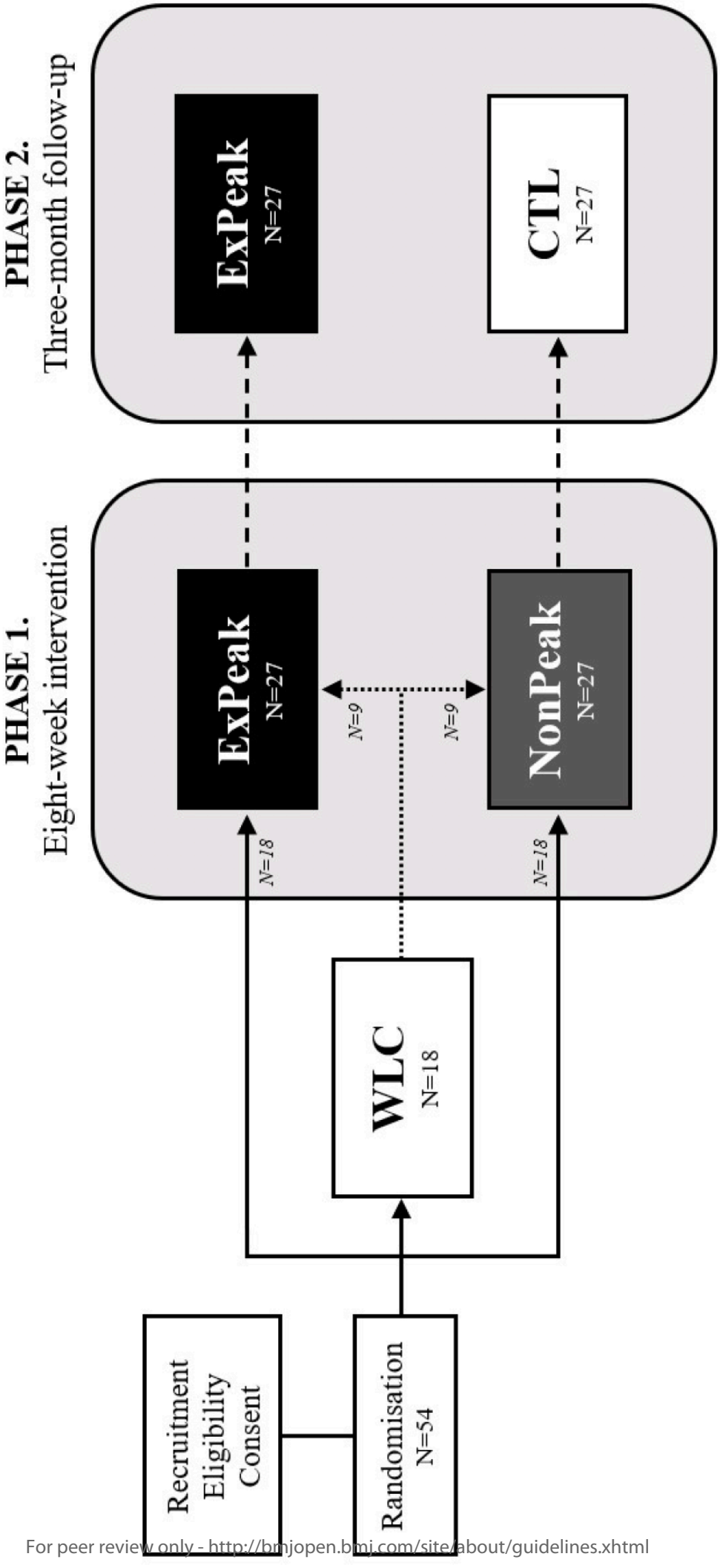
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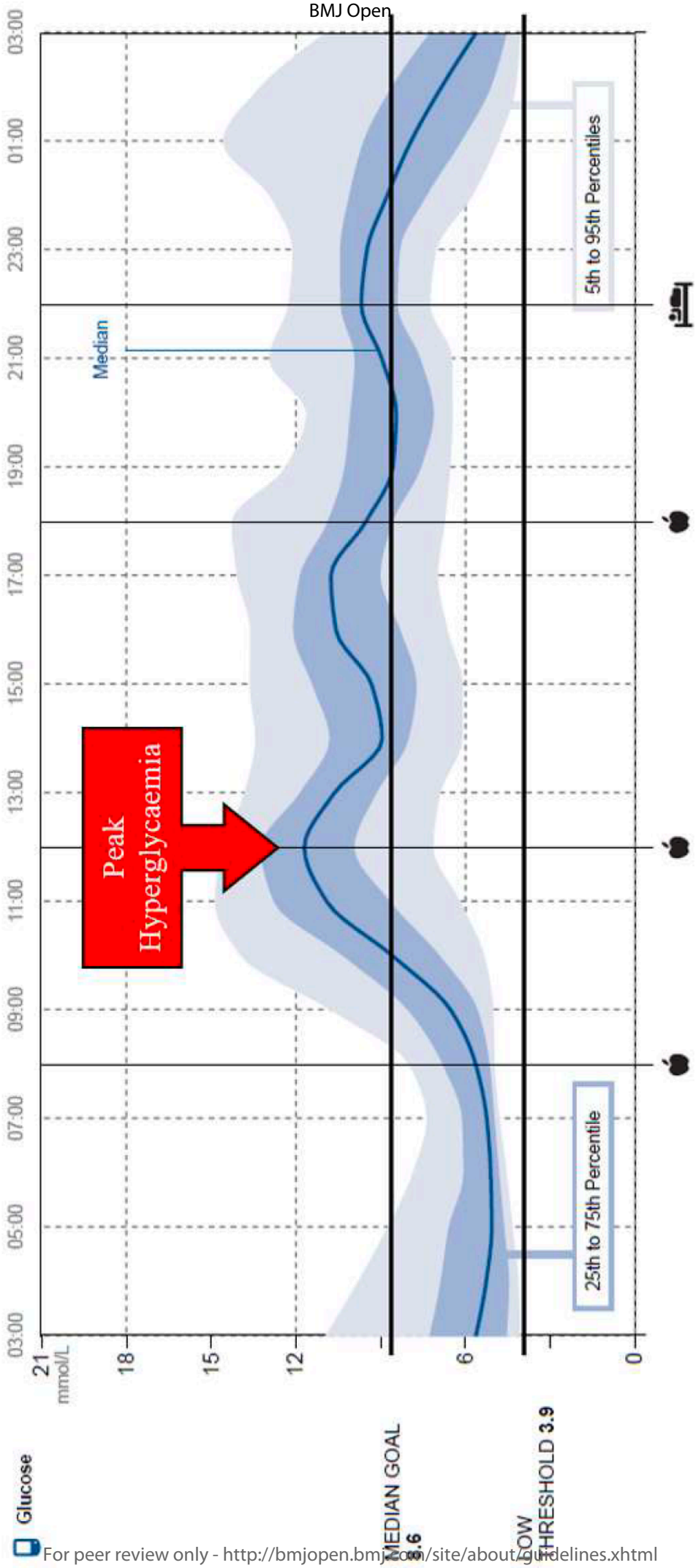
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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

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		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14

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Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	1
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	1
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6

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Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	2
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	22
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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Personalising activity to target peak hyperglycaemia and improve cardiometabolic health in people with type 2 diabetes: protocol for a randomised controlled trial

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Personalising activity to target peak hyperglycaemia and improve cardiometabolic health in people with type 2 diabetes: protocol for a randomised controlled trial

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ABSTRACT

Introduction: The benefits of physical activity for glycaemic control in type 2 diabetes (T2D) are well-known. However, whether established glycaemic and cardiovascular benefits can be maximised by exercising at a certain time of day is unknown. Given postprandial glucose peaks contribute to worsening glycated haemoglobin (HbA1c) and cardiovascular risk factors, and that exercise immediately lowers blood glucose, prescribing exercise at a specific time of day to attenuate peak hyperglycaemia may improve glycaemic control and reduce the burden of cardiovascular disease in people with T2D.

Methods and analysis: A single centre randomised controlled trial will be conducted by the University of Wollongong, Australia. Individuals with T2D (N=70, aged 40-75 years, body mass index 27-40 kg/m^2) will be recruited and randomly allocated (1:1), stratified for sex and insulin, to one of three groups: i) exercise at time of peak hyperglycaemia (ExPeak, personalised), ii) exercise not at time of peak hyperglycaemia (NonPeak), or iii) waitlist control (WLC, standard-care). The trial will be five months, comprising an eight-week intervention and three-month follow up. Primary outcome is the change in HbA1c pre- to post-intervention. Secondary outcomes include vascular function (endothelial function and arterial stiffness), metabolic control (blood lipids and inflammation) and body composition (anthropometrics and dual-energy x-ray absorptiometry [DEXA]). Tertiary outcomes will examine adherence.

Ethics and dissemination: The joint UOW and ISLHD Ethics Committee approved protocol (2019/ETH09856) prospectively registered at the Australian New Zealand Clinical Trials Registry. Written informed consent will be obtained from all eligible individuals prior to commencement of the trial. Study results will be published as peer-reviewed articles, presented at national/international conferences and media reports.

Trial registration number: ACTRN12619001049167

Keywords: T2D, exercise, timing, adherence, peak hyperglycaemia, cardiovascular risk

Strengths and Limitations of this Study

- A strength of this randomised controlled trial is the use of continuous glucose monitoring for personalising exercise timing to attenuate peak hyperglycaemia, as well as the inclusion of an active placebo control condition.

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- This study will employ a variety of data collection methods (in-lab and free-living) to measure changes in cardiovascular and metabolic health, physical activity and behaviour change.
- Recruitment of participants across Australia (urban and rural) with remote delivery is both a strength in diversity and inclusion and a limitation given the reliance on dried blood spot home collection, and vascular/body composition measures will not be available for those unable to attend the university visits.
- This study is robust in its adaptation to the COVID-19 pandemic, while retaining high-quality study design and data collection with strong external validity.

INTRODUCTION

Approximately 463 million adults are living with type 2 diabetes (T2D) and this number is expected to increase to 700 million by 2045 [1]. Individuals with T2D have a twofold greater risk of developing atherosclerotic cardiovascular disease (CVD; e.g., myocardial infarction, stroke, etc.) and CVD accounts for ~70% of deaths in T2D patients [2]. T2D is characterised by elevated fasting and postprandial blood glucose levels [3]. Large excursions in blood glucose, especially during the postprandial period (i.e., postprandial hyperglycaemia) cause oxidative stress, inflammation, and endothelial dysfunction, which mechanistically links impaired glucose regulation with the development of CVD in people with T2D [4, 5]. Acute and chronic exercise training improve blood glucose regulation and reduce cardiovascular risk factors. The benefits of exercise training on glycaemic control are largely attributed to the accumulated effects of individual exercise sessions [6, 7] increasing contraction- and insulin-mediated glucose uptake [7, 8] consistently and overtime. The current guidelines for physical activity recommend adults accumulate ~150-300 min of moderate intensity aerobic activity throughout the week to improve or maintain health [9], including glycaemic control (i.e., glycated haemoglobin [HbA1c]) in people with T2D [10]. However, mounting evidence [11–15] indicates that exercise timing (e.g., pre- vs post-meal, or morning vs afternoon) influences glycaemic responses, yet there are no consistent guidelines on exercise timing in any current physical activity recommendations globally.

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Multiple systematic reviews have recently examined the effects of exercise timing on measures of glycaemic control in people with T2D and suggest the best time to exercise is within the first few hours after a meal [11–13]. However, performing exercise at different times of the day (i.e., morning vs afternoon) has also shown to influence glycaemic responses [14, 15]. For example, Savikj et al. (2019) recently demonstrated that two weeks of high intensity interval training (HIIT; three days/week) performed in the afternoon improved 24 h glucose concentration by -0.6 mmol/L more than HIIT in the morning [14], whereas a separate study by Teo et al. (2019) found no significant differences in any glycaemic outcomes (HbA1c, fasting or postprandial glucose) after 12 weeks of exercise (three days/week) performed in the morning vs afternoon [15]. Given the inconsistent findings and broad recommendations in the current literature (i.e., exercise timing relative to time of day or meal consumption), a more personalised approach may be needed to target CVD and for practitioners to prescribe exercise timing for people with T2D. Postprandial hyperglycaemia is linked to CVD and timing exercise to specifically target the largest postprandial excursion (i.e., peak hyperglycaemia) of the day may lead to greater glycaemic benefits and reduced cardiovascular risk.

It is unknown if prescribing daily exercise at a specific time of day, to attenuate peak hyperglycaemia, will lead to greater improvements in HbA1c compared to the current physical activity guidelines of accumulating ~150-300 min/week at any time. Further, the vascular effects of exercising specifically to attenuate peak hyperglycaemia are unknown. The endothelium is a key regulator of vascular homeostasis and endothelial function is an early risk factor for CVD [16, 17]. Hyperglycaemia increases production of reactive oxygen species [18] and the resulting oxidative stress reduces vascular homeostasis (i.e., by increasing vasoconstriction and decreasing vasodilation) which can lead to endothelial dysfunction and CVD over time. A longer-term intervention of daily exercise is now warranted to garner a better understanding of exercise timing on glycaemic control and to examine whether exercising at the time of peak hyperglycaemia improves HbA1c and reduces cardiovascular risk factors.

The aim of this trial is to determine whether exercising to attenuate peak hyperglycaemia (exercise beginning ~30 min before peak hyperglycaemia) improves glycaemic control (HbA1c and 24 h mean, fasting and postprandial glucose) and reduces cardiovascular risk factors (including lipids,

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c-reactive protein, vascular function), more than exercising not at time of peak hyperglycaemia (exercise ~90 min after peak hyperglycaemia) or at any time of the day (no prescribed exercise time i.e., physical activity guidelines) in people with T2D. The efficacy, feasibility, and adherence to prescribing an exercise time will also be explored during a three-month follow-up. Given that postprandial hyperglycaemia is associated with worsening HbA1c [19] and endothelial dysfunction [20] in T2D, we hypothesise that exercising to attenuate peak hyperglycaemia will lead to the greatest improvements in glycaemic control, which in turn will improve vascular function and reduce cardiovascular risk.

METHODS AND ANALYSIS

A single centre randomised controlled trial will be conducted at the University of Wollongong, Australia from July 2019 to December 2022 (Figure 1). Participants will be recruited through online advertising using a clinical trials recruitment company (Trial Facts). A medical screening questionnaire and informed consent (Supplementary Material) will be obtained from all eligible individuals prior to participation. Study data will be collected and managed using the secure online REDCap (Research Electronic Data Capture) tools hosted at the University of Wollongong, Australia [21, 22].

Participants

Inclusion criteria:

- Physician diagnosed T2D (registration with the National Diabetes Services Scheme)
- HbA1c between 6.5-9.0%
- Aged between 40 and 75 years
- BMI between 27-40 kg/m^2
- Diabetes treated with lifestyle, oral medications and/or intermediate/long-acting insulin
- Stable weight for previous 3 months (± 4 kg)
- Stable medications for previous 3 months
- Able to speak and understand English

Exclusion criteria:

- Any absolute contraindications to exercise (i.e., musculoskeletal/joint injury, etc.)

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- Presence or history of CVD, kidney or liver disease
- Diagnosed diabetes complications i.e., neuropathy, retinopathy etc.
- Diabetes treated with short acting insulin
- Uncontrolled hypertension (>160/90 mmHg)
- >150 min of moderate to vigorous intensity exercise/week (per Godin leisure time physical activity questionnaire)

Study Design

Seventy males and females (aged 40-75 years, BMI 27-40 kg/m^2) will be recruited and randomised to one of three groups for eight weeks: i) exercise at time of peak hyperglycaemia (ExPeak), ii) exercise not at time of peak hyperglycaemia (NonPeak) or, iii) waitlist control (WLC). Participants allocated to the WLC group will be re-randomised to the ExPeak or NonPeak intervention group following the waitlist period. During the eight-week intervention (Phase 1), all groups will be prescribed ~150 min/week of physical activity as per the current guidelines. The intervention groups will be prescribed daily exercise at a specific time. During the exercise intervention, participants will have five telehealth consults with an accredited exercise physiologist, in line with Australia's Medicare health plan for people with diabetes. An automatic computer-generated random number table will be used to perform random allocation of participants (1:1 ratio), stratified for sex and exogenous insulin usage. A sealed envelope system will be used to blind researchers from group allocations. Allocations will be sealed in an opaque envelope (by a person independent to the clinical trial) until a participant is enrolled and needing to commence the intervention.

Participants will undergo a three-month follow-up (Phase 2) where adherence to exercising at a prescribed time (with minimal contact from the research team) will be assessed. During Phase 2, participants in the ExPeak group will be advised to continue exercising daily at their time of peak hyperglycaemia and participants in the NonPeak group will be advised to exercise in accordance with the World Health Organization 2020 guidelines for physical activity i.e., accumulate ~150-300 min of physical activity per week at any time of day [9], thus becoming the control group.

[INSERT STUDY DESIGN FIGURE HERE]

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Interventions

All exercise sessions will be performed in a free-living setting (home-based) for the duration of this trial. Participants in the ExPeak and NonPeak groups will be prescribed ~22 min of daily moderate-intensity physical activity (aerobic exercise e.g., walking, cycling, swimming, etc.) for eight weeks, to align with the physical activity guidelines of accumulating at least 150 min of aerobic activity per week. The pre-intervention Continuous Glucose Monitoring (CGM) data (*outlined below*) will be used to determine time of peak hyperglycaemia. The ExPeak group will begin exercising ~30 min before their peak hyperglycaemia typically occurs and the NonPeak group will begin exercising ~90 min after their peak hyperglycaemia typically occurs. Participants in the control groups will exercise in accordance with the physical activity guidelines [9]. Exercise intensity will be determined using the Borg Scale to indicate Rate of Perceived Exertion, which uses numbered categories from 6-20 (i.e., no exertion at all to maximal exertion) to gauge how hard a person 'feels' they are working [23]. Daily exercise should be completed as one continuous bout but may be accumulated over a 30 min period depending on individual needs (ideally accumulated in bouts of >10 min, interspersed with short periods of rest). Participants will have two phone consults and five telehealth video consults with an accredited exercise physiologist on alternate weeks throughout the eight-week exercise intervention, in addition to maintaining standard care treatment with health care professionals and habitual medication and diet.

Experimental Protocol

The intervention period will be five months in total, with the eight-week intervention (Phase 1) commencing after two weeks of pre-intervention monitoring, and the three-month follow-up (Phase 2) commencing after two weeks of post-intervention monitoring. Pre- and post-assessments will be conducted at the University of Wollongong to evaluate glycaemic and metabolic control, vascular function, and body composition (Figure 2). Participants will be instructed to abstain from physical activity for >24 h and to fast for ~10 h before each in-lab assessment.

A two-week monitoring period will be conducted pre-intervention, midway through, post-intervention and after the three-month follow-up. Participants in the WLC group will have two additional weeks of baseline monitoring before the waitlist period commences. Participants will

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maintain normal daily activity and dietary patterns during each monitoring period, except for the midpoint assessment where they will continue to follow intervention protocol. During the three-month follow-up, participants will complete three short surveys (one at the end of each month, seven questions each) to assess adherence to the exercise prescription but will otherwise have no formal contact with the research team (Figure 2). Other than the prescribed exercise, participants will be asked to maintain normal dietary habits and medication usage throughout the study period.

[INSERT PROTOCOL TIMELINE FIGURE HERE]

Determination of Peak Hyperglycaemia

The 'Glucose Pattern Insights' report (automatically generated via LibreView software), for the two-week pre-intervention CGM (Freestyle Libre, Abbott), will be used to determine the average time that peak hyperglycaemia occurs for each participant (Figure 3). Trained researchers will verify time of peak hyperglycaemia by analysing the raw CGM data using the following methods: After the CGM data is cleaned and separated into full days (i.e., >24 h of uninterrupted data), maximum glucose and the time it occurs will be calculated for each day of the two-week monitoring period. The average time of day that peak hyperglycaemia occurs will be then determined for each participant —if peak hyperglycaemia occurs at the same time of day (or within ~30 min) on five or more occasions over the 14 d CGM period, that time of day will be identified as the time of peak hyperglycaemia. Alternatively, time of peak hyperglycaemia will be calculated as an average from 14 days of continuous glucose measurements. Exercise for the ExPeak group will be prescribed in relation to the highest peak (i.e., greatest glucose excursion); if there are multiple glucose excursions throughout the day with the same peak level, participants will be given an option of the times to exercise, but must stick with one time for the duration of the intervention. Time of peak hyperglycaemia will be re-assessed following the waitlist period for participants initially randomised to the WLC group and again in the ExPeak group for the three-month follow up.

[INSERT GLUCOSE PATTERN INSIGHT EXAMPLE HERE]

Outcome Measures

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The primary outcome is the change in HbA1c following the eight-week intervention. Secondary outcome measures will examine additional indices of glycaemic control (via CGM derived variables [including 24 h mean, area under the curve, glycaemic variability, time in range etc.] and a mixed meal tolerance test [MMTT]), vascular function (endothelial function and arterial stiffness), metabolic control (blood lipids and inflammation) and body composition (BMI, total and regional fat, and fat-free mass). Tertiary outcome measures will focus on the efficacy, feasibility, and adherence to exercise prescription (accelerometer and surveys). Apart from the mid-intervention assessment, participants will resume normal daily living (not exercise at their prescribed time) to assess training effects.

Glycaemic Control

The primary outcome of glycaemic control will be assessed by measuring HbA1c. A finger prick blood sample will be collected using a HbA1c (~2 µL) specific test disc and immediately analysed with the Cobas b 101 System (Roche Diagnostics).

Secondary glycaemic outcomes will also be assessed with CGM and a MMTT (low glycaemic index, Glucerna©). From each two-week CGM, we will calculate mean 24 h glucose, 24 h and 3 h postprandial area under the curve (AUC) and incremental area under the curve (iAUC) calculated using the trapezoid method [24], hyperglycaemia (time spent ≥10 mmol/L), glycaemic variability (mean amplitude of glycaemic variability [MAGE]) and nocturnal glucose profiles. We will also calculate mean glucose, total AUC and iAUC for 2 h following the MMTT. The MMTT will begin after an overnight fast (>10 h), and blood glucose will be measured with the CGM and finger pricks (0, 15, 30, 60, 90 and 120 min) following drink consumption.

Metabolic Control

Metabolic control will be assessed by measuring blood lipids (triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein) and inflammation (CRP). Finger prick blood samples will be collected via lipid (~19 µL) or inflammation (~12 µL) specific test discs and immediately analysed with the Cobas b 101 System.

Body Composition

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Waist to hip ratio, height, and weight will be measured to the nearest 0.1 cm and 0.1 kg, respectively, using standard scales, a stadiometer and measuring tape. Total and regional fat and fat-free mass will be measured by dual-energy x-ray absorptiometry ([DEXA], MedixDR Whole Body DEXA, SYD, AU).

Vascular Function

Endothelial function will be assessed by measuring endothelium-dependent flow-mediated dilation (FMD). This technique uses ultrasound imaging (Terason uSmart® 3300) of the brachial artery. Following 10-15 min of laying supine (at rest), a longitudinal section of the brachial artery, 2-3 cm above the antecubital fossa, will be imaged using B-mode ultrasound imaging (insonation angle of 60°). A blood pressure cuff placed around the forearm, 1-2 cm below the olecranon process, will then be rapidly inflated to ~60 mmHg above resting systolic blood pressure for 5 min. Brachial artery diameter and blood flow velocity will be recorded for 1 min before cuff inflation (baseline), ~30 s prior to cuff release (ischemic stimulus), and 3 min following cuff release (recovery) [25, 26]. The ~5 min recording will then be analysed with custom-designed edge-detection and wall-tracking software (Cardiovascular Suite, Quipu, Italy) which reduces user bias and increases accuracy. FMD will be reported as an absolute change in artery diameter (absolute FMD = $\text{postocclusion}_{\text{mean diameter}} - \text{preocclusion}_{\text{mean diameter}}$), and a relative change in artery diameter from baseline [%FMD = 100 × (absolute FMD/$\text{preocclusion}_{\text{mean diameter}}$)]. Allometric scaling will be used to account for potential confounders from baseline diameter [26, 27].

Blood flow (mL/min) will be measured using non-invasive Doppler from the cross-sectional area and blood velocity [velocity × π × (diameter2/4) × 60]. Shear rate (s-1) will then be determined from the diameter and velocity measures (four times velocity/diameter) [28]. Shear rate area under the curve (SR_{AUC}) will automatically be calculated from the diameter and velocity measures from the time of cuff release to peak dilation of the artery. Antegrade and retrograde mean blood velocities will be used to calculate baseline antegrade and retrograde shear rates (four times mean baseline antegrade or retrograde velocity ÷ mean baseline diameter), and the mean blood flow to mean arterial pressure ratio will be used to measure vascular conductance (mL/min/mmHg) [25, 26].

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Central arterial stiffness will be assessed via pulse wave analysis (PWA) and pulse wave velocity (PWV) measurements (SphygmoCor® XCEL System, AtCor Medical). PWA will be used to measure central blood pressure. A brachial blood pressure cuff will be inflated and the central aortic pressure waveform, derived from pulsations at the brachial artery, will be recorded for 5 s and then automatically analysed through the SphygmoCor software. Key parameters of central blood pressure and arterial stiffness will be determined from the aortic waveform including systolic pressure, diastolic pressure, pulse pressure, aortic pressure, augmentation index and mean arterial pressure. PWV will be measured by holding a tonometer on the carotid artery for 10-15 s, while a femoral blood pressure cuff is automatically inflated. Once fully inflated, the femoral cuff and carotid tonometer will simultaneously record a 10 s capture of the carotid and femoral pressure waveforms. PWV will then be calculated by dividing the carotid-femoral distance by the pulse transit time; the carotid-femoral distance will be calculated by subtracting the proximal distance (distance between the carotid artery and sternal notch) from the distal distance (distance between the sternal notch and proximal edge of the femoral cuff) [PWV (m/s) = (distal – $\text{proximal}_{\text{distance}}$)/transit time] [29]. Measurements will be performed in duplicate. A third measurement will be taken if the difference between the two PWV values is >0.5 m/s and the average of the three values will be used.

An automatic blood pressure monitor (Oscar2 Ambulatory Blood Pressure Monitor with SphygmoCor interfacing, SunTech Medical) will also be used to continuously assess blood pressure and pulse wave analyses every hour for 24 hours. We will report 24 h blood pressure as an average of 24 measurements.

Diet and Physical Activity Monitoring

Participants will complete a 7 d diet record during each two-week monitoring period. Food diaries will be analysed (using FoodWorks10 Nutrition Software) to confirm macronutrient composition and total energy intake are consistent throughout the study period. Physical activity will be monitored during the same 7 d period using an accelerometer (ActiGraph Bluetooth® Smart wGT3X-BT), worn around the waist during wake hours. Physical activity and sedentary time will be compared between groups at each timepoint during wake hours. The accelerometers will also be used to confirm exercise intensity and compliance to the exercise prescription. A heart rate

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monitor (Polar H7 Bluetooth® Heart Rate Monitor) will be worn during the midpoint monitoring period on the same days as the accelerometer, only during the exercise sessions, to assess exercise intensity.

Adherence and Lifestyle Questionnaires

Participants will complete a quality of life (SF-36) survey and a self-regulatory efficacy and physical activity questionnaire during each two-week monitoring period. Participants will also complete three surveys during the follow-up period, one at the end of each month that is specific to their exercise group, to assess adherence to exercise prescription between the ExPeak and control groups. Surveys will include questions on known perceived facilitators and barriers to filling the exercise prescription and, in turn, support or aggravation of intervention efficacy. Such factors will include the availability of nearby green and open spaces (e.g. beaches, parks) [30] and levels of felt safety to exercise outdoors during the day and evening hours [31].

Remote Participants

Participants who cannot attend the university (e.g., due to COVID-19 restrictions) for in-lab assessments will receive a home-based testing kit (via mail) which includes: a dried blood spot test kit (ZRT Laboratory kit for measurement of HbA1c, lipids, CRP, and insulin), CGM, accelerometer and Glucerna MMTT drink. Instructions will be provided and followed-up via a phone or video call. All other study protocols will be the same, however data for the DEXA and vascular assessments will not be available.

Statistical Analysis

Sample size

Sample size was calculated based on a previous study investigating the effect of exercise timing in people with T2D, where they reported a difference of -0.6 mmol/L in 24 h blood glucose between exercise performed in the morning vs afternoon [14]. To detect a clinically meaningful change in HbA1c between groups, with a moderate effect size of 0.2, statistical power of 80%, and an alpha level of 0.05 (two-sided), a total of ~54 participants (27 per intervention group) is required for this trial. The power calculation is based on the change in HbA1c from a previous trial in our

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lab in people with T2D [32]. To account for an expected 30% drop-out rate, 70 participants will be recruited.

Statistics

This study will be reported according to the CONSORT 2010 Statement and the CONSERVE 2021 Statement for randomised controlled trials. Descriptive statistics will be assessed (means, standard deviation and frequencies), and histograms, Q-Q plots and the Shapiro-Wilk test will be used to identify outliers and test for normality. Linear mixed models (with time x intervention, and main effect of time) will be used to assess differences between groups, for primary (HbA1c) and secondary (CGM, MMTT, vascular function, metabolic control, and body composition) outcomes. Tertiary outcomes (e.g., adherence to the exercise prescription) will be analysed from the accelerometer and follow-up surveys (Qualtrics^{XM}). Attention to treat analyses will be performed for primary analyses (Phase 1) and per protocol analyses will be undertaken for secondary and tertiary outcomes (Phase 2). Data with skewed distribution will be log-transformed or square-rooted prior to the statistical analysis. For the three-month follow-up, intention to treat analysis will be used and missing data will not be imputed.

Patient and Public Involvement

No patient involved.

ETHICS AND DISSEMINATION

This research has been reviewed and approved by the University of Wollongong Human Research Ethics Committee (2019/ETH09856). This trial was prospectively registered at the Australian New Zealand Clinical Trials Registry (ACTRN12619001049167). Written informed consent will be obtained from all eligible individuals prior to commencement of the trial. Participants will remain anonymous, and all collected data will be de-identified and coded. An alpha-numerical code (stored on a password protected central spreadsheet) will be allocated to each participant and used for identification on all subsequent paperwork. All results from the study will be published as peer-reviewed articles in international journals, presented at international conferences and promoted through social media. Changes to the protocol due to COVID-19 will be reported according to the CONSERVE 2021 Statement [33].

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DISCUSSION

The primary objective of this trial is to determine if strategically timing exercise, to reduce daily peak hyperglycaemia, will improve glycaemic control and lower cardiovascular risk factors in people with T2D. This is the first study to investigate whether prescribing exercise that is personalised to target daily peak hyperglycaemia, using CGM, can improve cardiovascular risk factors in T2D. Based on evidence from prior research [11, 34–36], it is hypothesised that strategically timing daily exercise to attenuate peak hyperglycaemia will improve glycaemic control (HbA1c), and the reduction in peak glycemia will improve vascular function (endothelial function and arterial stiffness), blood lipids and CRP, more than exercising not at peak hyperglycaemia or control standard-care (i.e., physical activity guidelines).

Recent evidence suggests exercise timing may be important to offset circadian rhythms [14] and to target postprandial hyperglycaemia [11] in T2D. However, there are no recommendations for exercise timing in the current physical activity guidelines (i.e., physical activity can be accumulated at any time throughout the week). Further, adherence to the current recommendations is notoriously poor. Regardless of the effectiveness for an intervention to improve diabetes management, findings will only be translatable if patients comply with and adopt to the treatment over the long-term. Therefore, adherence to prescribed daily exercise time (i.e., creating more of a habit) will be assessed for three months following the eight-week intervention. Exercising at the time of peak hyperglycaemia may improve self-efficacy to the exercise prescription, as results from the CGM data (pre/mid/post eight-week intervention) will allow participants to see the direct impact of exercise on blood glucose levels. Use of CGM in this trial not only offers the distinct advantage of determining time of peak hyperglycaemia, but will also allow us to examine any changes in daily glycaemic patterns, such as glycaemic variability, which are more closely related to cardiovascular risk than HbA1c [37]. If strategically timing exercise to attenuate peak hyperglycaemia improves long-term glycaemic control (HbA1c), reduces cardiovascular risk (endothelial dysfunction and arterial stiffness), and improves exercise adherence then this may be an alternative recommendation for physical activity prescription in people with T2D.

Strengths and Limitations

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This is the first randomised controlled trial to examine the effects of personalising exercise timing to attenuate peak hyperglycaemia (determined via continuous glucose monitoring technology) on cardiometabolic and vascular health outcomes in individuals with type 2 diabetes. This study will be conducted in free-living conditions, with exercise performed at home and contact/delivery of *Phase 1* (8-week exercise intervention) mirroring standard-care (five telehealth calls with an exercise physiologist), while *Phase 2* (3-month follow-up) will assess adherence to the exercise prescription (with minimal contact from the research team); thus informing us of the real-world applicability of the proposed exercise prescription. In addition, this study will utilise a variety of data collection methods (in-lab and free-living) to objectively measure cardiometabolic health, vascular function, physical activity, and behaviour change across the trial. Due to the COVID-19 pandemic remote participants from across rural and urban Australia will be included, allowing for a wider range of individuals to be recruited while adhering to the COVID-19 restrictions. However, this is also a limitation as the vascular and body composition measures will be excluded for those who cannot attend university assessments, and dried blood spot testing kits will be used rather than the gold-standard plasma measurement of HbA1c. Finally, a limitation of the waitlist control group is the potential overestimation of intervention effects and bias in favour of the treatment group. Nevertheless, inclusion of the waitlist control group will provide insight on the cause-effect relationship between the intervention and subsequent health outcomes/behaviour changes, as these participants will follow a delayed-start design (i.e., will receive treatment following the waitlist period), thus allowing for direct comparisons to be made under various conditions with reduced error variance and not withholding treatment to individuals.

COMPETING INTERESTS

The authors have no conflicts of interest to disclose.

CONTRIBUTORS

CRC drafted the manuscript. MEF, CRC, BMR, and TAB conceived and contributed to the design of the study and plan for analysis. MEF and CRC will conduct the study, collect data, and analyse data. MEF, CRC and TAB will analyse and interpret the data. All authors reviewed and approved the final manuscript.

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FIGURES

Figure 1. Study design and flow chart

Eligible participants will be randomised (N=54) to one of three groups: i) exercise at peak hyperglycaemia (ExPeak; N=18), ii) exercise after peak hyperglycaemia (NonPeak; N=18), or iii) waitlist control (WLC; N=18). Participants randomised to WLC will be re-randomised to ExPeak or NonPeak after the waitlist period. Following the eight-week intervention (Phase 1), the ExPeak (N=27) group will continue to exercise at peak hyperglycaemia, whereas the NonPeak (N=27) group will become the control (CTL; N=27) group for the three-month follow-up (Phase 2). Participants in the WLC and CTL groups will receive standard care advice to exercise in accordance with the World Health Organization physical activity guidelines.

Figure 2. Timeline of study protocol

Participants randomised to the waitlist control (WLC) group will undergo measures before and after an eight-week waitlist control period. Then are randomised to one of two intervention groups for eight weeks: i) exercise at peak hyperglycaemia ([ExPeak] ExRx: begin exercise ~30 min before peak hyperglycaemia) or ii) exercise after peak hyperglycaemia ([NonPeak] ExRx: begin exercise ~90 min after peak hyperglycaemia). All groups undergo pre-intervention CGM to measure time of peak hyperglycemia prior to interventions. **PHASE 1. Eight-week intervention:** Both intervention groups will perform ~22 min of daily exercise at their prescribed time. Participants will receive two phone consults and five telehealth video consults (via zoom or skype) with an Accredited Exercise Physiologist. **PHASE 2. Three-month follow-up:** The ExPeak group will continue to exercise for ~22 min/day at peak hyperglycaemia and the NonPeak group will exercise according to the physical activity guidelines. Three adherence surveys will be conducted (at the end of each month), but no formal contact. **Free Living Assessments:** 14 d CGM, 2 h MMTT, 7 d ActiGraph activity monitoring, 7 d HR monitoring (midpoint only; Polar Bluetooth HR monitor worn on same days as ActiGraph, only during prescribed exercise), 7 d diet record,

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quality of life survey, and self-regulatory efficacy and physical activity questionnaire. **In-Lab Assessments:** i) blood sample HbA1c, CRP, and blood lipids (TG, TC, HDL, and LDL); ii) vascular measures FMD and arterial stiffness via PWV/PWA; and iii) anthropometrics (height and weight) and body composition DEXA.

Abbreviations: waitlist control, WLC; exercise at peak hyperglycaemia (intervention group), ExPeak; exercise after peak (intervention group), NonPeak; exercise prescription, ExRx; accredited exercise physiologist, AEP; continuous glucose monitoring, CGM; mixed meal tolerance test, MMTT; heart rate, HR; glycated hemoglobin, HbA1c; c-reactive protein, CRP; triglyceride, TG; total cholesterol, TC; high-density lipoprotein, HDL; low-density lipoprotein, LDL; flow-mediated dilation, FMD; pulse wave velocity, PWV; pulse wave analysis, PWA; and dual-r-ray absorptiometry, DEXA.

Figure 3. Example 'Glucose Pattern Insights' Report

Via LibreView, of a 24 h blood glucose curve averaged from 14 days of continuous glucose measurements.

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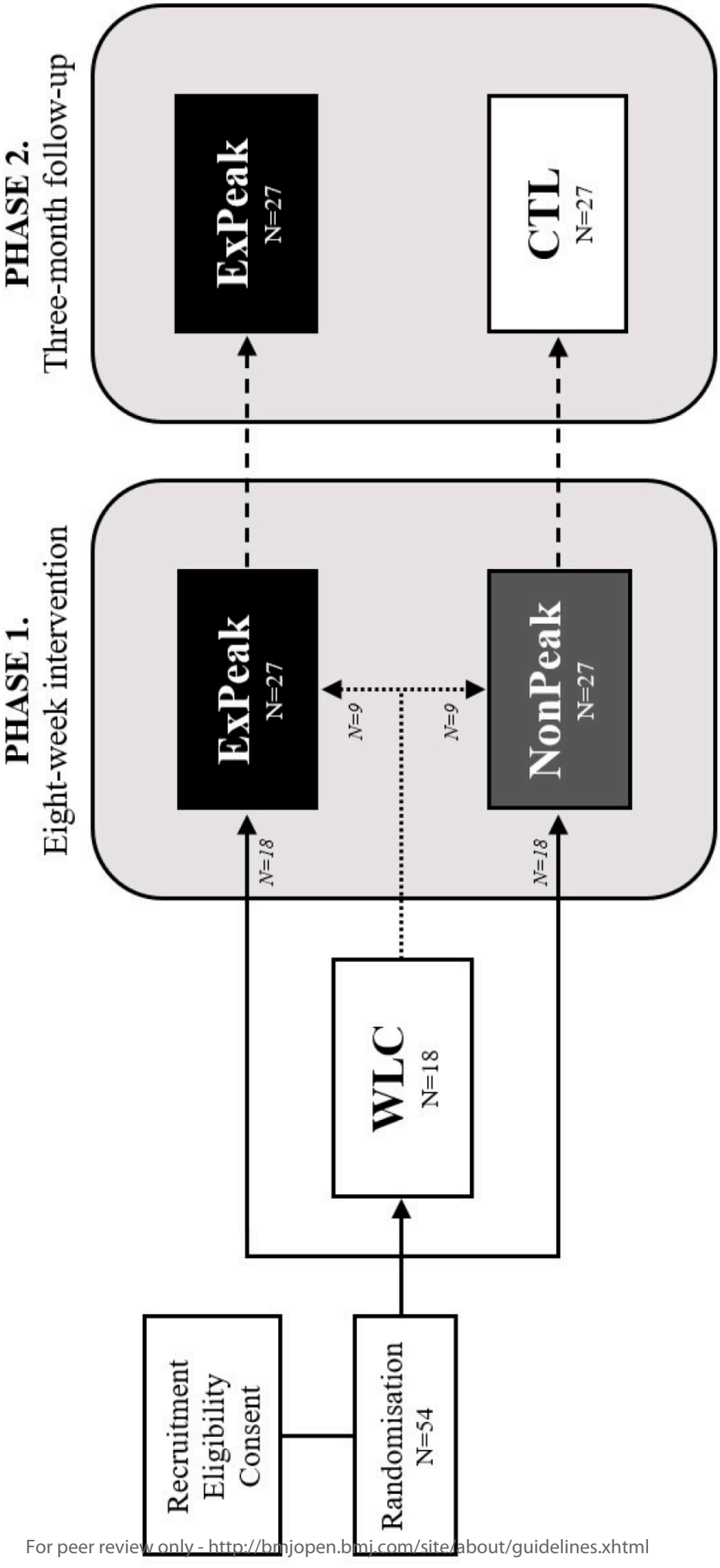
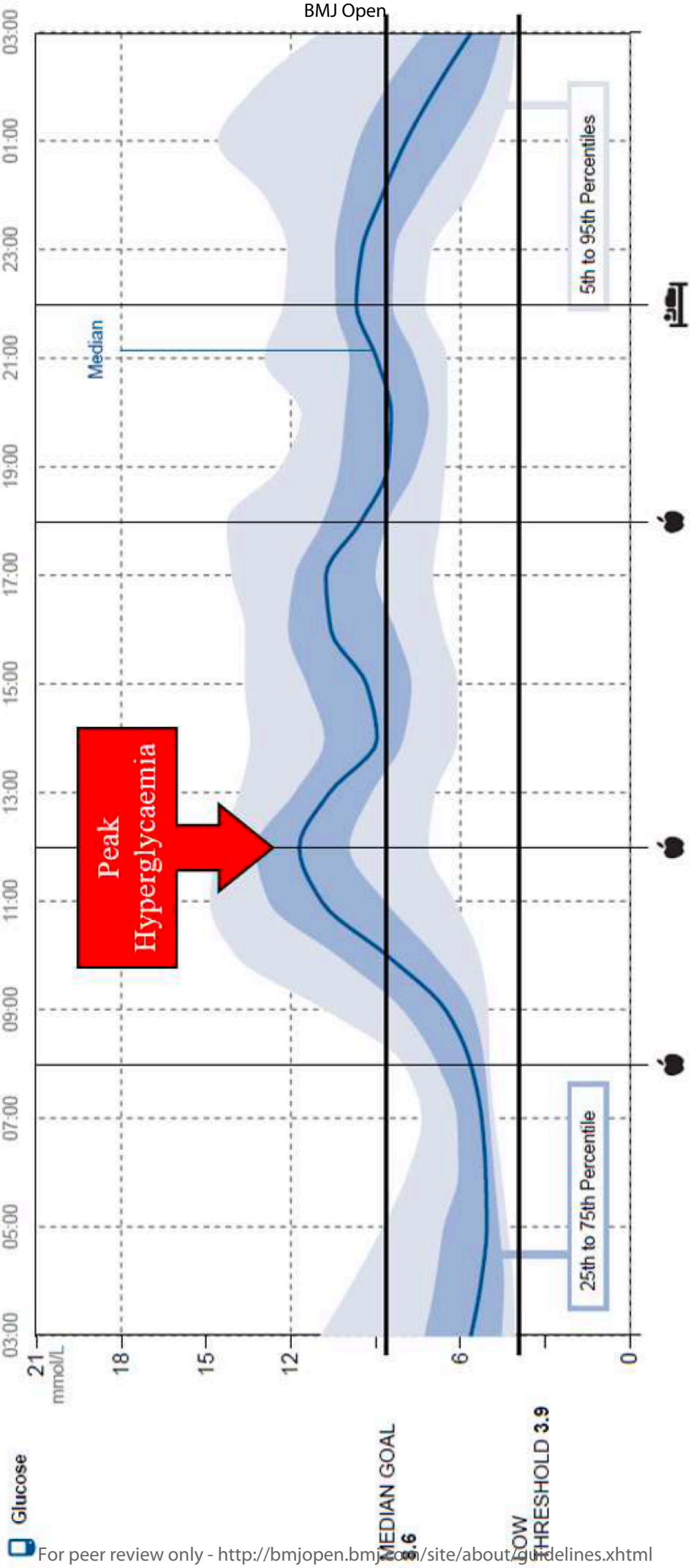

PHASE 2.
Three-month follow-up
ExPeak
N=27
CTL
N=27
PHASE 1.
Eight-week intervention
ExPeak
N=27
N=9
N=9
NonPeak
N=27
N=18
N=18
WLC
N=18
Recruitment
Eligibility
Consent
Randomisation
N=54

PHASE 1. Eight-week intervention
PHASE 2. Three-month follow-up
Phone Consult
App Telehealth Video Consult
Adherence Survey
WLC
Baseline Monitoring WLC only
Physical Activity Guidelines (eight-week waitlist control, standard-care)
ExPeak
NonPeak
Pre-intervention Monitoring
Midpoint Monitoring
ExRx: 22 min/day, at peak hyperglycaemia
ExRx: 22 min/day, after peak hyperglycaemia
Re-randomised to ExPeak or NonPeak
Post-intervention Monitoring
ExRx: 22 min/day, at peak hyperglycaemia
Physical Activity Guidelines (control, standard-care)
ExPeak or NonPeak procedures
Post Follow-up Monitoring
Assessments Free Living & In-Lab
Assessments Free Living Only
week
-12
-11
-10
-2
-1
1
2
4
5
6
8
9
10
11
14
18
22
23
24


Glucose
mmol/L
21
18
15
12
9
6
0
03:00
05:00
07:00
09:00
11:00
13:00
15:00
17:00
19:00
21:00
23:00
01:00
03:00
Median
5th to 95th Percentiles
25th to 75th Percentile
Peak Hyperglycaemia
MEDIAN GOAL
6.6
LOW THRESHOLD 3.9

UNIVERSITY OF WOLLONGONG AUSTRALIA

NSW GOVERNMENT Health Illawarra Shoalhaven Local Health District

INFORMED CONSENT

PROJECT: **Preventing Cardiovascular Disease in Type 2 Diabetes: When is the Right Time to Move?**

Principal Investigator: Dr Monique Francois, School of Medicine, University of Wollongong, ph. 0431730065, francois@uow.edu.au

I have been given and read the information sheet on the *Research Study: Preventing Cardiovascular Disease in Type 2 Diabetes: When is the Right Time to Move?* and had an opportunity to ask the researchers any questions I may have about the research project and my participation.

If I have any enquiries about the study, I can contact the research team at:
uowtimingstudy@gmail.com

By signing below, I am indicating my consent to (please tick):

Participate in a research study which includes advice to exercise according to the physical activity guidelines for approximately 22 min per day. In addition, there will be 6 study visits to UOW (pending COVID-19 restrictions) to assess cardiovascular fitness/risk, blood glucose, activity levels and biometric data (not all completed at each visit).

I Understand that my participation in this study involves:

- ☐ Four 14-day continuous glucose monitoring and activity measure periods (pre-intervention, mid-intervention, post intervention and 3-month follow up)
- ☐ Continuing Standard-care treatment with my doctor and my diabetes management team.
- ☐ Three Oral Glucose Tolerance Tests (mixed-meal drink), vascular health measures (pending COVID-19 restrictions) and 24-h blood pressure monitoring periods
- ☐ Three phone consults & 5 telehealth consultations with an Accredited Exercise Physiologist
- ☐ My participation is voluntary, and I can withdraw from the study at any time without disadvantage to present or future care and treatment or research participation at The University of Wollongong.

I know that:

- ☐ I will receive detailed information on my blood glucose patterns and levels, daily activity, and blood pressure.
- ☐ No remuneration or compensation will be given for my time. However, parking will be free, and the UOW visits will be negotiated to occur at a time that is convenient to me.
- ☐ The data will be destroyed at the conclusion of the project but any raw data on which the results of the project depend will be retained in secure storage for five years, after which they will be destroyed
- ☐ The results of the project may be published but my anonymity will be preserved.

For further information about the conduct of human experiments, please contact the Secretary of the Human Research Ethics Committee, University of Wollongong (phone: 02-4221-4457).

SIGNED DATE	**Name (please print)**
..../...../.....	.....

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

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		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14

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Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	1
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	1
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6

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Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	2
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	22
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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