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# BMJ Open

## 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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3 1 **Personalising Activity to Target Peak Hyperglycaemia and Prevent Cardiovascular Disease**  
4 **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<sup>2</sup>) 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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3 **63 Article Summary: Strengths and Limitations of this Study**  
4

- 5 64 • This is the first randomised controlled trial to determine the effects of personalising  
6 exercise to attenuate peak hyperglycaemia, on long-term glycaemic control,  
7 65 cardiovascular risk, and exercise adherence in people with T2D.  
8 66  
9 67 • This study will be conducted in free-living conditions, with contact/delivery of the  
10 68 intervention for the first eight weeks mirroring standard-care, thus increasing real-world  
11 applicability of the proposed exercise prescription.  
12 69  
13 70 • Due to the COVID-19 pandemic, this study will be a combination of remote and local  
14 data collection methods. For participants who are unable to attend the university for in-  
15 lab assessments due to COVID-19 restrictions, dried blood spot testing kits will be used  
16 (to measure glycaemic control, inflammation, and blood lipids), or HbA1c will be  
17 71 reported from the most recent routine blood test, and vascular/DEXA measurements will  
18 be excluded.  
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## 94 INTRODUCTION

95 Approximately 463 million adults are living with type 2 diabetes (T2D) and this number is  
96 expected to increase to 700 million by 2045 [1]. Individuals with T2D have a twofold greater risk  
97 of developing atherosclerotic cardiovascular disease (CVD; e.g., myocardial infarction, stroke,  
98 etc.) and CVD accounts for ~70% of deaths in T2D patients [2]. T2D is characterised by elevated  
99 fasting and postprandial blood glucose levels [3]. Large excursions in blood glucose, especially  
100 during the postprandial period (i.e., postprandial hyperglycaemia) cause oxidative stress,  
101 inflammation, and endothelial dysfunction, which mechanistically links impaired glucose  
102 regulation with the development of CVD in people with T2D [4, 5]. Acute and chronic exercise  
103 training improve blood glucose regulation and reduce cardiovascular risk factors. The benefits of  
104 exercise training on glycaemic control are largely attributed to the accumulated effects of  
105 individual exercise sessions [6, 7] increasing contraction- and insulin-mediated glucose uptake [7,  
106 8] consistently and overtime. The current guidelines for physical activity recommend adults  
107 accumulate ~150-300 min of moderate intensity aerobic activity throughout the week to improve  
108 or maintain health [9], including glycaemic control (i.e., glycated haemoglobin [HbA1c]) in people  
109 with T2D [10]. However, mounting evidence [11–15] indicates that exercise timing (e.g., pre- vs  
110 post-meal, or morning vs afternoon) influences glycaemic responses, yet there are no consistent  
111 guidelines on exercise timing in any current physical activity recommendations globally.

112  
113 Multiple systematic reviews have recently examined the effects of exercise timing on measures of  
114 glycaemic control in people with T2D and suggest the best time to exercise is within the first few  
115 hours after a meal [11–13]. However, performing exercise at different times of the day (i.e.,  
116 morning vs afternoon) has also shown to influence glycaemic responses [14, 15]. For example,  
117 Savikj et al. (2019) recently demonstrated that two weeks of high intensity interval training (HIIT;  
118 three days/week) performed in the afternoon improved 24 h glucose concentration by -0.6 mmol/L  
119 more than HIIT in the morning [14], whereas a separate study by Teo et al. (2019) found no  
120 significant differences in any glycaemic outcomes (HbA1c, fasting or postprandial glucose) after  
121 12 weeks of exercise (three days/week) performed in the morning vs afternoon [15]. Given the  
122 inconsistent findings and broad recommendations in the current literature (i.e., exercise timing  
123 relative to time of day or meal consumption), a more personalised approach may be needed to  
124 target CVD and for practitioners to prescribe exercise timing for people with T2D. Postprandial

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3 125 hyperglycaemia is linked to CVD and timing exercise to specifically target the largest postprandial  
4 126 excursion (i.e., peak hyperglycaemia) of the day may lead to greater glycaemic benefits and  
5 127 reduced cardiovascular risk.  
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10 129 It is unknown if prescribing daily exercise at a specific time of day, to attenuate peak  
11 130 hyperglycaemia, will lead to greater improvements in HbA1c compared to the current physical  
12 131 activity guidelines of accumulating ~150-300 min/week at any time. Further, the vascular effects  
13 132 of exercising specifically to attenuate peak hyperglycaemia are unknown. The endothelium is a  
14 133 key regulator of vascular homeostasis and endothelial function is an early risk factor for CVD [16,  
15 134 17]. Hyperglycaemia increases production of reactive oxygen species [18] and the resulting  
16 135 oxidative stress reduces vascular homeostasis (i.e., by increasing vasoconstriction and decreasing  
17 136 vasodilation) which can lead to endothelial dysfunction and CVD over time. A longer-term  
18 137 intervention of daily exercise is now warranted to garner a better understanding of exercise timing  
19 138 on glycaemic control and to examine whether exercising at the time of peak hyperglycaemia  
20 139 improves HbA1c and reduces cardiovascular risk factors.  
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31 141 The aim of this trial is to determine whether exercising to attenuate peak hyperglycaemia (exercise  
32 142 beginning ~30 min before peak hyperglycaemia) improves glycaemic control (HbA1c and 24 h  
33 143 mean, fasting and postprandial glucose) and reduces cardiovascular risk factors (including lipids,  
34 144 c-reactive protein, vascular function), more than exercising not at time of peak hyperglycaemia  
35 145 (exercise ~90 min after peak hyperglycaemia) or at any time of the day (no prescribed exercise  
36 146 time i.e., physical activity guidelines) in people with T2D. The efficacy, feasibility, and adherence  
37 147 to prescribing an exercise time will also be explored during a three-month follow-up. Given that  
38 148 postprandial hyperglycaemia is associated with worsening HbA1c [19] and endothelial  
39 149 dysfunction [20] in T2D, we hypothesise that exercising to attenuate peak hyperglycaemia will  
40 150 lead to the greatest improvements in glycaemic control, which in turn will improve vascular  
41 151 function and reduce cardiovascular risk.  
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## 51 153 **METHODS**

52  
53 154 A single centre randomised controlled trial will be conducted at the University of  
54 155 Wollongong, Australia from July 2019 to December 2022 (Figure 1). Participants will be recruited  
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3 156 through online advertising using a clinical trials recruitment company (Trial Facts). A medical  
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5 157 screening questionnaire and informed consent will be obtained from all participants prior to  
6  
7 158 participation. Data will be collected and stored in RedCap data management software.  
8  
9 159

## 10 160 **Participants**

11  
12 161 Inclusion criteria:

- 13 162 • Physician diagnosed T2D (registration with the National Diabetes Services Scheme)
- 14 163 • HbA1c between 6.5-9.0%
- 15 164 • Aged between 40 and 75 years
- 16 165 • BMI between 27-40 kg/m<sup>2</sup>
- 17 166 • Diabetes treated with lifestyle, oral medications and/or intermediate/long-acting insulin
- 18 167 • Stable weight for previous 3 months ( $\pm$  4 kg)
- 19 168 • Stable medications for previous 3 months
- 20 169 • Able to speak and understand English

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30 171 Exclusion criteria:

- 31 172 • Any absolute contraindications to exercise (i.e., musculoskeletal/joint injury, etc.)
- 32 173 • Presence or history of CVD, kidney or liver disease
- 33 174 • Diagnosed diabetes complications i.e., neuropathy, retinopathy etc.
- 34 175 • Diabetes treated with short acting insulin
- 35 176 • Uncontrolled hypertension (>160/90 mmHg)
- 36 177 • >150-300 min exercise/week (per Godin leisure time physical activity questionnaire)

## 37 178 38 179 **Study Design**

39 180 Fifty-four (N=54) males and females (aged 40-75 years, BMI 27-40 kg/m<sup>2</sup>) will be recruited and  
40 181 randomised to one of three groups for eight weeks: i) exercise at time of peak hyperglycaemia  
41 182 (ExPeak), ii) exercise not at time of peak hyperglycaemia (NonPeak) or, iii) waitlist control  
42 183 (WLC). Participants allocated to the WLC group will be re-randomised to the ExPeak or NonPeak  
43 184 intervention group following the waitlist period. During the eight-week intervention (Phase 1), all  
44 185 groups will be prescribed ~150 min/week of physical activity as per the current guidelines. The  
45 186 intervention groups will be prescribed daily exercise at a specific time. During the exercise



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3 187 intervention, participants will have five telehealth consults with an accredited exercise  
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5 188 physiologist, in line with Australia's Medicare health plan for people with diabetes. An automatic  
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7 189 computer-generated random number table will be used to perform random allocation of  
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9 190 participants (1:1 ratio), stratified for sex and exogenous insulin usage. A sealed envelope system  
10  
11 191 will be used to blind researchers from group allocations. Allocations will be sealed in an opaque  
12  
13 192 envelope (by a person independent to the clinical trial) until a participant is enrolled and needing  
14  
15 193 to commence the intervention.

16 194  
17 195 Participants will undergo a three-month follow-up (Phase 2) where adherence to exercising at a  
18  
19 196 prescribed time (with minimal contact from the research team) will be assessed. During Phase 2,  
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21 197 participants in the ExPeak group will be advised to continue exercising daily at their time of peak  
22  
23 198 hyperglycaemia and participants in the NonPeak group will be advised to exercise in accordance  
24  
25 199 with the World Health Organization 2020 guidelines for physical activity i.e., accumulate ~150-  
26  
27 200 300 min of physical activity per week at any time of day [9], thus becoming the control group.

28 201

29 202 **[INSERT STUDY DESIGN FIGURE HERE]**

30 203

### 31 204 **Interventions**

32 205 All exercise sessions will be performed in a free-living setting (home-based) for the duration of  
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34 206 this trial. Participants in the ExPeak and NonPeak groups will be prescribed ~22 min of daily  
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36 207 moderate-intensity physical activity (aerobic exercise e.g., walking, cycling, swimming, etc.) for  
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38 208 eight weeks, to align with the physical activity guidelines of accumulating at least 150 min of  
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40 209 aerobic activity per week. The pre-intervention Continuous Glucose Monitoring (CGM) data  
41  
42 210 (*outlined below*) will be used to determine time of peak hyperglycaemia. The ExPeak group will  
43  
44 211 begin exercising ~30 min before their peak hyperglycaemia typically occurs and the NonPeak  
45  
46 212 group will begin exercising ~90 min after their peak hyperglycaemia typically occurs. Participants  
47  
48 213 in the control groups will exercise in accordance with the physical activity guidelines [9]. Exercise  
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50 214 intensity will be determined using the Borg Scale to indicate Rate of Perceived Exertion, which  
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52 215 uses numbered categories from 6-20 (i.e., no exertion at all to maximal exertion) to gauge how  
53  
54 216 hard a person 'feels' they are working [21]. Daily exercise should be completed as one continuous  
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56 217 bout but may be accumulated over a 30 min period depending on individual needs (ideally

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3 218 accumulated in bouts of >10 min, interspersed with short periods of rest). Participants will have  
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5 219 two phone consults and five telehealth video consults with an accredited exercise physiologist on  
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7 220 alternate weeks throughout the eight-week exercise intervention, in addition to maintaining  
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9 221 standard care treatment with health care professionals and habitual medication and diet.

10 222

## 11 223 **Experimental Protocol**

12 224 The intervention period will be five months in total, with the eight-week intervention (Phase 1)  
13  
14 225 commencing after two weeks of pre-intervention monitoring, and the three-month follow-up  
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16 226 (Phase 2) commencing after two weeks of post-intervention monitoring. Pre- and post-assessments  
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18 227 will be conducted at the University of Wollongong to evaluate glycaemic and metabolic control,  
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20 228 vascular function, and body composition (Figure 2). Participants will be instructed to abstain from  
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22 229 physical activity for >24 h and to fast for ~10 h before each in-lab assessment.

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26 231 A two-week monitoring period will be conducted pre-intervention, midway through, post-  
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28 232 intervention and after the three-month follow-up. Participants in the WLC group will have two  
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30 233 additional weeks of baseline monitoring before the waitlist period commences. Participants will  
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32 234 maintain normal daily activity and dietary patterns during each monitoring period, except for the  
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34 235 midpoint assessment where they will continue to follow intervention protocol. During the three-  
35  
36 236 month follow-up, participants will complete three short surveys (one at the end of each month,  
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38 237 seven questions each) to assess adherence to the exercise prescription but will otherwise have no  
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40 238 formal contact with the research team (Figure 2). Other than the prescribed exercise, participants  
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42 239 will be asked to maintain normal dietary habits and medication usage throughout the study period.

41 240

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43 241 **[INSERT PROTOCOL TIMELINE FIGURE HERE]**

44 242

### 45 243 *Determination of Peak Hyperglycaemia*

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47 244 The 'Glucose Pattern Insights' report (automatically generated via LibreView software), for the  
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49 245 two-week pre-intervention CGM (Freestyle Libre, Abbott), will be used to determine the average  
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51 246 time that peak hyperglycaemia occurs for each participant (Figure 3). Trained researchers will  
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53 247 verify time of peak hyperglycaemia by analysing the raw CGM data using the following methods:  
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55 248 After the CGM data is cleaned and separated into full days (i.e., >24 h of uninterrupted data),

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3 249 maximum glucose and the time it occurs will be calculated for each day of the two-week  
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5 250 monitoring period. The average time of day that peak hyperglycaemia occurs will be then  
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7 251 determined for each participant—if peak hyperglycaemia occurs at the same time of day (or within  
8  
9 252 ~30 min) on five or more occasions over the 14 d CGM period, that time of day will be identified  
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11 253 as the time of peak hyperglycaemia. Alternatively, time of peak hyperglycaemia will be calculated  
12  
13 254 as an average from 14 days of continuous glucose measurements. Time of peak hyperglycaemia  
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15 255 will be re-assessed following the waitlist period for participants initially randomised to the WLC  
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17 256 group and again in the ExPeak group for the three-month follow up.  
18

19 258 **[INSERT GLUCOSE PATTERN INSIGHT EXAMPLE HERE]**  
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## 22 260 **Outcome Measures**

23  
24 261 The primary outcome is the change in HbA1c following the eight-week intervention. Secondary  
25  
26 262 outcome measures will examine additional indices of glycaemic control (via CGM derived  
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28 263 variables [e.g., 24 h mean, area under the curve, glycaemic variability, time in range etc.] and a  
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30 264 mixed meal tolerance test [MMTT]), vascular function (endothelial function and arterial stiffness),  
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32 265 metabolic control (blood lipids and inflammation) and body composition (BMI, total and regional  
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34 266 fat, and fat-free mass). Tertiary outcome measures will focus on the efficacy, feasibility, and  
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36 267 adherence to exercise prescription (accelerometer and surveys). Apart from the mid-intervention  
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38 268 assessment, participants will resume normal daily living (not exercise at their prescribed time) to  
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40 269 assess training effects.

### 41 271 *Glycaemic Control*

42  
43 272 The primary outcome of glycaemic control will be assessed by measuring HbA1c. A finger prick  
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45 273 blood sample will be collected using a HbA1c (~2 µL) specific test disc and immediately analysed  
46  
47 274 with the Cobas b 101 System (Roche Diagnostics).  
48

49  
50 276 Secondary glycaemic outcomes will also be assessed with CGM and a MMTT (low glycaemic  
51  
52 277 index, Glucerna<sup>®</sup>). From each two-week CGM, we will calculate mean 24 h glucose, 24 h and 3 h  
53  
54 278 postprandial area under the curve (AUC) and incremental area under the curve (iAUC) calculated  
55  
56 279 using the trapezoid method [22], hyperglycaemia (time spent  $\geq 10$  mmol/L), glycaemic variability  
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3 280 (mean amplitude of glycaemic variability [MAGE]) and nocturnal glucose profiles. We will also  
4  
5 281 calculate mean glucose total AUC and iAUC for 2 h following the MMTT. The MMTT will begin  
6  
7 282 after an overnight fast (>10 h), and blood glucose will be measured with the CGM and finger  
8  
9 283 pricks (0, 15, 30, 60, 90 and 120 min) following drink consumption.

284

### 285 *Metabolic Control*

13 286 Metabolic control will be assessed by measuring blood lipids (triglyceride, total cholesterol, high-  
14  
15 287 density lipoprotein, and low-density lipoprotein) and inflammation (CRP). Finger prick blood  
16  
17 288 samples will be collected via lipid (~19 µL) or inflammation (~12 µL) specific test discs and  
18  
19 289 immediately analysed with the Cobas b 101 System.

290

### 291 *Body Composition*

22 292 Waist to hip ratio, height, and weight will be measured to the nearest 0.1 cm and 0.1 kg,  
23  
24 293 respectively, using standard scales, a stadiometer and measuring tape. Total and regional fat and  
25  
26 294 fat-free mass will be measured by dual-energy x-ray absorptiometry ([DEXA], MedixDR Whole  
27  
28 295 Body DEXA, SYD, AU).

296

### 297 *Vascular Function*

32 298 Endothelial function will be assessed by measuring endothelium-dependent flow-mediated  
33  
34 299 dilation (FMD). This technique uses ultrasound imaging (Terason uSmart® 3300) of the brachial  
35  
36 300 artery. Following 10-15 min of laying supine (at rest), a longitudinal section of the brachial  
37  
38 301 artery, 2-3 cm above the antecubital fossa, will be imaged using B-mode ultrasound imaging (insonation  
39  
40 302 angle of 60°). A blood pressure cuff placed around the forearm, 1-2 cm below the olecranon  
41  
42 303 process, will then be rapidly inflated to ~60 mmHg above resting systolic blood pressure for 5 min.  
43  
44 304 Brachial artery diameter and blood flow velocity will be recorded for 1 min before cuff inflation  
45  
46 305 (baseline), ~30 s prior to cuff release (ischemic stimulus), and 3 min following cuff release  
47  
48 306 (recovery) [23, 24]. The ~5 min recording will then be analysed with custom-designed edge-  
49  
50 307 detection and wall-tracking software (Cardiovascular Suite, Quipu, Italy) which reduces user bias  
51  
52 308 and increases accuracy. FMD will be reported as an absolute change in artery diameter (absolute  
53  
54 309  $FMD = \text{postocclusion}_{\text{mean diameter}} - \text{preocclusion}_{\text{mean diameter}}$ ), and a relative change in artery diameter

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2  
3 310 from baseline [%FMD =  $100 \times (\text{absolute FMD}/\text{preocclusion}_{\text{mean diameter}})$ ]. Allometric scaling will  
4  
5 311 be used to account for potential confounders from baseline diameter [24, 25].  
6

7 312  
8 313 Blood flow (mL/min) will be measured using non-invasive Doppler from the cross-sectional area  
9  
10 314 and blood velocity [velocity  $\times \pi \times (\text{diameter}^2/4) \times 60$ ]. Shear rate (s<sup>-1</sup>) will then be determined  
11  
12 315 from the diameter and velocity measures (four times velocity/diameter) [26]. Shear rate area under  
13  
14 316 the curve (SR<sub>AUC</sub>) will automatically be calculated from the diameter and velocity measures from  
15  
16 317 the time of cuff release to peak dilation of the artery. Antegrade and retrograde mean blood  
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18 318 velocities will be used to calculate baseline antegrade and retrograde shear rates (four times mean  
19  
20 319 baseline antegrade or retrograde velocity  $\div$  mean baseline diameter), and the mean blood flow to  
21  
22 320 mean arterial pressure ratio will be used to measure vascular conductance (mL/min/mmHg) [23,  
23  
24 321 24].  
25

26 322  
27 323 Central arterial stiffness will be assessed via pulse wave analysis (PWA) and pulse wave velocity  
28  
29 324 (PWV) measurements (SphygmoCor® XCEL System, AtCor Medical). PWA will be used to  
30  
31 325 measure central blood pressure. A brachial blood pressure cuff will be inflated and the central  
32  
33 326 aortic pressure waveform, derived from pulsations at the brachial artery, will be recorded for 5 s  
34  
35 327 and then automatically analysed through the SphygmoCor software. Key parameters of central  
36  
37 328 blood pressure and arterial stiffness will be determined from the aortic waveform including systolic  
38  
39 329 pressure, diastolic pressure, pulse pressure, aortic pressure, augmentation index and mean arterial  
40  
41 330 pressure. PWV will be measured by holding a tonometer on the carotid artery for 10-15 s, while a  
42  
43 331 femoral blood pressure cuff is automatically inflated. Once fully inflated, the femoral cuff and  
44  
45 332 carotid tonometer will simultaneously record a 10 s capture of the carotid and femoral pressure  
46  
47 333 waveforms. PWV will then be calculated by dividing the carotid-femoral distance by the pulse  
48  
49 334 transit time; the carotid-femoral distance will be calculated by subtracting the proximal distance  
50  
51 335 (distance between the carotid artery and sternal notch) from the distal distance (distance between  
52  
53 336 the sternal notch and proximal edge of the femoral cuff) [PWV (m/s) = (distal –  
54  
55 337 proximal<sub>distance</sub>)/transit time] [27]. Measurements will be performed in duplicate. A third  
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57 338 measurement will be taken if the difference between the two PWV values is  $>0.5$  m/s and the  
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59 339 average of the three values will be used.  
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3 341 An automatic blood pressure monitor (Oscar2 Ambulatory Blood Pressure Monitor with  
4 342 SphygmoCor interfacing, SunTech Medical) will also be used to continuously assess blood  
5 343 pressure and pulse wave analyses every hour for 24 hours. We will report 24 h blood pressure as  
6 344 an average of 24 measurements.  
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### 11 346 *Diet and Physical Activity Monitoring*

12 347 Participants will complete a 7 d diet record during each two-week monitoring period. Food diaries  
13 348 will be analysed (using FoodWorks10 Nutrition Software) to confirm macronutrient composition  
14 349 and total energy intake are consistent throughout the study period. Physical activity will be  
15 350 monitored during the same 7 d period using an accelerometer (ActiGraph Bluetooth® Smart  
16 351 wGT3X-BT), worn around the waist during wake hours. Physical activity and sedentary time will  
17 352 be compared between groups at each timepoint during wake hours. The accelerometers will also  
18 353 be used to confirm exercise intensity and compliance to the exercise prescription. A heart rate  
19 354 monitor (Polar H7 Bluetooth® Heart Rate Monitor) will be worn during the midpoint monitoring  
20 355 period on the same days as the accelerometer, only during the exercise sessions, to assess exercise  
21 356 intensity.  
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### 32 358 *Adherence and Lifestyle Questionnaires*

33 359 Participants will complete a quality of life (SF-36) survey and a self-regulatory efficacy and  
34 360 physical activity questionnaire during each two-week monitoring period. Participants will also  
35 361 complete three surveys during the follow-up period, one at the end of each month that is specific  
36 362 to their exercise group, to assess adherence to exercise prescription between the ExPeak and  
37 363 control groups. Surveys will include questions on known perceived facilitators and barriers to  
38 364 filling the exercise prescription and, in turn, support or aggravation of intervention efficacy. Such  
39 365 factors will include the availability of nearby green and open spaces (e.g. beaches, parks) [28] and  
40 366 levels of felt safety to exercise outdoors during the day and evening hours [29].  
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### 50 368 *Remote Participants*

51 369 Participants who cannot attend the university (e.g., due to COVID-19 restrictions) for in-lab  
52 370 assessments will receive a home-based testing kit (via mail) which includes: a dried blood spot  
53 371 test kit (ZRT Laboratory kit for measurement of HbA1c, lipids, CRP, and insulin), CGM,  
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3 372 accelerometer and Glucerna MMTT drink. Instructions will be provided and followed-up via a  
4 373 phone or video call. All other study protocols will be the same, however data for the DEXA and  
5 374 vascular assessments will not be available.  
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## 376 **Patient and Public Involvement**

11 377 No patient involved.  
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## 380 **Statistical Analysis**

### 381 *Sample size*

20 382 Sample size was calculated based on a previous study investigating the effect of exercise timing  
21 383 in people with T2D, where they reported a difference of -0.6 mmol/L in 24 h blood glucose  
22 384 between exercise performed in the morning vs afternoon [14]. To detect a clinically meaningful  
23 385 change in HbA1c between groups, with a moderate effect size of 0.2, statistical power of 80%, and  
24 386 an alpha level of 0.05 (two-sided), a total of ~54 participants is required for this trial. The power  
25 387 calculation is based on the change in HbA1c from a previous trial in our lab in people with T2D  
26 388 [30]. To account for an expected 15% drop-out rate, 63 participants will be recruited.  
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### 390 *Statistics*

36 391 This study will be reported according to the CONSORT 2010 Statement and the CONSERVE  
37 392 2021 Statement for randomised controlled trials. Descriptive statistics will be assessed (means,  
38 393 standard deviation and frequencies), and histograms, Q-Q plots and the Shapiro-Wilk test will be  
39 394 used to identify outliers and test for normality. Linear mixed models (with time x intervention, and  
40 395 main effect of time) will be used to assess differences between groups, for primary (HbA1c) and  
41 396 secondary (CGM, MMTT, vascular function, metabolic control, and body composition) outcomes.  
42 397 Tertiary outcomes (e.g., adherence to the exercise prescription) will be analysed from the  
43 398 accelerometer and follow-up surveys (Qualtrics<sup>XM</sup>). Attention to treat analyses will be performed  
44 399 for primary analyses (Phase 1) and per protocol analyses will be undertaken for secondary and  
45 400 tertiary outcomes (Phase 2). Data with skewed distribution will be log-transformed or square-  
46 401 rooted prior to the statistical analysis. For the three-month follow-up, intention to treat analysis  
47 402 will be used and missing data will not be imputed.  
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5 404 **DISCUSSION**

6 405 The primary objective of this trial is to determine if strategically timing exercise, to reduce  
7 406 daily peak hyperglycaemia, will improve glycaemic control and lower cardiovascular risk factors  
8 407 in people with T2D. This is the first study to investigate whether prescribing exercise that is  
9 408 personalised to target daily peak hyperglycaemia, using CGM, can improve cardiovascular risk  
10 409 factors in T2D. Based on evidence from prior research [11, 31–33], it is hypothesised that  
11 410 strategically timing daily exercise to attenuate peak hyperglycaemia will improve glycaemic  
12 411 control (HbA1c), and the reduction in peak glycemia will improve vascular function (endothelial  
13 412 function and arterial stiffness), blood lipids and CRP, more than exercising not at peak  
14 413 hyperglycaemia or control standard-care (i.e., physical activity guidelines).

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16 415 Recent evidence suggests exercise timing may be important to offset circadian rhythms [14] and  
17 416 to target postprandial hyperglycaemia [11] in T2D. However, there are no recommendations for  
18 417 exercise timing in the current physical activity guidelines (i.e., physical activity can be  
19 418 accumulated at any time throughout the week). Further, adherence to the current recommendations  
20 419 is notoriously poor. Regardless of the effectiveness for an intervention to improve diabetes  
21 420 management, findings will only be translatable if patients comply with and adopt to the treatment  
22 421 over the long-term. Therefore, adherence to prescribed daily exercise time (i.e., creating more of  
23 422 a habit) will be assessed for three months following the eight-week intervention. Exercising at the  
24 423 time of peak hyperglycaemia may improve self-efficacy to the exercise prescription, as results  
25 424 from the CGM data (pre/mid/post eight-week intervention) will allow participants to see the direct  
26 425 impact of exercise on blood glucose levels. Use of CGM in this trial not only offers the distinct  
27 426 advantage of determining time of peak hyperglycaemia, but will also allow us to examine any  
28 427 changes in daily glycaemic patterns, such as glycaemic variability, which are more closely related  
29 428 to cardiovascular risk than HbA1c [34]. If strategically timing exercise to attenuate peak  
30 429 hyperglycaemia improves long-term glycaemic control (HbA1c), reduces cardiovascular risk  
31 430 (endothelial dysfunction and arterial stiffness), and improves exercise adherence then this may be  
32 431 an alternative recommendation for physical activity prescription in people with T2D.

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3 433 Due to the COVID-19 pandemic, the vascular (endothelial function, arterial stiffness, 24 h blood  
4 434 pressure) and body composition (DEXA) measures will be unavailable for participants who are  
5 435 unable to attend the university due to COVID restrictions. Blood spot testing kits will be provided  
6 436 to assess HbA1c, blood lipids and inflammation.  
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12 438 were optional (from August-December 2020). Participants were also given the option to submit  
13 439 blood samples via dried blood spot testing kits (to assess HbA1c, blood lipids and inflammation),  
14 440 rather than having a blood sample collected at the university. All participants enrolled after  
15 441 December 2020 will be required to attend face-to-face assessments unless prohibited due to further  
16 442 COVID-19 restrictions.  
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22 444 **ETHICS AND DISSEMINATION**  
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24 445 This research has been reviewed and approved by the University of Wollongong Human Research  
25 446 Ethics Committee (2019/ETH09856). This trial was prospectively registered at the Australian New  
26 447 Zealand Clinical Trials Registry (ACTRN12619001049167). Participants will remain anonymous,  
27 448 and all collected data will be de-identified and coded. An alpha-numerical code (stored on a  
28 449 password protected central spreadsheet) will be allocated to each participant and used for  
29 450 identification on all subsequent paperwork. All results from the study will be published as peer-  
30 451 reviewed articles in international journals, presented at international conferences and promoted  
31 452 through social media. Changes to the protocol due to COVID-19 will be reported according to the  
32 453 CONSERVE 2021 Statement [35].  
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41 455 **COMPETING INTERESTS**  
42  
43 456 The authors have no conflicts of interest to disclose.  
44 457 Data can be made available on request.  
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48 459 **AUTHOR CONTRIBUTIONS**  
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50 460 CRC drafted the manuscript. MEF, CRC, BMR, and TAB conceived and contributed to the design  
51 461 of the study and plan for analysis. MEF and CRC will conduct the study, collect data, and analyse  
52 462 data. MEF, CRC and TAB will analyse and interpret the data. All authors reviewed and approved  
53 463 the final manuscript.  
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5 465 **FUNDING STATEMENT**

6 466 This research received no specific grant from any funding agency in the public, commercial, or  
7  
8 467 not-for-profit sectors. This trial was funded by a University of Wollongong Small Grant and  
9  
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11  
12 469 Council (NHMRC) Investigator Grant (APP1177234). TAB's time was supported by a NHMRC  
13  
14 470 Boosting Dementia Research Leader Fellowship (GNT1140317).

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17 472 **FIGURES**18  
19 473

20 474 **Figure 1. Study Design and Flow Chart.** Eligible participants will be randomised (N=54) to one  
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22 475 of three groups: i) exercise at peak hyperglycaemia (ExPeak; N=18), ii) exercise after peak  
23  
24 476 hyperglycaemia (NonPeak; N=18), or iii) waitlist control (WLC; N=18). Participants randomised  
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26 477 to WLC will be re-randomised to ExPeak or NonPeak after the waitlist period. Following the eight-  
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28 478 week intervention (Phase 1), the ExPeak (N=27) group will continue to exercise at peak  
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30 479 hyperglycaemia, whereas the NonPeak (N=27) group will become the control (CTL; N=27) group  
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32 480 for the three-month follow-up (Phase 2). Participants in the WLC and CTL groups will receive  
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34 481 standard care advice to exercise in accordance with the World Health Organization physical  
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36 482 activity guidelines.

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38 484 **Figure 2. TIMELINE OF STUDY PROTOCOL.** Participants randomised to the waitlist control  
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40 485 (WLC) group will undergo measures before and after an eight-week waitlist control period. Then  
41  
42 486 are randomised to one of two intervention groups for eight weeks: i) exercise at peak  
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44 487 hyperglycaemia ([ExPeak] ExRx: begin exercise ~30 min before peak hyperglycaemia) or ii)  
45  
46 488 exercise after peak hyperglycaemia ([NonPeak] ExRx: begin exercise ~90 min after peak  
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48 489 hyperglycaemia). All groups undergo pre-intervention CGM to measure time of peak  
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50 490 hyperglycemia prior to interventions. **PHASE 1. Eight-week intervention:** Both intervention  
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52 491 groups will perform ~22 min of daily exercise at their prescribed time. Participants will receive  
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54 492 two phone consults and five telehealth video consults (via zoom or skype) with an Accredited  
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56 493 Exercise Physiologist. **PHASE 2. Three-month follow-up:** The ExPeak group will continue to  
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58 494 exercise for ~22 min/day at peak hyperglycaemia and the NonPeak group will exercise according

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3 495 to the physical activity guidelines. Three adherence surveys will be conducted (at the end of each  
4 496 month), but no formal contact. **Free Living Assessments:** 14 d CGM, 2 h MMTT, 7 d ActiGraph  
5 497 activity monitoring, 7 d HR monitoring (midpoint only; Polar Bluetooth HR monitor worn on same  
6 498 days as ActiGraph, only during prescribed exercise), 7 d diet record, quality of life survey, and  
7 499 self-regulatory efficacy and physical activity questionnaire. **In-Lab Assessments:** i) blood sample  
8 500 HbA1c, CRP, and blood lipids (TG, TC, HDL, and LDL); ii) vascular measures FMD and arterial  
9 501 stiffness via PWV/PWA; and iii) anthropometrics (height and weight) and body composition  
10 502 DEXA.

11 503 *Abbreviations:* waitlist control, WLC; exercise at peak hyperglycaemia (intervention group),  
12 504 ExPeak; exercise after peak (intervention group), NonPeak; exercise prescription, ExRx;  
13 505 accredited exercise physiologist, AEP; continuous glucose monitoring, CGM; mixed meal  
14 506 tolerance test, MMTT; heart rate, HR; glycated hemoglobin, HbA1c; c-reactive protein, CRP;  
15 507 triglyceride, TG; total cholesterol, TC; high-density lipoprotein, HDL; low-density lipoprotein,  
16 508 LDL; flow-mediated dilation, FMD; pulse wave velocity, PWV; pulse wave analysis, PWA; and  
17 509 dual-r-ray absorptiometry, DEXA.

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31 511 **Figure 3. Example ‘Glucose Pattern Insights’ Report**, via LibreView, of a 24 h blood glucose  
32 512 curve averaged from 14 days of continuous glucose measurements.

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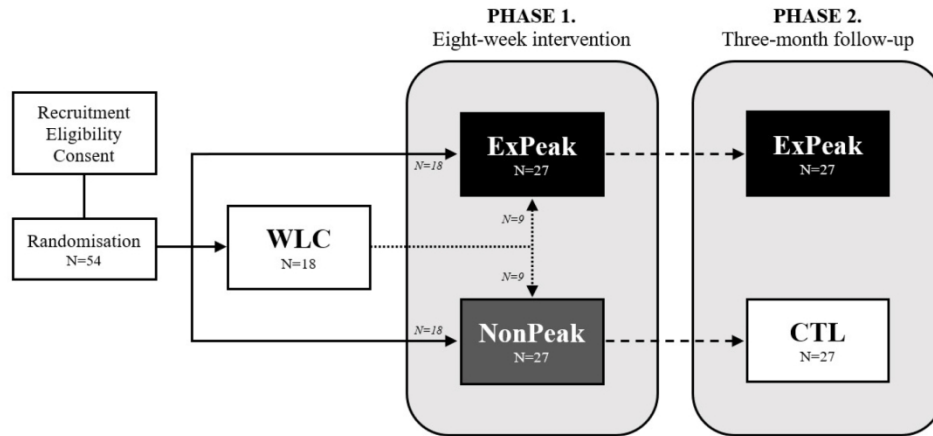


Figure 1. Study Design and Flow Chart. Eligible participants will be randomised (N=54) to one of three groups: i) exercise at peak hyperglycaemia (ExPeak; N=18), ii) exercise after peak hyperglycaemia (NonPeak; N=18), or iii) waitlist control (WLC; N=18). Participants randomised to WLC will be re-randomised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

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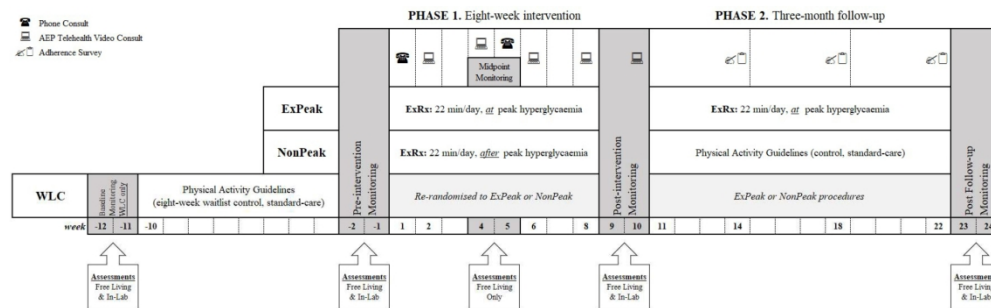


Figure 2. TIMELINE OF STUDY PROTOCOL. Participants randomised to the waitlist control (WLC) group will undergo measures before and after an eight-week waitlist control period. Then are randomised to one of two intervention groups for eight weeks: i) exercise at peak hyperglycaemia ([ExPeak] ExRx: begin 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, LDL; flow-mediated dilation, FMD; pulse wave velocity, PWV; pulse wave analysis, PWA; and dual-r-ray absorptiometry, DEXA.

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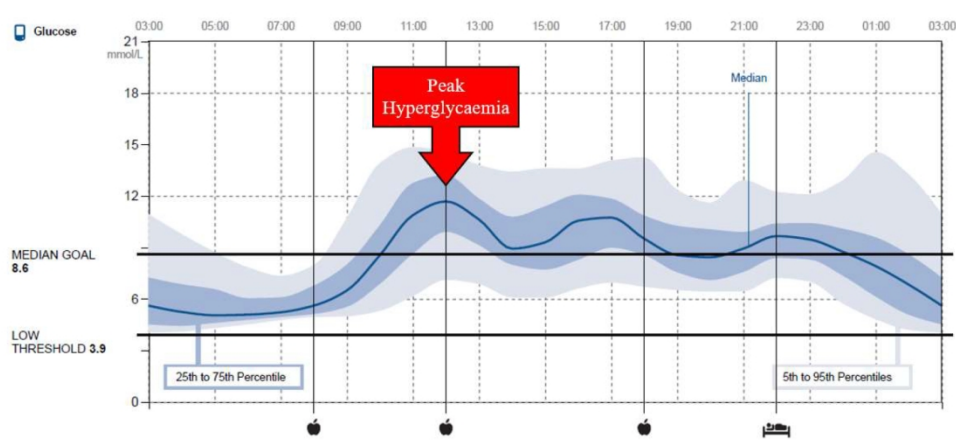


Figure 3. Example 'Glucose Pattern Insights' Report, via LibreView, of a 24 h blood glucose curve averaged from 14 days of continuous glucose measurements.

871x414mm (57 x 57 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

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

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	N/A
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	N/A
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
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23				
24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	5
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	6-8
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	5
38				
39				
40	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	6
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46	<b>Methods:</b>			
47	<b>Participants,</b>			
48	<b>interventions, and</b>			
49	<b>outcomes</b>			
50				
51				
52				
53	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	5
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
56				
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1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
2				
3				
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5				
6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
7	description			
8				
9				
10	Interventions:	<a href="#">#11b</a>	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
11	modifications			
12				
13				
14				
15	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
16	adherence			
17				
18				
19				
20	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
21	concomitant care			
22				
23				
24	Outcomes	<a href="#">#12</a>	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
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33				
34	Participant timeline	<a href="#">#13</a>	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
35				
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39				
40	Sample size	<a href="#">#14</a>	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
41				
42				
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44				
45	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	6
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47				
48				
49	<b>Methods: Assignment</b>			
50	<b>of interventions (for</b>			
51	<b>controlled trials)</b>			
52				
53				
54	Allocation: sequence	<a href="#">#16a</a>	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
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central	7
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),	
6			describing any steps to conceal the sequence until interventions	
7	mechanism		are assigned	
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11	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol	7
12	implementation		participants, and who will assign participants to interventions	
13				
14				
15	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial	7
16			participants, care providers, outcome assessors, data analysts),	
17			and how	
18				
19				
20	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible,	N/A
21	emergency unblinding		and procedure for revealing a participant's allocated intervention	
22			during the trial	
23				
24				
25	<b>Methods: Data</b>			
26	<b>collection,</b>			
27	<b>management, and</b>			
28	<b>analysis</b>			
29				
30				
31				
32	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and	6
33			other trial data, including any related processes to promote data	
34			quality (eg, duplicate measurements, training of assessors) and a	
35			description of study instruments (eg, questionnaires, laboratory	
36			tests) along with their reliability and validity, if known.	
37			Reference to where data collection forms can be found, if not in	
38			the protocol	
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42				
43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up,	14
44	retention		including list of any outcome data to be collected for participants	
45			who discontinue or deviate from intervention protocols	
46				
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48				
49	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any	6
50			related processes to promote data quality (eg, double data entry;	
51			range checks for data values). Reference to where details of data	
52			management procedures can be found, if not in the protocol	
53				
54				
55	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary	14
56			outcomes. Reference to where other details of the statistical	
57			analysis plan can be found, if not in the protocol	
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1	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	14
2	analyses		analyses)	
3				
4	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	14
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
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9				
10	<b>Methods: Monitoring</b>			
11				
12	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of	1
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
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22	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	N/A
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	N/A
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
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33	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	1
34			whether the process will be independent from investigators and	
35			the sponsor	
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37				
38	<b>Ethics and</b>			
39	<b>dissemination</b>			
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41				
42	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	2
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	2
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
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53	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	6
54			participants or authorised surrogates, and how (see Item 32)	
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
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6	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	6
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators	14
12			for the overall trial and each study site	
13				
14				
15	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and	14
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results	2
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
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33	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	2
34	authorship		professional writers	
35				
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37	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	2
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	<b>Appendices</b>			
42				
43	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given to	22
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
50				
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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057183.R1
Article Type:	Protocol
Date Submitted by the Author:	27-Jan-2022
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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
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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3 1 **Personalising Activity to Target Peak Hyperglycaemia and Improve Cardiometabolic**  
4 **Health in People with Type 2 Diabetes: A Protocol for A Randomised Controlled Trial**

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6 3  
7  
8 4 Courtney R. Chang<sup>1,2</sup>, Thomas Astell-Burt<sup>1,3,4,5,6</sup> Brooke M. Russell<sup>1,2</sup>, Monique E. Francois<sup>1,2\*</sup>  
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34 22  
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38 26 **Word count:** 4029  
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41 29 Protocol version 1 September 2021  
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43 31 Trial Sponsor: University of Wollongong [research-services@uow.edu.au](mailto:research-services@uow.edu.au)  
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## 32 ABSTRACT

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

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

50 **Ethics and dissemination:** The joint UOW and ISLHD Ethics Committee approved protocol  
51 (2019/ETH09856) prospectively registered at the Australian New Zealand Clinical Trials  
52 Registry. Study results will be published as peer-reviewed articles, presented at  
53 national/international conferences and media reports. Findings will impart new knowledge to the  
54 scientific community, general public, and practitioners, regarding the benefits of personalising  
55 exercise timing in people with T2D.

56  
57 **Abstract word count:** 271

58  
59 **Trial registration number:** ACTRN12619001049167

60  
61 **Keywords:** T2D, exercise, timing, adherence, peak hyperglycaemia, cardiovascular risk  
62

### 63 **Strengths and Limitations of this Study**

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

94

## 95 INTRODUCTION

96 Approximately 463 million adults are living with type 2 diabetes (T2D) and this number is  
97 expected to increase to 700 million by 2045 [1]. Individuals with T2D have a twofold greater risk  
98 of developing atherosclerotic cardiovascular disease (CVD; e.g., myocardial infarction, stroke,  
99 etc.) and CVD accounts for ~70% of deaths in T2D patients [2]. T2D is characterised by elevated  
100 fasting and postprandial blood glucose levels [3]. Large excursions in blood glucose, especially  
101 during the postprandial period (i.e., postprandial hyperglycaemia) cause oxidative stress,  
102 inflammation, and endothelial dysfunction, which mechanistically links impaired glucose  
103 regulation with the development of CVD in people with T2D [4, 5]. Acute and chronic exercise  
104 training improve blood glucose regulation and reduce cardiovascular risk factors. The benefits of  
105 exercise training on glycaemic control are largely attributed to the accumulated effects of  
106 individual exercise sessions [6, 7] increasing contraction- and insulin-mediated glucose uptake [7,  
107 8] consistently and overtime. The current guidelines for physical activity recommend adults  
108 accumulate ~150-300 min of moderate intensity aerobic activity throughout the week to improve  
109 or maintain health [9], including glycaemic control (i.e., glycated haemoglobin [HbA1c]) in people  
110 with T2D [10]. However, mounting evidence [11–15] indicates that exercise timing (e.g., pre- vs  
111 post-meal, or morning vs afternoon) influences glycaemic responses, yet there are no consistent  
112 guidelines on exercise timing in any current physical activity recommendations globally.

113

114 Multiple systematic reviews have recently examined the effects of exercise timing on measures of  
115 glycaemic control in people with T2D and suggest the best time to exercise is within the first few  
116 hours after a meal [11–13]. However, performing exercise at different times of the day (i.e.,  
117 morning vs afternoon) has also shown to influence glycaemic responses [14, 15]. For example,  
118 Savikj et al. (2019) recently demonstrated that two weeks of high intensity interval training (HIIT;  
119 three days/week) performed in the afternoon improved 24 h glucose concentration by -0.6 mmol/L  
120 more than HIIT in the morning [14], whereas a separate study by Teo et al. (2019) found no  
121 significant differences in any glycaemic outcomes (HbA1c, fasting or postprandial glucose) after  
122 12 weeks of exercise (three days/week) performed in the morning vs afternoon [15]. Given the  
123 inconsistent findings and broad recommendations in the current literature (i.e., exercise timing  
124 relative to time of day or meal consumption), a more personalised approach may be needed to

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2  
3 125 target CVD and for practitioners to prescribe exercise timing for people with T2D. Postprandial  
4 126 hyperglycaemia is linked to CVD and timing exercise to specifically target the largest postprandial  
5 127 excursion (i.e., peak hyperglycaemia) of the day may lead to greater glycaemic benefits and  
6 128 reduced cardiovascular risk.  
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12 130 It is unknown if prescribing daily exercise at a specific time of day, to attenuate peak  
13 131 hyperglycaemia, will lead to greater improvements in HbA1c compared to the current physical  
14 132 activity guidelines of accumulating ~150-300 min/week at any time. Further, the vascular effects  
15 133 of exercising specifically to attenuate peak hyperglycaemia are unknown. The endothelium is a  
16 134 key regulator of vascular homeostasis and endothelial function is an early risk factor for CVD [16,  
17 135 17]. Hyperglycaemia increases production of reactive oxygen species [18] and the resulting  
18 136 oxidative stress reduces vascular homeostasis (i.e., by increasing vasoconstriction and decreasing  
19 137 vasodilation) which can lead to endothelial dysfunction and CVD over time. A longer-term  
20 138 intervention of daily exercise is now warranted to garner a better understanding of exercise timing  
21 139 on glycaemic control and to examine whether exercising at the time of peak hyperglycaemia  
22 140 improves HbA1c and reduces cardiovascular risk factors.  
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31 141  
32 142 The aim of this trial is to determine whether exercising to attenuate peak hyperglycaemia (exercise  
33 143 beginning ~30 min before peak hyperglycaemia) improves glycaemic control (HbA1c and 24 h  
34 144 mean, fasting and postprandial glucose) and reduces cardiovascular risk factors (including lipids,  
35 145 c-reactive protein, vascular function), more than exercising not at time of peak hyperglycaemia  
36 146 (exercise ~90 min after peak hyperglycaemia) or at any time of the day (no prescribed exercise  
37 147 time i.e., physical activity guidelines) in people with T2D. The efficacy, feasibility, and adherence  
38 148 to prescribing an exercise time will also be explored during a three-month follow-up. Given that  
39 149 postprandial hyperglycaemia is associated with worsening HbA1c [19] and endothelial  
40 150 dysfunction [20] in T2D, we hypothesise that exercising to attenuate peak hyperglycaemia will  
41 151 lead to the greatest improvements in glycaemic control, which in turn will improve vascular  
42 152 function and reduce cardiovascular risk.  
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## 154 **METHODS**

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

### 163 **Participants**

164 Inclusion criteria:

- 165 • Physician diagnosed T2D (registration with the National Diabetes Services Scheme)
- 166 • HbA1c between 6.5-9.0%
- 167 • Aged between 40 and 75 years
- 168 • BMI between 27-40 kg/m<sup>2</sup>
- 169 • Diabetes treated with lifestyle, oral medications and/or intermediate/long-acting insulin
- 170 • Stable weight for previous 3 months ( $\pm$  4 kg)
- 171 • Stable medications for previous 3 months
- 172 • Able to speak and understand English

174 Exclusion criteria:

- 175 • Any absolute contraindications to exercise (i.e., musculoskeletal/joint injury, etc.)
- 176 • Presence or history of CVD, kidney or liver disease
- 177 • Diagnosed diabetes complications i.e., neuropathy, retinopathy etc.
- 178 • Diabetes treated with short acting insulin
- 179 • Uncontrolled hypertension (>160/90 mmHg)
- 180 • >150 min of moderate to vigorous intensity exercise/week (per Godin leisure time  
181 physical activity questionnaire)

### 183 **Study Design**

1  
2  
3 184 Seventy males and females (aged 40-75 years, BMI 27-40 kg/m<sup>2</sup>) will be recruited and randomised  
4  
5 185 to one of three groups for eight weeks: i) exercise at time of peak hyperglycaemia (ExPeak), ii)  
6  
7 186 exercise not at time of peak hyperglycaemia (NonPeak) or, iii) waitlist control (WLC). Participants  
8  
9 187 allocated to the WLC group will be re-randomised to the ExPeak or NonPeak intervention group  
10  
11 188 following the waitlist period. During the eight-week intervention (Phase 1), all groups will be  
12  
13 189 prescribed ~150 min/week of physical activity as per the current guidelines. The intervention  
14  
15 190 groups will be prescribed daily exercise at a specific time. During the exercise intervention,  
16  
17 191 participants will have five telehealth consults with an accredited exercise physiologist, in line with  
18  
19 192 Australia's Medicare health plan for people with diabetes. An automatic computer-generated  
20  
21 193 random number table will be used to perform random allocation of participants (1:1 ratio),  
22  
23 194 stratified for sex and exogenous insulin usage. A sealed envelope system will be used to blind  
24  
25 195 researchers from group allocations. Allocations will be sealed in an opaque envelope (by a person  
26  
27 196 independent to the clinical trial) until a participant is enrolled and needing to commence the  
28  
29 197 intervention.

30  
31 198  
32  
33 199 Participants will undergo a three-month follow-up (Phase 2) where adherence to exercising at a  
34  
35 200 prescribed time (with minimal contact from the research team) will be assessed. During Phase 2,  
36  
37 201 participants in the ExPeak group will be advised to continue exercising daily at their time of peak  
38  
39 202 hyperglycaemia and participants in the NonPeak group will be advised to exercise in accordance  
40  
41 203 with the World Health Organization 2020 guidelines for physical activity i.e., accumulate ~150-  
42  
43 204 300 min of physical activity per week at any time of day [9], thus becoming the control group.

44  
45 205  
46  
47 206 **[INSERT STUDY DESIGN FIGURE HERE]**

48  
49 207  
50  
51 208 **Interventions**

52  
53 209 All exercise sessions will be performed in a free-living setting (home-based) for the duration of  
54  
55 210 this trial. Participants in the ExPeak and NonPeak groups will be prescribed ~22 min of daily  
56  
57 211 moderate-intensity physical activity (aerobic exercise e.g., walking, cycling, swimming, etc.) for  
58  
59 212 eight weeks, to align with the physical activity guidelines of accumulating at least 150 min of  
60  
213 aerobic activity per week. The pre-intervention Continuous Glucose Monitoring (CGM) data  
214  
(*outlined below*) will be used to determine time of peak hyperglycaemia. The ExPeak group will



1  
2  
3 215 begin exercising ~30 min before their peak hyperglycaemia typically occurs and the NonPeak  
4  
5 216 group will begin exercising ~90 min after their peak hyperglycaemia typically occurs. Participants  
6  
7 217 in the control groups will exercise in accordance with the physical activity guidelines [9]. Exercise  
8  
9 218 intensity will be determined using the Borg Scale to indicate Rate of Perceived Exertion, which  
10  
11 219 uses numbered categories from 6-20 (i.e., no exertion at all to maximal exertion) to gauge how  
12  
13 220 hard a person 'feels' they are working [23]. Daily exercise should be completed as one continuous  
14  
15 221 bout but may be accumulated over a 30 min period depending on individual needs (ideally  
16  
17 222 accumulated in bouts of >10 min, interspersed with short periods of rest). Participants will have  
18  
19 223 two phone consults and five telehealth video consults with an accredited exercise physiologist on  
20  
21 224 alternate weeks throughout the eight-week exercise intervention, in addition to maintaining  
22  
23 225 standard care treatment with health care professionals and habitual medication and diet.  
24

## 226 227 **Experimental Protocol**

25  
26 228 The intervention period will be five months in total, with the eight-week intervention (Phase 1)  
27  
28 229 commencing after two weeks of pre-intervention monitoring, and the three-month follow-up  
29  
30 230 (Phase 2) commencing after two weeks of post-intervention monitoring. Pre- and post-assessments  
31  
32 231 will be conducted at the University of Wollongong to evaluate glycaemic and metabolic control,  
33  
34 232 vascular function, and body composition (Figure 2). Participants will be instructed to abstain from  
35  
36 233 physical activity for >24 h and to fast for ~10 h before each in-lab assessment.  
37

38 234  
39 235 A two-week monitoring period will be conducted pre-intervention, midway through, post-  
40  
41 236 intervention and after the three-month follow-up. Participants in the WLC group will have two  
42  
43 237 additional weeks of baseline monitoring before the waitlist period commences. Participants will  
44  
45 238 maintain normal daily activity and dietary patterns during each monitoring period, except for the  
46  
47 239 midpoint assessment where they will continue to follow intervention protocol. During the three-  
48  
49 240 month follow-up, participants will complete three short surveys (one at the end of each month,  
50  
51 241 seven questions each) to assess adherence to the exercise prescription but will otherwise have no  
52  
53 242 formal contact with the research team (Figure 2). Other than the prescribed exercise, participants  
54  
55 243 will be asked to maintain normal dietary habits and medication usage throughout the study period.  
56

57  
58  
59 244  
60 **[INSERT PROTOCOL TIMELINE FIGURE HERE]**



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2  
3 246  
4  
5 247 *Determination of Peak Hyperglycaemia*  
6  
7 248 The ‘Glucose Pattern Insights’ report (automatically generated via LibreView software), for the  
8  
9 249 two-week pre-intervention CGM (Freestyle Libre, Abbott), will be used to determine the average  
10  
11 250 time that peak hyperglycaemia occurs for each participant (Figure 3). Trained researchers will  
12  
13 251 verify time of peak hyperglycaemia by analysing the raw CGM data using the following methods:  
14  
15 252 After the CGM data is cleaned and separated into full days (i.e., >24 h of uninterrupted data),  
16  
17 253 maximum glucose and the time it occurs will be calculated for each day of the two-week  
18  
19 254 monitoring period. The average time of day that peak hyperglycaemia occurs will be then  
20  
21 255 determined for each participant—if peak hyperglycaemia occurs at the same time of day (or within  
22  
23 256 ~30 min) on five or more occasions over the 14 d CGM period, that time of day will be identified  
24  
25 257 as the time of peak hyperglycaemia. Alternatively, time of peak hyperglycaemia will be calculated  
26  
27 258 as an average from 14 days of continuous glucose measurements. Time of peak hyperglycaemia  
28  
29 259 will be re-assessed following the waitlist period for participants initially randomised to the WLC  
30  
31 260 group and again in the ExPeak group for the three-month follow up.

32  
33 261  
34 262 **[INSERT GLUCOSE PATTERN INSIGHT EXAMPLE HERE]**  
35

### 36 263

### 37 264 **Outcome Measures**

38 265 The primary outcome is the change in HbA1c following the eight-week intervention. Secondary  
39  
40 266 outcome measures will examine additional indices of glycaemic control (via CGM derived  
41  
42 267 variables [including 24 h mean, area under the curve, glycaemic variability, time in range etc.] and  
43  
44 268 a mixed meal tolerance test [MMTT]), vascular function (endothelial function and arterial  
45  
46 269 stiffness), metabolic control (blood lipids and inflammation) and body composition (BMI, total  
47  
48 270 and regional fat, and fat-free mass). Tertiary outcome measures will focus on the efficacy,  
49  
50 271 feasibility, and adherence to exercise prescription (accelerometer and surveys). Apart from the  
51  
52 272 mid-intervention assessment, participants will resume normal daily living (not exercise at their  
53  
54 273 prescribed time) to assess training effects.

55  
56 274  
57  
58 275 *Glycaemic Control*  
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1  
2  
3 276 The primary outcome of glycaemic control will be assessed by measuring HbA1c. A finger prick  
4 277 blood sample will be collected using a HbA1c (~2 µL) specific test disc and immediately analysed  
5 278 with the Cobas b 101 System (Roche Diagnostics).  
6  
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9

10 280 Secondary glycaemic outcomes will also be assessed with CGM and a MMTT (low glycaemic  
11 281 index, Glucerna®). From each two-week CGM, we will calculate mean 24 h glucose, 24 h and 3 h  
12 282 postprandial area under the curve (AUC) and incremental area under the curve (iAUC) calculated  
13 283 using the trapezoid method [24], hyperglycaemia (time spent ≥10 mmol/L), glycaemic variability  
14 284 (mean amplitude of glycaemic variability [MAGE]) and nocturnal glucose profiles. We will also  
15 285 calculate mean glucose, total AUC and iAUC for 2 h following the MMTT. The MMTT will begin  
16 286 after an overnight fast (>10 h), and blood glucose will be measured with the CGM and finger  
17 287 pricks (0, 15, 30, 60, 90 and 120 min) following drink consumption.  
18  
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#### 25 288

#### 26 289 *Metabolic Control*

27 290 Metabolic control will be assessed by measuring blood lipids (triglyceride, total cholesterol, high-  
28 291 density lipoprotein, and low-density lipoprotein) and inflammation (CRP). Finger prick blood  
29 292 samples will be collected via lipid (~19 µL) or inflammation (~12 µL) specific test discs and  
30 293 immediately analysed with the Cobas b 101 System.  
31  
32  
33  
34

#### 35 294

#### 36 295 *Body Composition*

37 296 Waist to hip ratio, height, and weight will be measured to the nearest 0.1 cm and 0.1 kg,  
38 297 respectively, using standard scales, a stadiometer and measuring tape. Total and regional fat and  
39 298 fat-free mass will be measured by dual-energy x-ray absorptiometry ([DEXA], MedixDR Whole  
40 299 Body DEXA, SYD, AU).  
41  
42  
43  
44

#### 45 300

#### 46 301 *Vascular Function*

47 302 Endothelial function will be assessed by measuring endothelium-dependent flow-mediated  
48 303 dilation (FMD). This technique uses ultrasound imaging (Terason uSmart® 3300) of the brachial  
49 304 artery. Following 10-15 min of laying supine (at rest), a longitudinal section of the brachial artery,  
50 305 2-3 cm above the antecubital fossa, will be imaged using B-mode ultrasound imaging (insonation  
51 306 angle of 60°). A blood pressure cuff placed around the forearm, 1-2 cm below the olecranon  
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1  
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3 307 process, will then be rapidly inflated to ~60 mmHg above resting systolic blood pressure for 5 min.  
4  
5 308 Brachial artery diameter and blood flow velocity will be recorded for 1 min before cuff inflation  
6  
7 309 (baseline), ~30 s prior to cuff release (ischemic stimulus), and 3 min following cuff release  
8  
9 310 (recovery) [25, 26]. The ~5 min recording will then be analysed with custom-designed edge-  
10  
11 311 detection and wall-tracking software (Cardiovascular Suite, Quipu, Italy) which reduces user bias  
12  
13 312 and increases accuracy. FMD will be reported as an absolute change in artery diameter (absolute  
14  
15 313  $\text{FMD} = \text{postocclusion}_{\text{mean diameter}} - \text{preocclusion}_{\text{mean diameter}}$ ), and a relative change in artery diameter  
16  
17 314 from baseline [ $\% \text{FMD} = 100 \times (\text{absolute FMD} / \text{preocclusion}_{\text{mean diameter}})$ ]. Allometric scaling will  
18  
19 315 be used to account for potential confounders from baseline diameter [26, 27].  
20

21 316  
22 317 Blood flow (mL/min) will be measured using non-invasive Doppler from the cross-sectional area  
23  
24 318 and blood velocity [ $\text{velocity} \times \pi \times (\text{diameter}^2/4) \times 60$ ]. Shear rate (s<sup>-1</sup>) will then be determined  
25  
26 319 from the diameter and velocity measures (four times velocity/diameter) [28]. Shear rate area under  
27  
28 320 the curve (SR<sub>AUC</sub>) will automatically be calculated from the diameter and velocity measures from  
29  
30 321 the time of cuff release to peak dilation of the artery. Antegrade and retrograde mean blood  
31  
32 322 velocities will be used to calculate baseline antegrade and retrograde shear rates (four times mean  
33  
34 323 baseline antegrade or retrograde velocity ÷ mean baseline diameter), and the mean blood flow to  
35  
36 324 mean arterial pressure ratio will be used to measure vascular conductance (mL/min/mmHg) [25,  
37  
38 325 26].  
39

40 326  
41 327 Central arterial stiffness will be assessed via pulse wave analysis (PWA) and pulse wave velocity  
42  
43 328 (PWV) measurements (SphygmoCor® XCEL System, AtCor Medical). PWA will be used to  
44  
45 329 measure central blood pressure. A brachial blood pressure cuff will be inflated and the central  
46  
47 330 aortic pressure waveform, derived from pulsations at the brachial artery, will be recorded for 5 s  
48  
49 331 and then automatically analysed through the SphygmoCor software. Key parameters of central  
50  
51 332 blood pressure and arterial stiffness will be determined from the aortic waveform including systolic  
52  
53 333 pressure, diastolic pressure, pulse pressure, aortic pressure, augmentation index and mean arterial  
54  
55 334 pressure. PWV will be measured by holding a tonometer on the carotid artery for 10-15 s, while a  
56  
57 335 femoral blood pressure cuff is automatically inflated. Once fully inflated, the femoral cuff and  
58  
59 336 carotid tonometer will simultaneously record a 10 s capture of the carotid and femoral pressure  
60  
337 waveforms. PWV will then be calculated by dividing the carotid-femoral distance by the pulse

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3 338 transit time; the carotid-femoral distance will be calculated by subtracting the proximal distance  
4 339 (distance between the carotid artery and sternal notch) from the distal distance (distance between  
5 340 the sternal notch and proximal edge of the femoral cuff) [PWV (m/s) = (distal –  
6 341 proximal<sub>distance</sub>)/transit time] [29]. Measurements will be performed in duplicate. A third  
7 342 measurement will be taken if the difference between the two PWV values is >0.5 m/s and the  
8 343 average of the three values will be used.  
9 344

10 345 An automatic blood pressure monitor (Oscar2 Ambulatory Blood Pressure Monitor with  
11 346 SphygmoCor interfacing, SunTech Medical) will also be used to continuously assess blood  
12 347 pressure and pulse wave analyses every hour for 24 hours. We will report 24 h blood pressure as  
13 348 an average of 24 measurements.  
14 349

#### 15 350 *Diet and Physical Activity Monitoring*

16 351 Participants will complete a 7 d diet record during each two-week monitoring period. Food diaries  
17 352 will be analysed (using FoodWorks10 Nutrition Software) to confirm macronutrient composition  
18 353 and total energy intake are consistent throughout the study period. Physical activity will be  
19 354 monitored during the same 7 d period using an accelerometer (ActiGraph Bluetooth® Smart  
20 355 wGT3X-BT), worn around the waist during wake hours. Physical activity and sedentary time will  
21 356 be compared between groups at each timepoint during wake hours. The accelerometers will also  
22 357 be used to confirm exercise intensity and compliance to the exercise prescription. A heart rate  
23 358 monitor (Polar H7 Bluetooth® Heart Rate Monitor) will be worn during the midpoint monitoring  
24 359 period on the same days as the accelerometer, only during the exercise sessions, to assess exercise  
25 360 intensity.  
26 361

#### 27 362 *Adherence and Lifestyle Questionnaires*

28 363 Participants will complete a quality of life (SF-36) survey and a self-regulatory efficacy and  
29 364 physical activity questionnaire during each two-week monitoring period. Participants will also  
30 365 complete three surveys during the follow-up period, one at the end of each month that is specific  
31 366 to their exercise group, to assess adherence to exercise prescription between the ExPeak and  
32 367 control groups. Surveys will include questions on known perceived facilitators and barriers to  
33 368 filling the exercise prescription and, in turn, support or aggravation of intervention efficacy. Such  
34 369

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

371  
372 *Remote Participants*  
373 Participants who cannot attend the university (e.g., due to COVID-19 restrictions) for in-lab  
374 assessments will receive a home-based testing kit (via mail) which includes: a dried blood spot  
375 test kit (ZRT Laboratory kit for measurement of HbA1c, lipids, CRP, and insulin), CGM,  
376 accelerometer and Glucerna MMTT drink. Instructions will be provided and followed-up via a  
377 phone or video call. All other study protocols will be the same, however data for the DEXA and  
378 vascular assessments will not be available.

379

## 380 **Statistical Analysis**

### 381 *Sample size*

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

390  
391 *Statistics*

392 This study will be reported according to the CONSORT 2010 Statement and the CONSERVE  
393 2021 Statement for randomised controlled trials. Descriptive statistics will be assessed (means,  
394 standard deviation and frequencies), and histograms, Q-Q plots and the Shapiro-Wilk test will be  
395 used to identify outliers and test for normality. Linear mixed models (with time x intervention, and  
396 main effect of time) will be used to assess differences between groups, for primary (HbA1c) and  
397 secondary (CGM, MMTT, vascular function, metabolic control, and body composition) outcomes.  
398 Tertiary outcomes (e.g., adherence to the exercise prescription) will be analysed from the  
399 accelerometer and follow-up surveys (Qualtrics<sup>XM</sup>). Attention to treat analyses will be performed

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3 400 for primary analyses (Phase 1) and per protocol analyses will be undertaken for secondary and  
4 401 tertiary outcomes (Phase 2). Data with skewed distribution will be log-transformed or square-  
5 402 rooted prior to the statistical analysis. For the three-month follow-up, intention to treat analysis  
6 403 will be used and missing data will not be imputed.  
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9

10 404

### 11 405 **Patient and Public Involvement**

12 406 No patient involved.  
13  
14  
15 407

16

### 17 408 **ETHICS AND DISSEMINATION**

18 409 This research has been reviewed and approved by the University of Wollongong Human Research  
19 410 Ethics Committee (2019/ETH09856). This trial was prospectively registered at the Australian New  
20 411 Zealand Clinical Trials Registry (ACTRN12619001049167). Participants will remain anonymous,  
21 412 and all collected data will be de-identified and coded. An alpha-numerical code (stored on a  
22 413 password protected central spreadsheet) will be allocated to each participant and used for  
23 414 identification on all subsequent paperwork. All results from the study will be published as peer-  
24 415 reviewed articles in international journals, presented at international conferences and promoted  
25 416 through social media. Changes to the protocol due to COVID-19 will be reported according to the  
26 417 CONSERVE 2021 Statement [33].  
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### 35 419 **DISCUSSION**

36 420 The primary objective of this trial is to determine if strategically timing exercise, to reduce  
37 421 daily peak hyperglycaemia, will improve glycaemic control and lower cardiovascular risk factors  
38 422 in people with T2D. This is the first study to investigate whether prescribing exercise that is  
39 423 personalised to target daily peak hyperglycaemia, using CGM, can improve cardiovascular risk  
40 424 factors in T2D. Based on evidence from prior research [11, 34–36], it is hypothesised that  
41 425 strategically timing daily exercise to attenuate peak hyperglycaemia will improve glycaemic  
42 426 control (HbA1c), and the reduction in peak glycemia will improve vascular function (endothelial  
43 427 function and arterial stiffness), blood lipids and CRP, more than exercising not at peak  
44 428 hyperglycaemia or control standard-care (i.e., physical activity guidelines).  
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3 430 Recent evidence suggests exercise timing may be important to offset circadian rhythms [14] and  
4  
5 431 to target postprandial hyperglycaemia [11] in T2D. However, there are no recommendations for  
6  
7 432 exercise timing in the current physical activity guidelines (i.e., physical activity can be  
8  
9 433 accumulated at any time throughout the week). Further, adherence to the current recommendations  
10  
11 434 is notoriously poor. Regardless of the effectiveness for an intervention to improve diabetes  
12  
13 435 management, findings will only be translatable if patients comply with and adopt to the treatment  
14  
15 436 over the long-term. Therefore, adherence to prescribed daily exercise time (i.e., creating more of  
16  
17 437 a habit) will be assessed for three months following the eight-week intervention. Exercising at the  
18  
19 438 time of peak hyperglycaemia may improve self-efficacy to the exercise prescription, as results  
20  
21 439 from the CGM data (pre/mid/post eight-week intervention) will allow participants to see the direct  
22  
23 440 impact of exercise on blood glucose levels. Use of CGM in this trial not only offers the distinct  
24  
25 441 advantage of determining time of peak hyperglycaemia, but will also allow us to examine any  
26  
27 442 changes in daily glycaemic patterns, such as glycaemic variability, which are more closely related  
28  
29 443 to cardiovascular risk than HbA1c [37]. If strategically timing exercise to attenuate peak  
30  
31 444 hyperglycaemia improves long-term glycaemic control (HbA1c), reduces cardiovascular risk  
32  
33 445 (endothelial dysfunction and arterial stiffness), and improves exercise adherence then this may be  
34  
35 446 an alternative recommendation for physical activity prescription in people with T2D.

447

#### 448 *Strengths and Limitations*

36 449 This is the first randomised controlled trial to examine the effects of personalising exercise timing  
37  
38 450 to attenuate peak hyperglycaemia (determined via continuous glucose monitoring technology) on  
39  
40 451 cardiometabolic and vascular health outcomes in individuals with type 2 diabetes. This study will  
41  
42 452 be conducted in free-living conditions, with exercise performed at home and contact/delivery of  
43  
44 453 *Phase 1* (8-week exercise intervention) mirroring standard-care (five telehealth calls with an  
45  
46 454 exercise physiologist), while *Phase 2* (3-month follow-up) will assess adherence to the exercise  
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48 455 prescription (with minimal contact from the research team); thus informing us of the real-world  
49  
50 456 applicability of the proposed exercise prescription. In addition, this study will utilise a variety of  
51  
52 457 data collection methods (in-lab and free-living) to objectively measure cardiometabolic health,  
53  
54 458 vascular function, physical activity, and behaviour change across the trial. Due to the COVID-19  
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56 459 pandemic remote participants from across rural and urban Australia will be included, allowing for  
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58 460 a wider range of individuals to be recruited while adhering to the COVID-19 restrictions. However,



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3 461 this is also a limitation as the vascular and body composition measures will be excluded for those  
4  
5 462 who cannot attend university assessments, and dried blood spot testing kits will be used rather than  
6  
7 463 the gold-standard plasma measurement of HbA1c. Finally, a limitation of the waitlist control group  
8  
9 464 is the potential overestimation of intervention effects and bias in favour of the treatment group.  
10  
11 465 Nevertheless, inclusion of the waitlist control group will provide insight on the cause-effect  
12  
13 466 relationship between the intervention and subsequent health outcomes/behaviour changes, as these  
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15 467 participants will follow a delayed-start design (i.e., will receive treatment following the waitlist  
16  
17 468 period), thus allowing for direct comparisons to be made under various conditions with reduced  
18  
19 469 error variance and not withholding treatment to individuals.  
20

470

## 471 **COMPETING INTERESTS**

472 The authors have no conflicts of interest to disclose.

473

## 474 **AUTHOR CONTRIBUTIONS**

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

479

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484 Council (NHMRC) Investigator Grant (APP1177234). TAB's time was supported by a NHMRC  
485 Boosting Dementia Research Leader Fellowship (GNT1140317).

486

## 487 **FIGURES**

488

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

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3 492 to WLC will be re-randomised to ExPeak or NonPeak after the waitlist period. Following the eight-  
4 493 week intervention (Phase 1), the ExPeak (N=27) group will continue to exercise at peak  
5 494 hyperglycaemia, whereas the NonPeak (N=27) group will become the control (CTL; N=27) group  
6 495 for the three-month follow-up (Phase 2). Participants in the WLC and CTL groups will receive  
7 496 standard care advice to exercise in accordance with the World Health Organization physical  
8 497 activity guidelines.  
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16 499 **Figure 2. TIMELINE OF STUDY PROTOCOL.** Participants randomised to the waitlist control  
17 500 (WLC) group will undergo measures before and after an eight-week waitlist control period. Then  
18 501 are randomised to one of two intervention groups for eight weeks: i) exercise at peak  
19 502 hyperglycaemia ([ExPeak] ExRx: begin exercise ~30 min before peak hyperglycaemia) or ii)  
20 503 exercise after peak hyperglycaemia ([NonPeak] ExRx: begin exercise ~90 min after peak  
21 504 hyperglycaemia). All groups undergo pre-intervention CGM to measure time of peak  
22 505 hyperglycemia prior to interventions. **PHASE 1. Eight-week intervention:** Both intervention  
23 506 groups will perform ~22 min of daily exercise at their prescribed time. Participants will receive  
24 507 two phone consults and five telehealth video consults (via zoom or skype) with an Accredited  
25 508 Exercise Physiologist. **PHASE 2. Three-month follow-up:** The ExPeak group will continue to  
26 509 exercise for ~22 min/day at peak hyperglycaemia and the NonPeak group will exercise according  
27 510 to the physical activity guidelines. Three adherence surveys will be conducted (at the end of each  
28 511 month), but no formal contact. **Free Living Assessments:** 14 d CGM, 2 h MMTT, 7 d ActiGraph  
29 512 activity monitoring, 7 d HR monitoring (midpoint only; Polar Bluetooth HR monitor worn on same  
30 513 days as ActiGraph, only during prescribed exercise), 7 d diet record, quality of life survey, and  
31 514 self-regulatory efficacy and physical activity questionnaire. **In-Lab Assessments:** i) blood sample  
32 515 HbA1c, CRP, and blood lipids (TG, TC, HDL, and LDL); ii) vascular measures FMD and arterial  
33 516 stiffness via PWV/PWA; and iii) anthropometrics (height and weight) and body composition  
34 517 DEXA.

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48 518 *Abbreviations:* waitlist control, WLC; exercise at peak hyperglycaemia (intervention group),  
49 519 ExPeak; exercise after peak (intervention group), NonPeak; exercise prescription, ExRx;  
50 520 accredited exercise physiologist, AEP; continuous glucose monitoring, CGM; mixed meal  
51 521 tolerance test, MMTT; heart rate, HR; glycated hemoglobin, HbA1c; c-reactive protein, CRP;  
52 522 triglyceride, TG; total cholesterol, TC; high-density lipoprotein, HDL; low-density lipoprotein,  
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3 523 LDL; flow-mediated dilation, FMD; pulse wave velocity, PWV; pulse wave analysis, PWA; and  
4 524 dual-r-ray absorptiometry, DEXA.

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8 526 **Figure 3. Example ‘Glucose Pattern Insights’ Report**, via LibreView, of a 24 h blood glucose  
9 527 curve averaged from 14 days of continuous glucose measurements.

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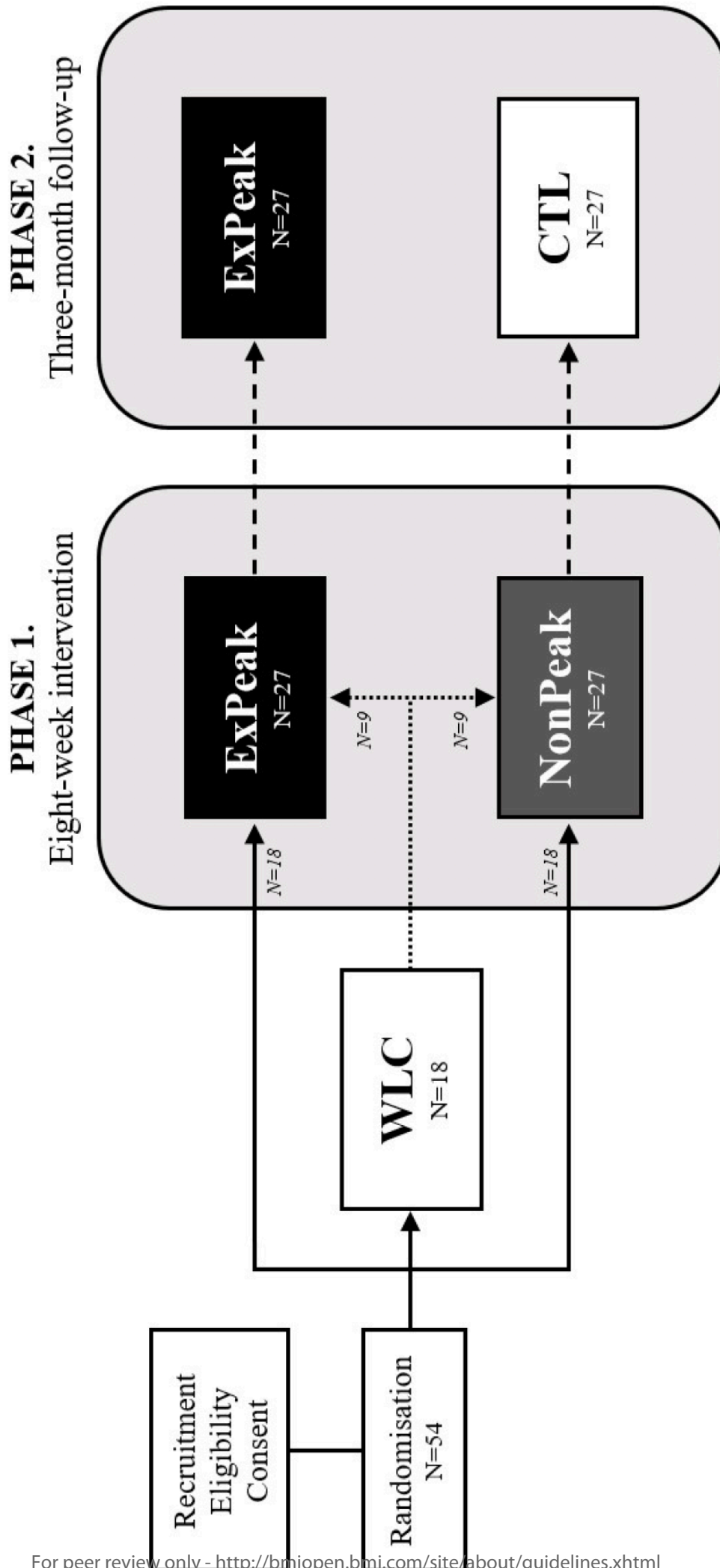
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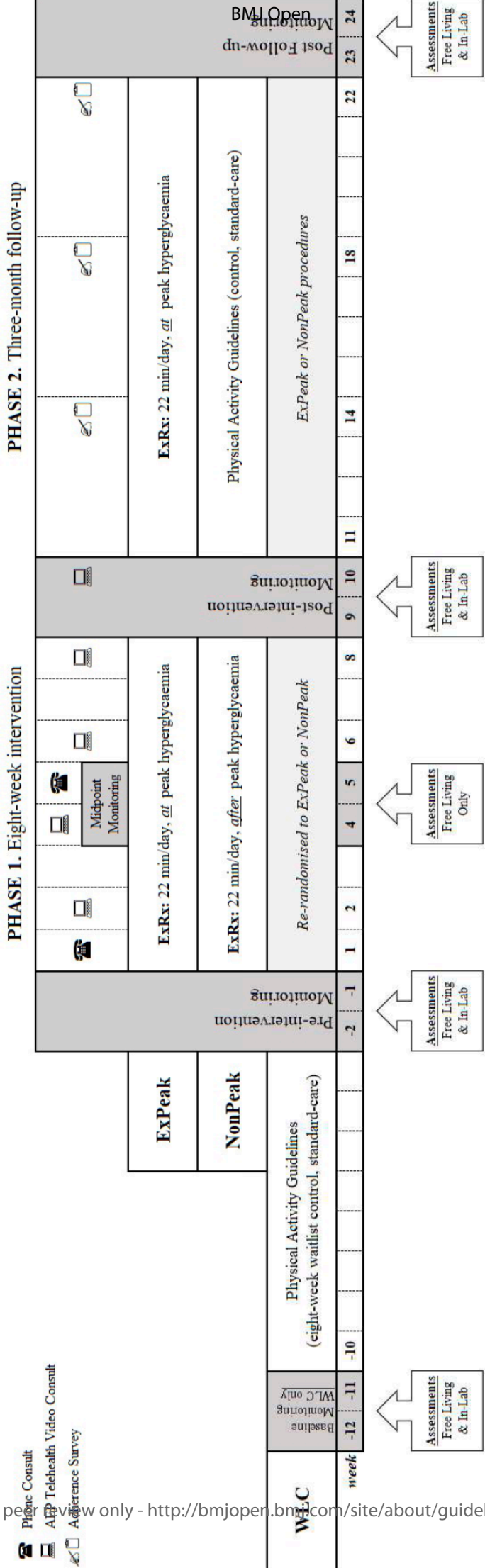
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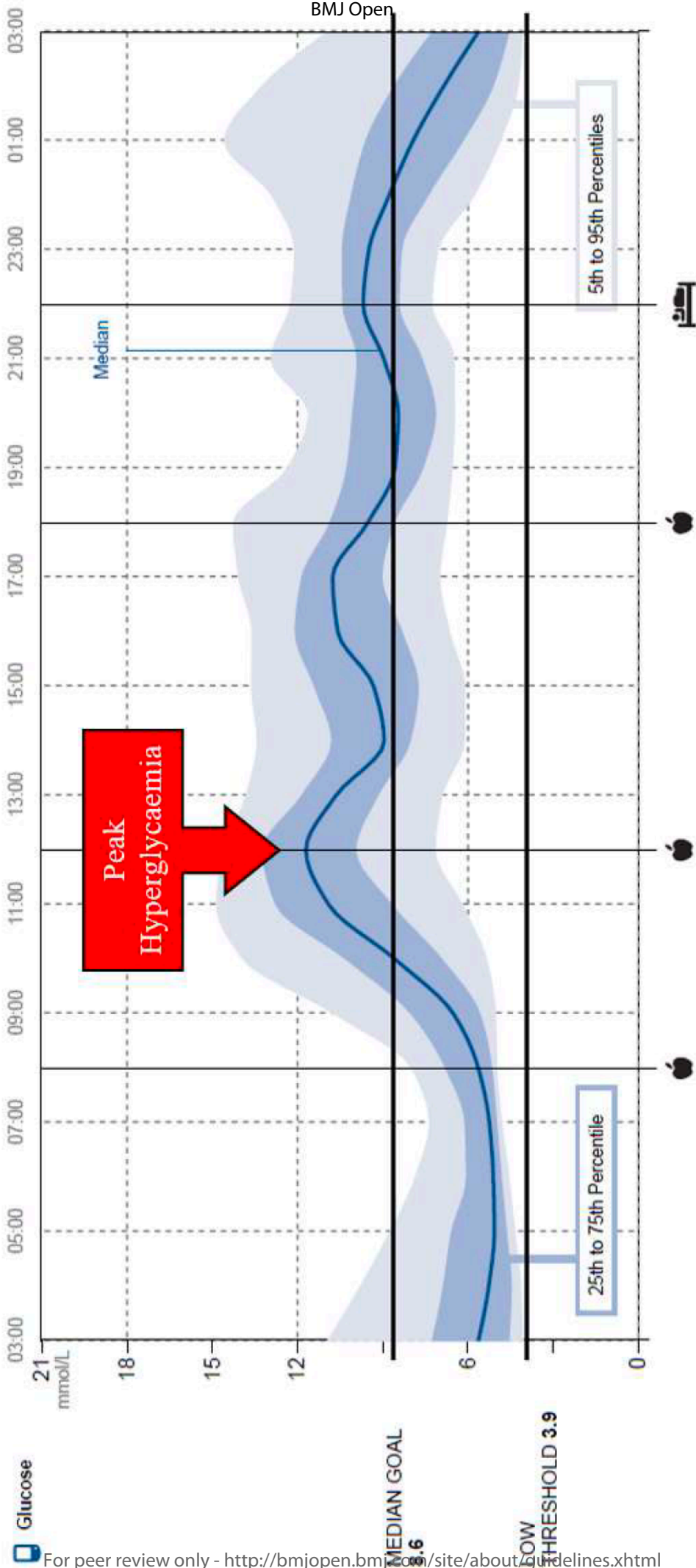


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# Reporting checklist for protocol of a clinical trial.

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

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	N/A
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	N/A
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	<b>Introduction</b>			
25				
26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	5
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	6-8
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	5
38				
39				
40	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	6
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46	<b>Methods:</b>			
47	<b>Participants,</b>			
48	<b>interventions, and</b>			
49	<b>outcomes</b>			
50				
51				
52				
53	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	5
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
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1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
2				
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6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
7	description			
8				
9				
10	Interventions:	<a href="#">#11b</a>	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
11	modifications			
12				
13				
14				
15	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
16	adherence			
17				
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19				
20	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
21	concomitant care			
22				
23				
24	Outcomes	<a href="#">#12</a>	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
25				
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34	Participant timeline	<a href="#">#13</a>	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
35				
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40	Sample size	<a href="#">#14</a>	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
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44				
45	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	6
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47				
48				
49	<b>Methods: Assignment</b>			
50	<b>of interventions (for</b>			
51	<b>controlled trials)</b>			
52				
53				
54	Allocation: sequence	<a href="#">#16a</a>	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
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol
12	implementation		participants, and who will assign participants to interventions
13			
14	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial
15			participants, care providers, outcome assessors, data analysts),
16			and how
17			
18			
19			
20	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible,
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	<b>Methods: Data</b>		
26	<b>collection,</b>		
27	<b>management, and</b>		
28	<b>analysis</b>		
29			
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31			
32	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
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42			
43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any
49			related processes to promote data quality (eg, double data entry;
50			range checks for data values). Reference to where details of data
51			management procedures can be found, if not in the protocol
52			
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54			
55	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
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1	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	14
2	analyses		analyses)	
3				
4	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	14
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
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10	<b>Methods: Monitoring</b>			
11				
12	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of	1
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
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22	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	N/A
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	N/A
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
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33	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	1
34			whether the process will be independent from investigators and	
35			the sponsor	
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38	<b>Ethics and</b>			
39	<b>dissemination</b>			
40				
41				
42	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	2
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	2
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
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53	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	6
54			participants or authorised surrogates, and how (see Item 32)	
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
5				
6	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	6
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators	14
12			for the overall trial and each study site	
13				
14				
15	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and	14
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results	2
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
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33	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	2
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	2
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	<b>Appendices</b>			
42				
43	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given to	22
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057183.R2
Article Type:	Protocol
Date Submitted by the Author:	05-Mar-2022
Complete List of Authors:	Chang, Courtney R.; University of Wollongong Astell-Burt, Thomas; University of Wollongong Faculty of Health and Behavioural Sciences, School of Science and Health Russell, Brooke M.; University of Wollongong Francois, Monique E; University of Wollongong
<b>Primary Subject Heading</b>:	Diabetes and endocrinology
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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3 1 **Personalising activity to target peak hyperglycaemia and improve cardiometabolic health**  
4 **in people with type 2 diabetes: protocol for a randomised controlled trial**  
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8 4 Courtney R. Chang<sup>1,2</sup>, Thomas Astell-Burt<sup>1,3,4,5,6</sup> Brooke M. Russell<sup>1,2</sup>, Monique E. Francois<sup>1,2\*</sup>  
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## 32 ABSTRACT

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

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

50 **Ethics and dissemination:** The joint UOW and ISLHD Ethics Committee approved protocol  
51 (2019/ETH09856) prospectively registered at the Australian New Zealand Clinical Trials  
52 Registry. Written informed consent will be obtained from all eligible individuals prior to  
53 commencement of the trial. Study results will be published as peer-reviewed articles, presented  
54 at national/international conferences and media reports.

55 **Trial registration number:** ACTRN12619001049167

56  
57 **Keywords:** T2D, exercise, timing, adherence, peak hyperglycaemia, cardiovascular risk

### 59 Strengths and Limitations of this Study

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

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

## 74 INTRODUCTION

75 Approximately 463 million adults are living with type 2 diabetes (T2D) and this number is  
76 expected to increase to 700 million by 2045 [1]. Individuals with T2D have a twofold greater risk  
77 of developing atherosclerotic cardiovascular disease (CVD; e.g., myocardial infarction, stroke,  
78 etc.) and CVD accounts for ~70% of deaths in T2D patients [2]. T2D is characterised by elevated  
79 fasting and postprandial blood glucose levels [3]. Large excursions in blood glucose, especially  
80 during the postprandial period (i.e., postprandial hyperglycaemia) cause oxidative stress,  
81 inflammation, and endothelial dysfunction, which mechanistically links impaired glucose  
82 regulation with the development of CVD in people with T2D [4, 5]. Acute and chronic exercise  
83 training improve blood glucose regulation and reduce cardiovascular risk factors. The benefits of  
84 exercise training on glycaemic control are largely attributed to the accumulated effects of  
85 individual exercise sessions [6, 7] increasing contraction- and insulin-mediated glucose uptake [7,  
86 8] consistently and overtime. The current guidelines for physical activity recommend adults  
87 accumulate ~150-300 min of moderate intensity aerobic activity throughout the week to improve  
88 or maintain health [9], including glycaemic control (i.e., glycated haemoglobin [HbA1c]) in people  
89 with T2D [10]. However, mounting evidence [11–15] indicates that exercise timing (e.g., pre- vs  
90 post-meal, or morning vs afternoon) influences glycaemic responses, yet there are no consistent  
91 guidelines on exercise timing in any current physical activity recommendations globally.

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3 93 Multiple systematic reviews have recently examined the effects of exercise timing on measures of  
4 94 glycaemic control in people with T2D and suggest the best time to exercise is within the first few  
5 95 hours after a meal [11–13]. However, performing exercise at different times of the day (i.e.,  
6 96 morning vs afternoon) has also shown to influence glycaemic responses [14, 15]. For example,  
7 97 Savikj et al. (2019) recently demonstrated that two weeks of high intensity interval training (HIIT;  
8 98 three days/week) performed in the afternoon improved 24 h glucose concentration by -0.6 mmol/L  
9 99 more than HIIT in the morning [14], whereas a separate study by Teo et al. (2019) found no  
10 100 significant differences in any glycaemic outcomes (HbA1c, fasting or postprandial glucose) after  
11 101 12 weeks of exercise (three days/week) performed in the morning vs afternoon [15]. Given the  
12 102 inconsistent findings and broad recommendations in the current literature (i.e., exercise timing  
13 103 relative to time of day or meal consumption), a more personalised approach may be needed to  
14 104 target CVD and for practitioners to prescribe exercise timing for people with T2D. Postprandial  
15 105 hyperglycaemia is linked to CVD and timing exercise to specifically target the largest postprandial  
16 106 excursion (i.e., peak hyperglycaemia) of the day may lead to greater glycaemic benefits and  
17 107 reduced cardiovascular risk.  
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22 109 It is unknown if prescribing daily exercise at a specific time of day, to attenuate peak  
23 110 hyperglycaemia, will lead to greater improvements in HbA1c compared to the current physical  
24 111 activity guidelines of accumulating ~150-300 min/week at any time. Further, the vascular effects  
25 112 of exercising specifically to attenuate peak hyperglycaemia are unknown. The endothelium is a  
26 113 key regulator of vascular homeostasis and endothelial function is an early risk factor for CVD [16,  
27 114 17]. Hyperglycaemia increases production of reactive oxygen species [18] and the resulting  
28 115 oxidative stress reduces vascular homeostasis (i.e., by increasing vasoconstriction and decreasing  
29 116 vasodilation) which can lead to endothelial dysfunction and CVD over time. A longer-term  
30 117 intervention of daily exercise is now warranted to garner a better understanding of exercise timing  
31 118 on glycaemic control and to examine whether exercising at the time of peak hyperglycaemia  
32 119 improves HbA1c and reduces cardiovascular risk factors.  
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34 120

35  
36 121 The aim of this trial is to determine whether exercising to attenuate peak hyperglycaemia (exercise  
37 122 beginning ~30 min before peak hyperglycaemia) improves glycaemic control (HbA1c and 24 h  
38 123 mean, fasting and postprandial glucose) and reduces cardiovascular risk factors (including lipids,  
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3 124 c-reactive protein, vascular function), more than exercising not at time of peak hyperglycaemia  
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5 125 (exercise ~90 min after peak hyperglycaemia) or at any time of the day (no prescribed exercise  
6  
7 126 time i.e., physical activity guidelines) in people with T2D. The efficacy, feasibility, and adherence  
8  
9 127 to prescribing an exercise time will also be explored during a three-month follow-up. Given that  
10  
11 128 postprandial hyperglycaemia is associated with worsening HbA1c [19] and endothelial  
12  
13 129 dysfunction [20] in T2D, we hypothesise that exercising to attenuate peak hyperglycaemia will  
14  
15 130 lead to the greatest improvements in glycaemic control, which in turn will improve vascular  
16  
17 131 function and reduce cardiovascular risk.  
18

## 19 133 **METHODS AND ANALYSIS**

20 134 A single centre randomised controlled trial will be conducted at the University of Wollongong,  
21  
22 135 Australia from July 2019 to December 2022 (Figure 1). Participants will be recruited through  
23  
24 136 online advertising using a clinical trials recruitment company (Trial Facts). A medical screening  
25  
26 137 questionnaire and informed consent (Supplementary Material) will be obtained from all eligible  
27  
28 138 individuals prior to participation. Study data will be collected and managed using the secure online  
29  
30 139 REDCap (Research Electronic Data Capture) tools hosted at the University of Wollongong,  
31  
32 140 Australia [21, 22].  
33

### 34 142 **Participants**

35  
36 143 Inclusion criteria:

- 37 144 • Physician diagnosed T2D (registration with the National Diabetes Services Scheme)
- 38 145 • HbA1c between 6.5-9.0%
- 39 146 • Aged between 40 and 75 years
- 40 147 • BMI between 27-40 kg/m<sup>2</sup>
- 41 148 • Diabetes treated with lifestyle, oral medications and/or intermediate/long-acting insulin
- 42 149 • Stable weight for previous 3 months ( $\pm$  4 kg)
- 43 150 • Stable medications for previous 3 months
- 44 151 • Able to speak and understand English

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53 153 Exclusion criteria:

- 54 154 • Any absolute contraindications to exercise (i.e., musculoskeletal/joint injury, etc.)



- 155 • Presence or history of CVD, kidney or liver disease
- 156 • Diagnosed diabetes complications i.e., neuropathy, retinopathy etc.
- 157 • Diabetes treated with short acting insulin
- 158 • Uncontrolled hypertension (>160/90 mmHg)
- 159 • >150 min of moderate to vigorous intensity exercise/week (per Godin leisure time  
160 physical activity questionnaire)

161

## 162 **Study Design**

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

177

178 Participants will undergo a three-month follow-up (Phase 2) where adherence to exercising at a  
179 prescribed time (with minimal contact from the research team) will be assessed. During Phase 2,  
180 participants in the ExPeak group will be advised to continue exercising daily at their time of peak  
181 hyperglycaemia and participants in the NonPeak group will be advised to exercise in accordance  
182 with the World Health Organization 2020 guidelines for physical activity i.e., accumulate ~150-  
183 300 min of physical activity per week at any time of day [9], thus becoming the control group.

184

185 **[INSERT STUDY DESIGN FIGURE HERE]**

186

**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.

205

**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.

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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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3 217 maintain normal daily activity and dietary patterns during each monitoring period, except for the  
4 218 midpoint assessment where they will continue to follow intervention protocol. During the three-  
5 219 month follow-up, participants will complete three short surveys (one at the end of each month,  
6 220 seven questions each) to assess adherence to the exercise prescription but will otherwise have no  
7 221 formal contact with the research team (Figure 2). Other than the prescribed exercise, participants  
8 222 will be asked to maintain normal dietary habits and medication usage throughout the study period.  
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224 **[INSERT PROTOCOL TIMELINE FIGURE HERE]**

225

226 *Determination of Peak Hyperglycaemia*

20 227 The ‘Glucose Pattern Insights’ report (automatically generated via LibreView software), for the  
21 228 two-week pre-intervention CGM (Freestyle Libre, Abbott), will be used to determine the average  
22 229 time that peak hyperglycaemia occurs for each participant (Figure 3). Trained researchers will  
23 230 verify time of peak hyperglycaemia by analysing the raw CGM data using the following methods:  
24 231 After the CGM data is cleaned and separated into full days (i.e., >24 h of uninterrupted data),  
25 232 maximum glucose and the time it occurs will be calculated for each day of the two-week  
26 233 monitoring period. The average time of day that peak hyperglycaemia occurs will be then  
27 234 determined for each participant—if peak hyperglycaemia occurs at the same time of day (or within  
28 235 ~30 min) on five or more occasions over the 14 d CGM period, that time of day will be identified  
29 236 as the time of peak hyperglycaemia. Alternatively, time of peak hyperglycaemia will be calculated  
30 237 as an average from 14 days of continuous glucose measurements. Exercise for the ExPeak group  
31 238 will be prescribed in relation to the highest peak (i.e., greatest glucose excursion); if there are  
32 239 multiple glucose excursions throughout the day with the same peak level, participants will be given  
33 240 an option of the times to exercise, but must stick with one time for the duration of the intervention.  
34 241 Time of peak hyperglycaemia will be re-assessed following the waitlist period for participants  
35 242 initially randomised to the WLC group and again in the ExPeak group for the three-month follow  
36 243 up.  
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245 **[INSERT GLUCOSE PATTERN INSIGHT EXAMPLE HERE]**

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247 **Outcome Measures**

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3 248 The primary outcome is the change in HbA1c following the eight-week intervention. Secondary  
4 249 outcome measures will examine additional indices of glycaemic control (via CGM derived  
5 250 variables [including 24 h mean, area under the curve, glycaemic variability, time in range etc.] and  
6 251 a mixed meal tolerance test [MMTT]), vascular function (endothelial function and arterial  
7 252 stiffness), metabolic control (blood lipids and inflammation) and body composition (BMI, total  
8 253 and regional fat, and fat-free mass). Tertiary outcome measures will focus on the efficacy,  
9 254 feasibility, and adherence to exercise prescription (accelerometer and surveys). Apart from the  
10 255 mid-intervention assessment, participants will resume normal daily living (not exercise at their  
11 256 prescribed time) to assess training effects.  
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### 21 258 *Glycaemic Control*

22 259 The primary outcome of glycaemic control will be assessed by measuring HbA1c. A finger prick  
23 260 blood sample will be collected using a HbA1c (~2 µL) specific test disc and immediately analysed  
24 261 with the Cobas b 101 System (Roche Diagnostics).  
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30 263 Secondary glycaemic outcomes will also be assessed with CGM and a MMTT (low glycaemic  
31 264 index, Glucerna®). From each two-week CGM, we will calculate mean 24 h glucose, 24 h and 3 h  
32 265 postprandial area under the curve (AUC) and incremental area under the curve (iAUC) calculated  
33 266 using the trapezoid method [24], hyperglycaemia (time spent  $\geq 10$  mmol/L), glycaemic variability  
34 267 (mean amplitude of glycaemic variability [MAGE]) and nocturnal glucose profiles. We will also  
35 268 calculate mean glucose, total AUC and iAUC for 2 h following the MMTT. The MMTT will begin  
36 269 after an overnight fast (>10 h), and blood glucose will be measured with the CGM and finger  
37 270 pricks (0, 15, 30, 60, 90 and 120 min) following drink consumption.  
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### 45 272 *Metabolic Control*

46 273 Metabolic control will be assessed by measuring blood lipids (triglyceride, total cholesterol, high-  
47 274 density lipoprotein, and low-density lipoprotein) and inflammation (CRP). Finger prick blood  
48 275 samples will be collected via lipid (~19 µL) or inflammation (~12 µL) specific test discs and  
49 276 immediately analysed with the Cobas b 101 System.  
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### 55 278 *Body Composition*

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3 279 Waist to hip ratio, height, and weight will be measured to the nearest 0.1 cm and 0.1 kg,  
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5 280 respectively, using standard scales, a stadiometer and measuring tape. Total and regional fat and  
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7 281 fat-free mass will be measured by dual-energy x-ray absorptiometry ([DEXA], MedixDR Whole  
8  
9 282 Body DEXA, SYD, AU).

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11 284 *Vascular Function*

12  
13 285 Endothelial function will be assessed by measuring endothelium-dependent flow-mediated  
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15 286 dilation (FMD). This technique uses ultrasound imaging (Terason uSmart® 3300) of the brachial  
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17 287 artery. Following 10-15 min of laying supine (at rest), a longitudinal section of the brachial artery,  
18  
19 288 2-3 cm above the antecubital fossa, will be imaged using B-mode ultrasound imaging (insonation  
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21 289 angle of 60°). A blood pressure cuff placed around the forearm, 1-2 cm below the olecranon  
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23 290 process, will then be rapidly inflated to ~60 mmHg above resting systolic blood pressure for 5 min.  
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25 291 Brachial artery diameter and blood flow velocity will be recorded for 1 min before cuff inflation  
26  
27 292 (baseline), ~30 s prior to cuff release (ischemic stimulus), and 3 min following cuff release  
28  
29 293 (recovery) [25, 26]. The ~5 min recording will then be analysed with custom-designed edge-  
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31 294 detection and wall-tracking software (Cardiovascular Suite, Quipu, Italy) which reduces user bias  
32  
33 295 and increases accuracy. FMD will be reported as an absolute change in artery diameter (absolute  
34  
35 296 FMD =  $\text{postocclusion}_{\text{mean diameter}} - \text{preocclusion}_{\text{mean diameter}}$ ), and a relative change in artery diameter  
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37 297 from baseline [ $\% \text{FMD} = 100 \times (\text{absolute FMD} / \text{preocclusion}_{\text{mean diameter}})$ ]. Allometric scaling will  
38  
39 298 be used to account for potential confounders from baseline diameter [26, 27].

39 299

40 300 Blood flow (mL/min) will be measured using non-invasive Doppler from the cross-sectional area  
41  
42 301 and blood velocity [ $\text{velocity} \times \pi \times (\text{diameter}^2/4) \times 60$ ]. Shear rate (s<sup>-1</sup>) will then be determined  
43  
44 302 from the diameter and velocity measures (four times velocity/diameter) [28]. Shear rate area under  
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46 303 the curve (SR<sub>AUC</sub>) will automatically be calculated from the diameter and velocity measures from  
47  
48 304 the time of cuff release to peak dilation of the artery. Antegrade and retrograde mean blood  
49  
50 305 velocities will be used to calculate baseline antegrade and retrograde shear rates (four times mean  
51  
52 306 baseline antegrade or retrograde velocity ÷ mean baseline diameter), and the mean blood flow to  
53  
54 307 mean arterial pressure ratio will be used to measure vascular conductance (mL/min/mmHg) [25,  
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56 308 26].

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3 310 Central arterial stiffness will be assessed via pulse wave analysis (PWA) and pulse wave velocity  
4 311 (PWV) measurements (SphygmoCor® XCEL System, AtCor Medical). PWA will be used to  
5 312 measure central blood pressure. A brachial blood pressure cuff will be inflated and the central  
6 313 aortic pressure waveform, derived from pulsations at the brachial artery, will be recorded for 5 s  
7 314 and then automatically analysed through the SphygmoCor software. Key parameters of central  
8 315 blood pressure and arterial stiffness will be determined from the aortic waveform including systolic  
9 316 pressure, diastolic pressure, pulse pressure, aortic pressure, augmentation index and mean arterial  
10 317 pressure. PWV will be measured by holding a tonometer on the carotid artery for 10-15 s, while a  
11 318 femoral blood pressure cuff is automatically inflated. Once fully inflated, the femoral cuff and  
12 319 carotid tonometer will simultaneously record a 10 s capture of the carotid and femoral pressure  
13 320 waveforms. PWV will then be calculated by dividing the carotid-femoral distance by the pulse  
14 321 transit time; the carotid-femoral distance will be calculated by subtracting the proximal distance  
15 322 (distance between the carotid artery and sternal notch) from the distal distance (distance between  
16 323 the sternal notch and proximal edge of the femoral cuff) [PWV (m/s) = (distal –  
17 324 proximal<sub>distance</sub>)/transit time] [29]. Measurements will be performed in duplicate. A third  
18 325 measurement will be taken if the difference between the two PWV values is >0.5 m/s and the  
19 326 average of the three values will be used.  
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34 328 An automatic blood pressure monitor (Oscar2 Ambulatory Blood Pressure Monitor with  
35 329 SphygmoCor interfacing, SunTech Medical) will also be used to continuously assess blood  
36 330 pressure and pulse wave analyses every hour for 24 hours. We will report 24 h blood pressure as  
37 331 an average of 24 measurements.  
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### 43 333 *Diet and Physical Activity Monitoring*

44 334 Participants will complete a 7 d diet record during each two-week monitoring period. Food diaries  
45 335 will be analysed (using FoodWorks10 Nutrition Software) to confirm macronutrient composition  
46 336 and total energy intake are consistent throughout the study period. Physical activity will be  
47 337 monitored during the same 7 d period using an accelerometer (ActiGraph Bluetooth® Smart  
48 338 wGT3X-BT), worn around the waist during wake hours. Physical activity and sedentary time will  
49 339 be compared between groups at each timepoint during wake hours. The accelerometers will also  
50 340 be used to confirm exercise intensity and compliance to the exercise prescription. A heart rate  
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3 341 monitor (Polar H7 Bluetooth® Heart Rate Monitor) will be worn during the midpoint monitoring  
4  
5 342 period on the same days as the accelerometer, only during the exercise sessions, to assess exercise  
6  
7 343 intensity.  
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9 344

#### 10 345 *Adherence and Lifestyle Questionnaires*

11 346 Participants will complete a quality of life (SF-36) survey and a self-regulatory efficacy and  
12  
13 347 physical activity questionnaire during each two-week monitoring period. Participants will also  
14  
15 348 complete three surveys during the follow-up period, one at the end of each month that is specific  
16  
17 349 to their exercise group, to assess adherence to exercise prescription between the ExPeak and  
18  
19 350 control groups. Surveys will include questions on known perceived facilitators and barriers to  
20  
21 351 filling the exercise prescription and, in turn, support or aggravation of intervention efficacy. Such  
22  
23 352 factors will include the availability of nearby green and open spaces (e.g. beaches, parks) [30] and  
24  
25 353 levels of felt safety to exercise outdoors during the day and evening hours [31].  
26  
27 354

#### 27 355 *Remote Participants*

28  
29 356 Participants who cannot attend the university (e.g., due to COVID-19 restrictions) for in-lab  
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31 357 assessments will receive a home-based testing kit (via mail) which includes: a dried blood spot  
32  
33 358 test kit (ZRT Laboratory kit for measurement of HbA1c, lipids, CRP, and insulin), CGM,  
34  
35 359 accelerometer and Glucerna MMTT drink. Instructions will be provided and followed-up via a  
36  
37 360 phone or video call. All other study protocols will be the same, however data for the DEXA and  
38  
39 361 vascular assessments will not be available.  
40  
41 362

### 41 363 **Statistical Analysis**

#### 42 364 *Sample size*

43  
44 365 Sample size was calculated based on a previous study investigating the effect of exercise timing  
45  
46 366 in people with T2D, where they reported a difference of -0.6 mmol/L in 24 h blood glucose  
47  
48 367 between exercise performed in the morning vs afternoon [14]. To detect a clinically meaningful  
49  
50 368 change in HbA1c between groups, with a moderate effect size of 0.2, statistical power of 80%, and  
51  
52 369 an alpha level of 0.05 (two-sided), a total of ~54 participants (27 per intervention group) is required  
53  
54 370 for this trial. The power calculation is based on the change in HbA1c from a previous trial in our  
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371 lab in people with T2D [32]. To account for an expected 30% drop-out rate, 70 participants will  
372 be recruited.

373

### 374 *Statistics*

375 This study will be reported according to the CONSORT 2010 Statement and the CONSERVE  
376 2021 Statement for randomised controlled trials. Descriptive statistics will be assessed (means,  
377 standard deviation and frequencies), and histograms, Q-Q plots and the Shapiro-Wilk test will be  
378 used to identify outliers and test for normality. Linear mixed models (with time x intervention, and  
379 main effect of time) will be used to assess differences between groups, for primary (HbA1c) and  
380 secondary (CGM, MMTT, vascular function, metabolic control, and body composition) outcomes.  
381 Tertiary outcomes (e.g., adherence to the exercise prescription) will be analysed from the  
382 accelerometer and follow-up surveys (Qualtrics<sup>XM</sup>). Attention to treat analyses will be performed  
383 for primary analyses (Phase 1) and per protocol analyses will be undertaken for secondary and  
384 tertiary outcomes (Phase 2). Data with skewed distribution will be log-transformed or square-  
385 rooted prior to the statistical analysis. For the three-month follow-up, intention to treat analysis  
386 will be used and missing data will not be imputed.

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### 388 **Patient and Public Involvement**

389 No patient involved.

390

### 391 **ETHICS AND DISSEMINATION**

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

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3 4024  
5 403 **DISCUSSION**

6 404 The primary objective of this trial is to determine if strategically timing exercise, to reduce daily  
7 405 peak hyperglycaemia, will improve glycaemic control and lower cardiovascular risk factors in  
8 406 people with T2D. This is the first study to investigate whether prescribing exercise that is  
9 407 personalised to target daily peak hyperglycaemia, using CGM, can improve cardiovascular risk  
10 408 factors in T2D. Based on evidence from prior research [11, 34–36], it is hypothesised that  
11 409 strategically timing daily exercise to attenuate peak hyperglycaemia will improve glycaemic  
12 410 control (HbA1c), and the reduction in peak glycemia will improve vascular function (endothelial  
13 411 function and arterial stiffness), blood lipids and CRP, more than exercising not at peak  
14 412 hyperglycaemia or control standard-care (i.e., physical activity guidelines).

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17 414 Recent evidence suggests exercise timing may be important to offset circadian rhythms [14] and  
18 415 to target postprandial hyperglycaemia [11] in T2D. However, there are no recommendations for  
19 416 exercise timing in the current physical activity guidelines (i.e., physical activity can be  
20 417 accumulated at any time throughout the week). Further, adherence to the current recommendations  
21 418 is notoriously poor. Regardless of the effectiveness for an intervention to improve diabetes  
22 419 management, findings will only be translatable if patients comply with and adopt to the treatment  
23 420 over the long-term. Therefore, adherence to prescribed daily exercise time (i.e., creating more of  
24 421 a habit) will be assessed for three months following the eight-week intervention. Exercising at the  
25 422 time of peak hyperglycaemia may improve self-efficacy to the exercise prescription, as results  
26 423 from the CGM data (pre/mid/post eight-week intervention) will allow participants to see the direct  
27 424 impact of exercise on blood glucose levels. Use of CGM in this trial not only offers the distinct  
28 425 advantage of determining time of peak hyperglycaemia, but will also allow us to examine any  
29 426 changes in daily glycaemic patterns, such as glycaemic variability, which are more closely related  
30 427 to cardiovascular risk than HbA1c [37]. If strategically timing exercise to attenuate peak  
31 428 hyperglycaemia improves long-term glycaemic control (HbA1c), reduces cardiovascular risk  
32 429 (endothelial dysfunction and arterial stiffness), and improves exercise adherence then this may be  
33 430 an alternative recommendation for physical activity prescription in people with T2D.

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35 43136 432 *Strengths and Limitations*37  
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3 433 This is the first randomised controlled trial to examine the effects of personalising exercise timing  
4 434 to attenuate peak hyperglycaemia (determined via continuous glucose monitoring technology) on  
5 435 cardiometabolic and vascular health outcomes in individuals with type 2 diabetes. This study will  
6 436 be conducted in free-living conditions, with exercise performed at home and contact/delivery of  
7 437 *Phase 1* (8-week exercise intervention) mirroring standard-care (five telehealth calls with an  
8 438 exercise physiologist), while *Phase 2* (3-month follow-up) will assess adherence to the exercise  
9 439 prescription (with minimal contact from the research team); thus informing us of the real-world  
10 440 applicability of the proposed exercise prescription. In addition, this study will utilise a variety of  
11 441 data collection methods (in-lab and free-living) to objectively measure cardiometabolic health,  
12 442 vascular function, physical activity, and behaviour change across the trial. Due to the COVID-19  
13 443 pandemic remote participants from across rural and urban Australia will be included, allowing for  
14 444 a wider range of individuals to be recruited while adhering to the COVID-19 restrictions. However,  
15 445 this is also a limitation as the vascular and body composition measures will be excluded for those  
16 446 who cannot attend university assessments, and dried blood spot testing kits will be used rather than  
17 447 the gold-standard plasma measurement of HbA1c. Finally, a limitation of the waitlist control group  
18 448 is the potential overestimation of intervention effects and bias in favour of the treatment group.  
19 449 Nevertheless, inclusion of the waitlist control group will provide insight on the cause-effect  
20 450 relationship between the intervention and subsequent health outcomes/behaviour changes, as these  
21 451 participants will follow a delayed-start design (i.e., will receive treatment following the waitlist  
22 452 period), thus allowing for direct comparisons to be made under various conditions with reduced  
23 453 error variance and not withholding treatment to individuals.  
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#### 41 455 **COMPETING INTERESTS**

42 456 The authors have no conflicts of interest to disclose.  
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#### 46 458 **CONTRIBUTORS**

47 459 CRC drafted the manuscript. MEF, CRC, BMR, and TAB conceived and contributed to the design  
48 460 of the study and plan for analysis. MEF and CRC will conduct the study, collect data, and analyse  
49 461 data. MEF, CRC and TAB will analyse and interpret the data. All authors reviewed and approved  
50 462 the final manuscript.  
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466 not-for-profit sectors. This trial was funded by a University of Wollongong Small Grant and  
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468 Council (NHMRC) Investigator Grant (APP1177234). TAB's time was supported by a NHMRC  
469 Boosting Dementia Research Leader Fellowship (GNT1140317).

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## 10 567 FIGURES

### 11 568

### 12 569 **Figure 1. Study design and flow chart**

13 570 Eligible participants will be randomised (N=54) to one of three groups: i) exercise at peak  
14 571 hyperglycaemia (ExPeak; N=18), ii) exercise after peak hyperglycaemia (NonPeak; N=18), or iii)  
15 572 waitlist control (WLC; N=18). Participants randomised to WLC will be re-randomised to ExPeak  
16 573 or NonPeak after the waitlist period. Following the eight-week intervention (Phase 1), the ExPeak  
17 574 (N=27) group will continue to exercise at peak hyperglycaemia, whereas the NonPeak (N=27)  
18 575 group will become the control (CTL; N=27) group for the three-month follow-up (Phase 2).  
19 576 Participants in the WLC and CTL groups will receive standard care advice to exercise in  
20 577 accordance with the World Health Organization physical activity guidelines.  
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### 29 578

### 30 579 **Figure 2. Timeline of study protocol**

31 580 Participants randomised to the waitlist control (WLC) group will undergo measures before and  
32 581 after an eight-week waitlist control period. Then are randomised to one of two intervention groups  
33 582 for eight weeks: i) exercise at peak hyperglycaemia ([ExPeak] ExRx: begin exercise ~30 min  
34 583 before peak hyperglycaemia) or ii) exercise after peak hyperglycaemia ([NonPeak] ExRx: begin  
35 584 exercise ~90 min after peak hyperglycaemia). All groups undergo pre-intervention CGM to  
36 585 measure time of peak hyperglycemia prior to interventions. **PHASE 1. Eight-week intervention:**  
37 586 Both intervention groups will perform ~22 min of daily exercise at their prescribed time.  
38 587 Participants will receive two phone consults and five telehealth video consults (via zoom or skype)  
39 588 with an Accredited Exercise Physiologist. **PHASE 2. Three-month follow-up:** The ExPeak group  
40 589 will continue to exercise for ~22 min/day at peak hyperglycaemia and the NonPeak group will  
41 590 exercise according to the physical activity guidelines. Three adherence surveys will be conducted  
42 591 (at the end of each month), but no formal contact. **Free Living Assessments:** 14 d CGM, 2 h  
43 592 MMTT, 7 d ActiGraph activity monitoring, 7 d HR monitoring (midpoint only; Polar Bluetooth  
44 593 HR monitor worn on same days as ActiGraph, only during prescribed exercise), 7 d diet record,  
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3 594 quality of life survey, and self-regulatory efficacy and physical activity questionnaire. **In-Lab**  
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5 595 **Assessments:** i) blood sample HbA1c, CRP, and blood lipids (TG, TC, HDL, and LDL); ii)  
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7 596 vascular measures FMD and arterial stiffness via PWV/PWA; and iii) anthropometrics (height and  
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9 597 weight) and body composition DEXA.

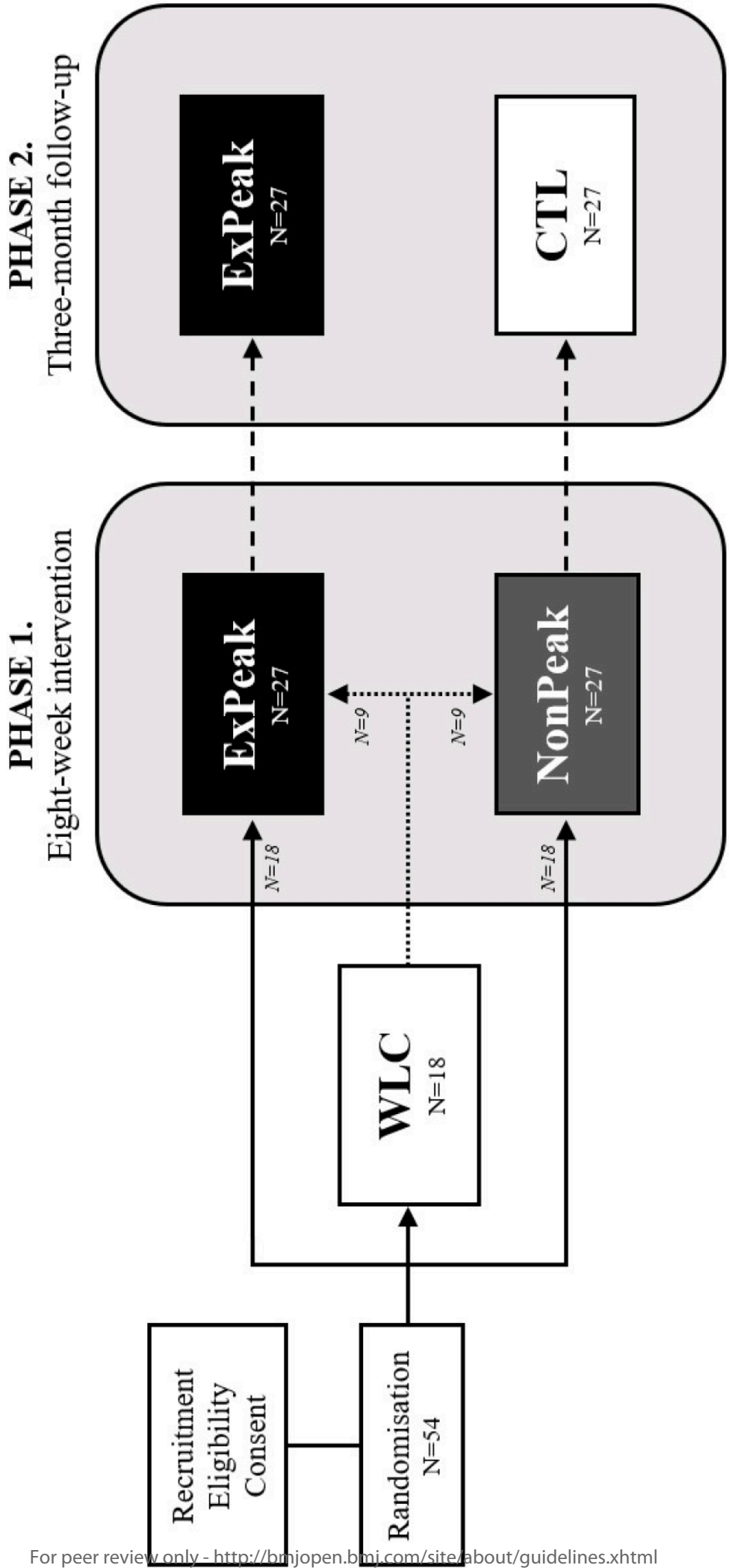
10 598 *Abbreviations:* waitlist control, WLC; exercise at peak hyperglycaemia (intervention group),  
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12 599 ExPeak; exercise after peak (intervention group), NonPeak; exercise prescription, ExRx;  
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14 600 accredited exercise physiologist, AEP; continuous glucose monitoring, CGM; mixed meal  
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16 601 tolerance test, MMTT; heart rate, HR; glycated hemoglobin, HbA1c; c-reactive protein, CRP;  
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18 602 triglyceride, TG; total cholesterol, TC; high-density lipoprotein, HDL; low-density lipoprotein,  
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20 603 LDL; flow-mediated dilation, FMD; pulse wave velocity, PWV; pulse wave analysis, PWA; and  
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22 604 dual-r-ray absorptiometry, DEXA.

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### 24 606 **Figure 3. Example ‘Glucose Pattern Insights’ Report**

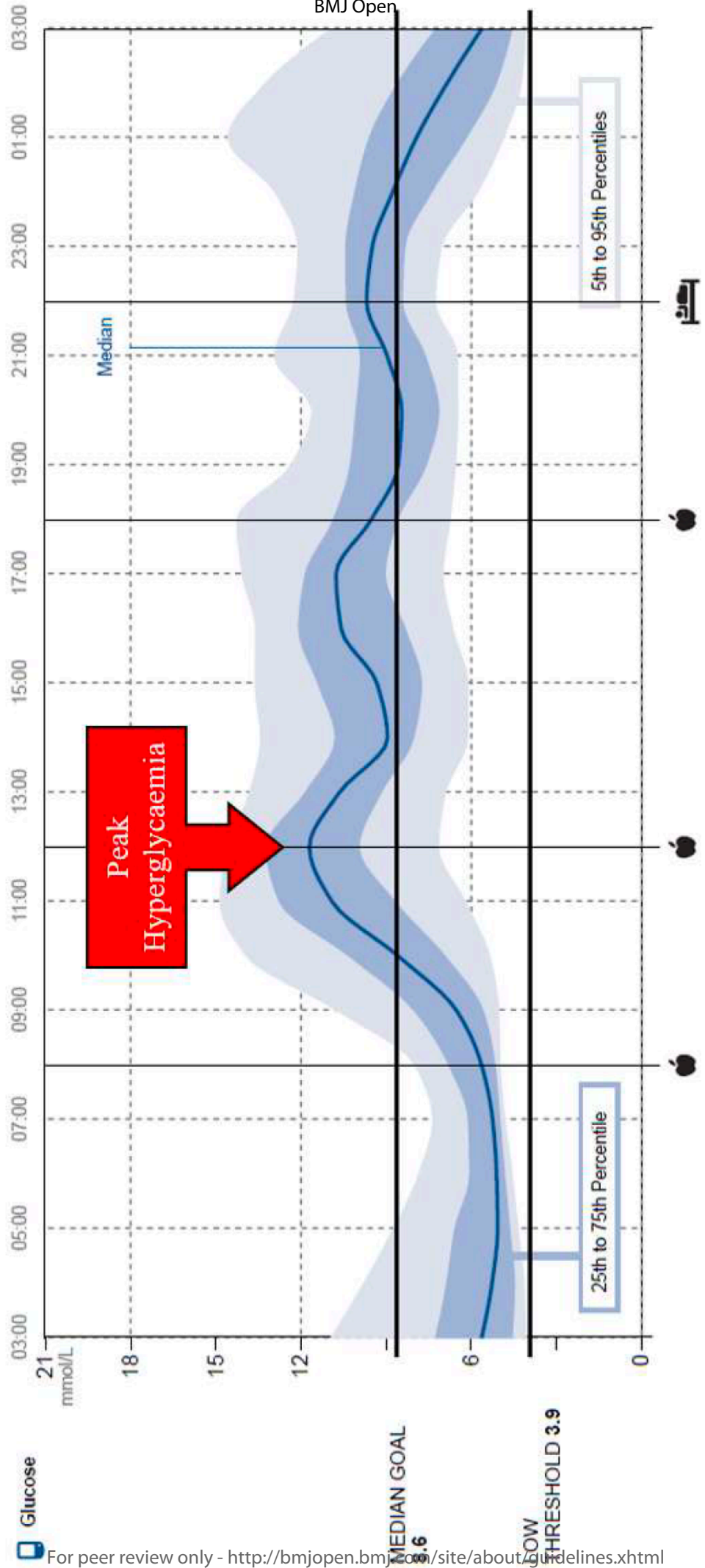
25 607 Via LibreView, of a 24 h blood glucose curve averaged from 14 days of continuous glucose  
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27 608 measurements.

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

1	Roles and	<a href="#">#5b</a>	Name and contact information for the trial sponsor	1
2	responsibilities:			
3	sponsor contact			
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8	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design;	N/A
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
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16	Roles and	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating	N/A
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
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24	<b>Introduction</b>			
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26				
27	Background and	<a href="#">#6a</a>	Description of research question and justification for undertaking	5
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
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32	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	6-8
33	rationale: choice of			
34	comparators			
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37	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	5
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40	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	6
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
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46	<b>Methods:</b>			
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48	<b>interventions, and</b>			
49	<b>outcomes</b>			
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53	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic	5
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
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1	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
2				
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6	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
7	description			
8				
9				
10	Interventions:	<a href="#">#11b</a>	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
11	modifications			
12				
13				
14				
15	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
16	adherence			
17				
18				
19				
20	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
21	concomitant care			
22				
23				
24	Outcomes	<a href="#">#12</a>	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
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34	Participant timeline	<a href="#">#13</a>	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
35				
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40	Sample size	<a href="#">#14</a>	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
41				
42				
43				
44				
45	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	6
46				
47				
48				
49	<b>Methods: Assignment</b>			
50	<b>of interventions (for</b>			
51	<b>controlled trials)</b>			
52				
53				
54	Allocation: sequence	<a href="#">#16a</a>	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
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

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4	Allocation	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol
12	implementation		participants, and who will assign participants to interventions
13			
14	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial
15			participants, care providers, outcome assessors, data analysts),
16			and how
17			
18			
19			
20	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible,
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	<b>Methods: Data</b>		
26	<b>collection,</b>		
27	<b>management, and</b>		
28	<b>analysis</b>		
29			
30			
31			
32	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
40			
41			
42			
43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-up,
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage, including any
49			related processes to promote data quality (eg, double data entry;
50			range checks for data values). Reference to where details of data
51			management procedures can be found, if not in the protocol
52			
53			
54			
55	Statistics: outcomes	<a href="#">#20a</a>	Statistical methods for analysing primary and secondary
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
58			
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1	Statistics: additional	<a href="#">#20b</a>	Methods for any additional analyses (eg, subgroup and adjusted	14
2	analyses		analyses)	
3				
4	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating to protocol non-	14
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
8				
9				
10	<b>Methods: Monitoring</b>			
11				
12	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring committee (DMC); summary of	1
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
19				
20				
21				
22	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and stopping guidelines,	N/A
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	<a href="#">#22</a>	Plans for collecting, assessing, reporting, and managing solicited	N/A
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
31				
32				
33	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing trial conduct, if any, and	1
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
37				
38	<b>Ethics and</b>			
39	<b>dissemination</b>			
40				
41				
42	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee / institutional review	2
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	<a href="#">#25</a>	Plans for communicating important protocol modifications (eg,	2
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
51				
52				
53	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from potential trial	6
54			participants or authorised surrogates, and how (see Item 32)	
55				
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1	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	N/A
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
5				
6	Confidentiality	<a href="#">#27</a>	How personal information about potential and enrolled	6
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	<a href="#">#28</a>	Financial and other competing interests for principal investigators	14
12			for the overall trial and each study site	
13				
14				
15	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset, and	14
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
19				
20	Ancillary and post trial	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial results	2
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
29				
30				
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32				
33	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	2
34	authorship		professional writers	
35				
36				
37	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	2
38	reproducible research		participant-level dataset, and statistical code	
39				
40				
41	<b>Appendices</b>			
42				
43	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given to	22
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
50				
51				

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