Received: 26 June 2023 | Revised: 31 July 2023 | Accepted: 8 August 2023

DOI: 10.1111/dom.15254

ORIGINAL ARTICLE

WILEY

Interrupting prolonged sitting with frequent short bouts of light-intensity activity in people with type 1 diabetes improves glycaemic control without increasing hypoglycaemia: The SIT-LESS randomised controlled trial

Matthew D. Campbell PhD[1,2,3] | Anwar M. Alobaid MSc[4,5] | Mark Hopkins PhD[4] | Paddy C. Dempsey PhD[3,6,7,8] | Sam M. Pearson MD[2] | Noppadol Kietsiriroje MD[2,9] | Rachel Churm PhD[10] | Ramzi A. Ajjan MD[2]

[1]John Dawson Drug Discovery and Development Institute, University of Sunderland, Sunderland, UK

[2]Leeds Institute of Cardiovascular and Metabolic Medicine, Faculty of Medicine, University of Leeds, Leeds, UK

[3]Institute of Metabolic Science, University of Cambridge, Cambridge, UK

[4]School of Food Science and Nutrition, Faculty of Environment, University of Leeds, Leeds, UK

[5]Ministry of Health, Farwaniya Hospital, Kuwait, Kuwait

[6]Diabetes Research Centre, University of Leicester, Leicester, UK

[7]Baker Heart and Diabetes Institute, Melbourne, Australia

[8]Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, Australia

[9]Endocrinology and Metabolism Unit, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[10]Applied Sports Technology, Exercise and Medicine (A-STEM) Research Centre, Faculty of Science and Engineering, Swansea University, Swansea, UK

Correspondence
Dr Matthew D. Campbell, John Dawson Drug Discovery and Development Institute, University of Sunderland, Sunderland UK,
Email: matthew.campbell@sunderland.ac.uk

Abstract

Aim: To examine the impact of interrupting prolonged sitting with frequent short bouts of light-intensity activity on glycaemic control in people with type 1 diabetes (T1D).

Materials and Methods: In total, 32 inactive adults with T1D [aged 27.9 ± 4.7 years, 15 men, diabetes duration 16.0 ± 6.9 years and glycated haemoglobin 8.4 ± 1.4% (68 ± 2.3 mmol/mol)] underwent two 7-h experimental conditions in a randomised crossover fashion with >7-day washout consisting of: uninterrupted sitting (SIT), or, interrupted sitting with 3-min bouts of self-paced walking at 30-min intervals (SIT-LESS). Standardised mixed-macronutrient meals were administered 3.5 h apart during each condition. Blinded continuous glucose monitoring captured interstitial glucose responses during the 7-h experimental period and for a further 48-h under free-living conditions.

Results: SIT-LESS reduced total mean glucose (SIT 8.2 ± 2.6 vs. SIT-LESS 6.9 ± 1.7 mmol/L, $p = .001$) and increased time in range (3.9-10.0 mmol/L) by 13.7% (SIT 71.5 ± 9.5 vs. SIT-LESS 85.1 ± 7.1%, $p = .002$). Hyperglycaemia (>10.0 mmol/L) was reduced by 15.0% under SIT-LESS (SIT 24.2 ± 10.8 vs. SIT-LESS 9.2 ± 6.4%, $p = .002$), whereas hypoglycaemia exposure (<3.9 mmol/L) (SIT 4.6 ± 3.0 vs. SIT-LESS 6.0 ± 6.0%, $p = .583$) was comparable across conditions. SIT-LESS reduced glycaemic variability (coefficient of variation %) by 7.8% across the observation window ($p = .021$). These findings were consistent when assessing discrete time periods, with SIT-LESS improving experimental and free-living postprandial, whole-day and night-time glycaemic outcomes ($p < .05$).

Funding information
Diabetes UK, Grant/Award Number: 20/0006154

Conclusions: Interrupting prolonged sitting with frequent short bouts of light-intensity activity improves acute postprandial and 48-h glycaemia in adults with T1D. This pragmatic strategy is an efficacious approach to reducing sedentariness and increasing physical activity levels without increasing risk of hypoglycaemia in T1D.

KEYWORDS
continuous glucose monitoring, exercise intervention, hypoglycaemia, type 1 diabetes

1 | INTRODUCTION

Physical activity is a critical element of diabetes care and is universally recommended to all individuals with diabetes.[1] Recently, guidelines have evolved to stipulate that in addition to traditional structured moderate-vigorous intensity physical activity, individuals should limit prolonged periods of sitting by incorporating frequent episodes of low-intensity physical activity into the day.[2] This recommendation is based upon data showing a dose-dependent relationship between sedentary behaviour and cardiometabolic morbidity, worsening glycaemic management, and increased weight gain, irrespective of physical activity status.[3,4] Furthermore, emerging evidence shows that interruption of prolonged sitting with frequent short bouts of activity improves acute postprandial and whole-day glucose levels, with glycaemic improvement continuing until the next morning,[5–9] resulting from enhanced contraction-induced and/or energy deficit-induced insulin sensitivity,[31] and/or a greater reliance on insulin-independent contraction-mediated glucose disposal.[32] However, these data remain preliminary and limited to individuals with, or at risk of developing, type 2 diabetes.

Within the context of type 1 diabetes (T1D), most individuals struggle to meet physical activity guidelines[10] and spend a greater proportion of time sedentary than people without T1D.[11] For example, a recent large cross-sectional survey of 18 028 adults with T1D, reported that ~60% did not achieve recommended physical activity levels[10] a finding that supports some,[12–14] but not all previous studies.[15]

Many people with T1D report fear of hypoglycaemia and an inability to manage their diabetes as major barriers to becoming active and engaging in regular moderate-to-vigorous physical activity participation,[14] yet, few mention this fear when asked about lower-intensity activities such as walking.[16] Although many individuals with T1D do little-to-no exercise, they are often willing to increase participation in lower-intensity physical activity and are keen to learn how to reduce sedentary behaviours.[14,16,17] However, little information is available for individuals with T1D or for the health care professionals who support them with regards to strategies for reducing sedentariness and their potential impact on hypoglycaemia risk.[14,16,17]

Should findings from recent research in individuals with type 2 diabetes translate to those with T1D, interrupting sitting with frequent, short, light-intensity activity breaks, may serve as a pragmatic strategy for enabling inactive T1D individuals to incorporate more physical activity into their everyday lives and improve glucose management. This may be particularly beneficial for those who are unable or unwilling to engage in structured moderate-vigorous physical activity and an important stepping-stone toward achieving physical activity recommendations. However, no research has investigated the impact of such a strategy on glucose control in people with T1D. Therefore, the aim of this study was to examine the acute postprandial and subsequent 48-h free-living glucose responses to interrupting prolonged sitting with frequent, short bouts of light-intensity activity in inactive people with T1D.

2 | METHODS

2.1 | Study design

This randomised crossover trial was undertaken at the University of Sunderland between May 2021 and December 2022. The study received ethical approval from the Health Research Authority (HRA; London - Surrey Research Ethics Committee; Ref 20/LO/0650) and was prospectively registered (ISRCTN13641847). All patients who participated provided written informed consent with study procedures complying with the Declaration of Helsinki. Participants completed an initial medical screening visit and two laboratory-based experimental visits each of which were separated by a minimum of 7 days (Figure S1). Experimental conditions were randomly assigned using a computerised random number generator (www.randomization.com) with study personnel and participants blinded to experimental condition order up until commencement of the first experimental visit.

2.2 | Participants

Patients with autoantibody confirmed T1D treated on a stable (>6 months) insulin regimen consisting of continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDIs) were recruited in-clinic and via university recruitment streams from the North-East region of the United Kingdom. Patients were eligible for inclusion if aged between 18 and 60 years with a duration of diabetes >2 years on enrolment and classified as inactive as per international physical activity guidelines[1,2]; specifically, this consisted of failing to achieve a minimum of 150 min of moderate-vigorous intensity physical activity per week. Exclusion criteria included pregnancy, presence of

significant functional limitations, dietary intolerances, overt diabetes complications, or hypoglycaemia unawareness, as determined by the Clarke method.[18]

2.3 | Pre-experimental procedures

After initial telephone screening, potentially eligible participants underwent medical screening at our laboratory for assessment of pre-treatment clinical characteristics including medical history, anthropometry, blood pressure and self-reported physical activity status using a validated assessment tool.[19] During this visit eligible participants then underwent initial study orientation and were fitted with a blinded continuous glucose monitoring (CGM) device (FreeStyle Libre Pro iQ; Abbott). Participants were provided with a food diary to record diet and insulin regimen and were provided with a pedometer to which recorded total step count during each 24-h period of the 48-h before and after the first experimental laboratory visit; this information was then used to replicate diet, insulin administration and physical activity levels during the second experimental period. During this time, participants were required to abstain from exercise, caffeine and alcohol in the 48-h before each experimental condition. Prearranged, standardised text messaging and/or email prompts were used to maximise participant compliance.

For standardisation of glycaemic control before each laboratory visit, a standardised mixed-macronutrient meal (Table S1) was provided to participants to consume on the evening before each experimental visit; following consumption of this meal, participants were instructed to avoid further food intake including calorific beverages, except for extremes of glucose readings managed as appropriate with corrective insulin boluses for hyperglycaemia and glucose supplementation for hypoglycaemia. The aim was to ensure fasting status upon arrival to each experimental visit as detailed below. On the morning of each experimental visit, study personnel contacted participants to ensure fasting status and confirm glucose levels were within the range 4-12 mmol/L. Experimental visits were rearranged if participants experienced one or more sustained (>90 min) hyperglycaemic or sustained (>30 min) hypoglycaemic episodes. To limit the potential impact of menses on glycaemic measures for menstruating female participants, procedures were arranged to occur within two-consecutive weeks during their follicular phase (self-reported).

2.4 | Experimental procedures

A schematic of the experimental procedures is presented in Figure S1. Participants attended our temperature-controlled (21-23°C) laboratory on a morning (~08:00 h) following an overnight fast. On both occasions participants consumed standardised mixed-macronutrient breakfast and lunch meals at 3.5-h apart with start time equivalent on both experimental arms. Each meal sought to replicate a typical Western diet with an energy density of ~855 kcal, and a macronutrient profile of ~42% energy from carbohydrate, ~16% energy from protein, and ~42% energy from fat (Table S1). The carbohydrate content of each meal was individualised equating to 1 g carbohydrate per kilogram body mass. Participants were instructed to administer their usual prandial insulin bolus immediately before each meal, the dose of which was calculated using an individuals' established insulin-to-carbohydrate ratio, with dose, timing and site of injection replicated across visits. Water was consumed ad libitum during the first visit with the volume recorded and replicated during visit 2; standardised (within subject) lavatory visits were incorporated into the protocol to minimise unscheduled physical activity; however, additional lavatory visits were permitted if needed. On one arm (SIT), participants remained at rest and seated in a reclining chair for the duration of the visit. On a second arm (SIT-LESS) study procedures were replicated but sitting was interrupted by performing 3-min bouts of self-paced light-intensity walking at 30-min intervals, commencing 60 min after each meal; this equated to a total of 36 min of physical activity across the 7-h period. During each laboratory visit, participants had access to television, books and internet, and were supervised consistently by study personnel to ensure resting periods were maintained. At 3.5 h post-lunch, participants were discharged from the laboratory with further free-living glycaemic assessment captured remotely via CGM for a further 48 h. To minimise potential confounding of food intake, participants were provided with an evening and breakfast meal to consume in sequence, replicating eating times within each study arm (Figure S1). Any additional nutritional intake during the subsequent 48-h observation window was recorded on visit 1, and subsequently replicated on visit 2. All meals provided to the participants consisted of commercially available foods with standardised heating and preparation instructions. During the >7-day washout between experimental conditions, participants resumed their habitual diet and physical activity patterns, excluding the 48-h pre-experimental period before the next experimental visit.

2.5 | Continuous glucose monitoring

Blinded CGM was used to capture interstitial glucose concentrations with sensor insertion a minimum of 72 h before each data capture window to minimise artefacts during initialisation. Sensors were inserted into the subcutaneous tissue on the back of the upper arm with insertion site marked with indelible ink to replicate the sensor insertion site during sensor replacement; existing CGM users continued to use their CGM as normal but were provided with a study-prescribed CGM to ensure consistency in CGM data capture. Data were retrospectively downloaded and analysed using manufacturer software (FreeStyle Libre software version 3.12; https://www.libreview.com) with the criterion of >80% data capture within each 24-h period across each experimental observation window (~5 days on each study arm) with no more than two consecutive hours of missing data during each 24-h period to be considered valid.[20] From downloaded data, mean glucose, percentage of time in range (TIR; 3.9-10.0 mmol/L), time above range (TAR; >10.0 mmol/L and >13.9 mmol/L) and time below range (TBR; <3.9 mmol/L and

TABLE 1 CGM outcomes for the experimental and free-living phases in response to SIT versus SIT-LESS

	SIT	SIT-LESS	*p*-Value
Pre-experimental phase (48-h run-in period)			
Mean glucose, mmol/L	7.7 ± 1.1	7.5 ± 2.1	.631
% TIR 3.9-10.0 mmol/L (70-180 mg/dl)	79.1 ± 12.5	81.1 ± 19.9	.561
% TAR >10.0 mmol/L (>180 mg/dl)	16.5 ± 12.5	14.7 ± 19.8	.638
% TAR >13.9 mmol/L (>250 mg/dl)	2.7 ± 4.1	4.9 ± 13.1	.293
% TBR <3.9 mmol/L (<70 mg/dl)	4.5 ± 5.2	4.3 ± 7.4	.903
% TBR <3.0 mmol/L (<54 mg/dl)	0.6 ± 1.4	4.0 ± 7.0	.326
Glycaemic variability, CV%	31.4 ± 10.6	28.7 ± 9.7	.104
Experimental phase response			
Mean glucose, mmol/L	8.5 ± 2.0	7.1 ± 1.8	.008**
% TIR 3.9-10.0 mmol/L (70-180 mg/dl)	70.9 ± 27.4	88.0 ± 19.9	.007**
% TAR >10.0 mmol/L (>180 mg/dl)	26.5 ± 27.5	8.6 ± 18.3	.004**
% TAR >13.9 mmol/L (>250 mg/dl)	6.9 ± 14.3	1.7 ± 6.5	.072
% TBR <3.9 mmol/L (<70 mg/dl)	2.7 ± 8.4	3.3 ± 10.2	.795
% TBR <3.0 mmol/L (<54 mg/dl)	0.7 ± 3.7	0.2 ± 1.2	.536
Glycaemic variability, CV%	24.4 ± 13.0	18.1 ± 9.2	.013*
Free-living phase response			
Mean glucose, mmol/L	8.1 ± 1.3	6.9 ± 1.5	<.001***
% TIR 3.9-10.0 mmol/L (70-180 mg/dl)	71.6 ± 19.3	84.6 ± 14.8	.004**
% TAR >10.0 mmol/L (>180 mg/dl)	23.8 ± 18.6	9.6 ± 11.6	<.001***
% TAR >13.9 mmol/L (>250 mg/dl)	4.5 ± 5.8	1.5 ± 3.67	.007**
% TBR <3.9 mmol/L (<70 mg/dl)	4.6 ± 5.0	6.0 ± 9.85	.568
% TBR <3.0 mmol/L (<54 mg/dl)	1.3 ± 2.3	1.8 ± 4.5	.529
Glycaemic variability, CV%	31.7 ± 12.4	24.5 ± 11.9	.035*
Combined free-living day time periods			
Mean glucose, mmol/L	8.2 ± 1.4	7.1 ± 1.7	.002**
% TIR 3.9-10.0 mmol/L (70-180 mg/dl)	71.0 ± 18.6	82.5 ± 19.0	.023*
% TAR >10.0 mmol/L (>180 mg/dl)	24.3 ± 18.8	11.0 ± 15.7	.003**
% TAR >13.9 mmol/L (>250 mg/dl)	19.6 ± 16.1	9.0 ± 12.1	.017*
% TBR <3.9 mmol/L (<70 mg/dl)	4.7 ± 6.1	11.0 ± 10.9	.478
% TBR <3.0 mmol/L (<54 mg/dl)	1.5 ± 3.6	2.2 ± 4.9	.536
Glycaemic variability, CV%	24.0 ± 7.6	19.2 ± 8.7	.044*
Combined free-living night-time periods			
Mean glucose, mmol/L	8.0 ± 1.5	6.7 ± 1.4	.003**
% TIR 3.9-10.0 mmol/L (70-180 mg/dl)	71.6 ± 23.3	86.6 ± 14.3	.003**
% TAR >10.0 mmol/L (>180 mg/dl)	22.9 ± 22.2	7.2 ± 11.1	.001**
% TAR >13.9 mmol/L (>250 mg/dl)	3.5 ± 6.3	0.5 ± 1.6	.007**
% TBR <3.9 mmol/L (<70 mg/dl)	5.4 ± 7.2	6.8 ± 11.0	.606
% TBR <3.0 mmol/L (<54 mg/dl)	0.9 ± 1.7	3.5 ± 5.9	.159
Glycaemic variability (CV%)	44.5 ± 18.3	39.4 ± 22.3	.374

Note: Day time and night-time periods calculated as the combined mean for each respective period. Data are presented as mean ± SD.

Abbreviations: CV, coefficient of variation; TAB, time above range; TBR, time below range; TIR, time in range.

*Statistically significant conditional difference at $p < .05$.**Statistically significant conditional difference at $p < .01$.***Statistically significant conditional difference at $p < .001$.

<3.0 mmol/L) and glycaemic variability [coefficient of variation (CV)%] were calculated as per international guidelines for the use of CGM in clinical trials.[20,21]

2.6 | Data analysis

The primary outcome was 48 h of glycaemic control as assessed by mean glucose. We estimated that 32 paired observations would be required to achieve 95% power to detect a 1.6 mmol/L between group difference in mean glucose with an SD of 1.5 mmol/L (moderate effect size; Cohen d = 0.64) in the primary outcome variable. Our post-hoc power assessment confirmed that our sample size was sufficient to achieve a minimum statistical power of 80% across our secondary outcomes (TIR, TAB, TBR, glycaemic variability). Across both conditions, a total of 26 368 individual CGM-derived glucose readings over a combined total of 10 days were analysed, with missing data accounting for <1% (211 of 26 368). CGM data were summarised into three periods: (a) 48-h pre-experimental phase, (b) experimental phase, and (c) 48-h post-experimental free-living phase. The 48-h post-experimental free-living phase was further summarised into free-living day time periods (awake time: 08:00-23:00 h) and night-time periods (sleep time: 23:00-08:00 h).

We employed a series of generalised linear mixed models with random intercepts and Bonferroni-corrected post-hoc pairwise comparisons to evaluate the differential effects of SIT versus SITLESS on acute postprandial and 48-h mean glucose, TIR, TBR and TAR, as well as glycaemic variability (CV%). Linear regression analyses were utilised to examine potential relationships between pre-treatment clinical characteristics, age, sex, body mass index (BMI), glycated haemoglobin (HbA1c), residual C-peptide, diabetes duration and treatment regimen (CSII vs. MDI) and the magnitude of treatment response across CGM metrics. Dietary intake, insulin administration and physical activity (total step count) were summarised for each 24-h period within the 48-h post-intervention period and assessed for conditional differences over time using repeated measures ANOVA. To assess

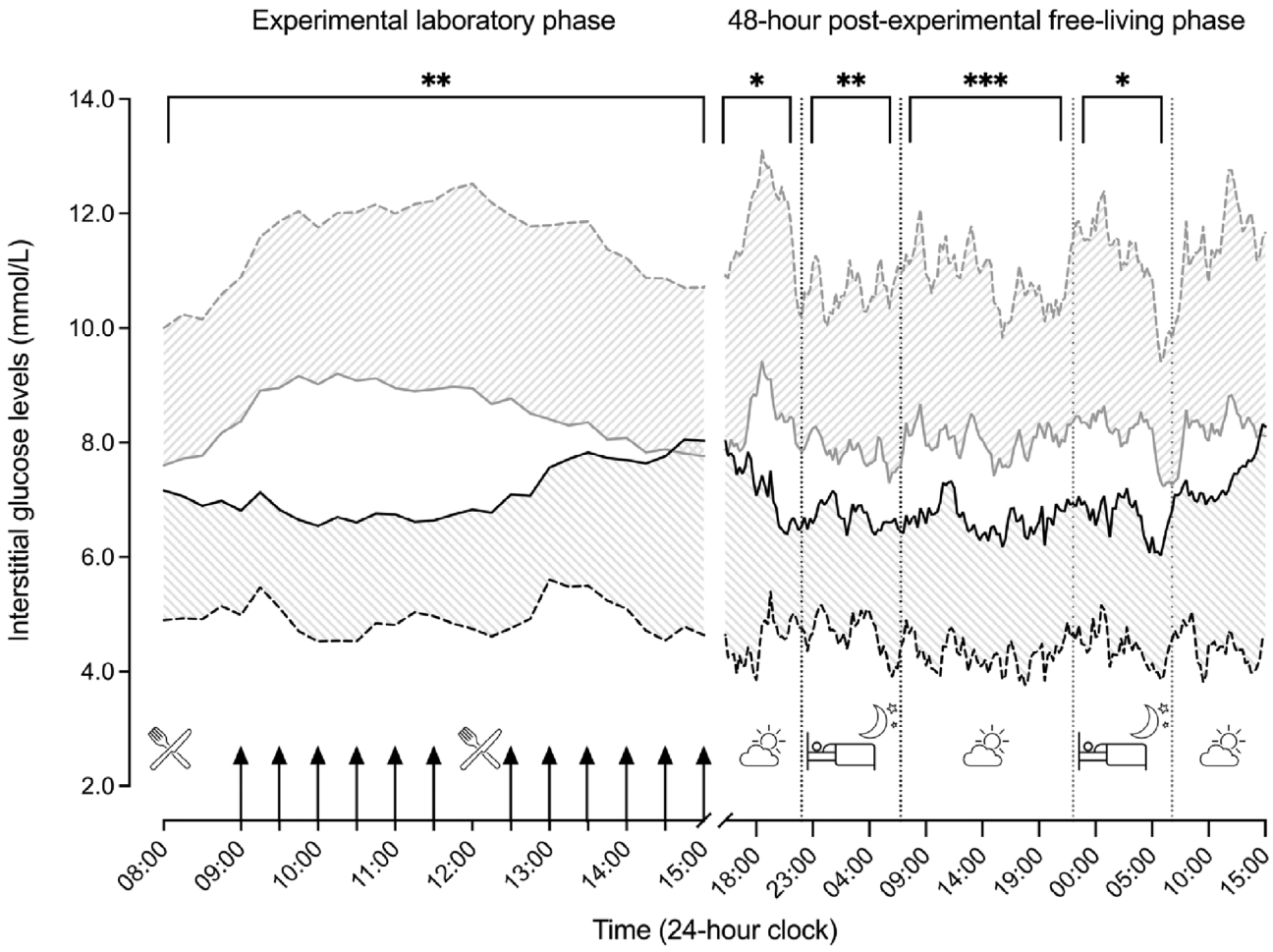

FIGURE 1 Glycaemic responses to interrupting sitting with frequent short bouts of light-intensity activity. Grey trace = SIT (uninterrupted sitting); Black trace = SIT-LESS (interrupted sitting with 3-minute bouts of self-paced light-intensity walking at 30-min intervals as indicated by black vertical arrows). Statistically significant conditional difference during each respective time period at: *$p < .05$; **$p < .01$; ***$p < .001$. Vertical dashed line breaks indicate nocturnal periods. Data presented as mean (solid trace) with SD (dashed trace); to improve clarity, +SD is presented for SIT, and SD is presented for SIT-LESS.

mealtime glucose exposure, we calculated net incremental area under the curve (net iAUC) as previously reported.[22] Statistical analyses were performed using SPSS software (version 28; IBM Corp.), with statistical significance accepted at a threshold of $p \leq .05$ and residuals examined for serial correlation, heteroscedasticity and normality. Data are presented as mean ± SD unless stated otherwise.

3 | RESULTS

Thirty-two participants with T1D [age 27.9 ± 4.7 years, 15/17 men/-women, BMI 26.5 ± 3.5 kg/m^2, diabetes duration 16.0 ± 6.9 years, HbA1c 8.4 ± 1.4% (68 ± 2 mmol/mol), CSII/MDI n = 15:17] were randomised and completed both experimental conditions (Figure S2). Patients displayed similar glycaemic control across the 48 h preceding each laboratory visit (Table 1), with similar mean glucose (SIT 7.7 ± 1.1 vs. SITLESS 7.5 ± 2.1 mmol/L; $p = .631$) and TIR (3.9-10.0 mmol/L; SIT 79.1 ± 12.5 vs. SITLESS 81.1 ± 19.9%; $p = .561$). Exposure to hyperglycaemia and hypoglycaemia were also comparable across conditions ($p > .01$; Table S1). Two patients rearranged their visits because of hypoglycaemia. Dietary intake, insulin regimen and physical activity levels were also similar across conditions ($p > .05$).

Glucose concentrations at experimental start time were comparable between conditions (SIT 7.3 ± 1.5 vs. SIT-LESS 7.2 ± 1.8 mmol/L, $p = .774$; Figure 1). During the laboratory phase, SIT-LESS attenuated postprandial glucose responses following administration of the breakfast (net iAUC: SIT 1690 ± 597 vs. SIT-LESS 1329 ± 420 mmol/L/min $p < .001$) and lunch (net iAUC: SIT 1754 ± 735 vs. SIT-LESS 1557 ± 558 mmol/L/min $p = .001$) test meals, resulting in lower mean glucose (SIT 8.5 ± 2.0 vs. SIT-LESS 7.1 ± 1.8 mmol/L, $p = .008$; Figure 1 and Table 1) and increased TIR by 17% (3.9-10.0 mmol/L; SIT 71.6 ± 19.3 vs. SIT-LESS 84.6 ± 14.8%, $p = .004$; Table 1) as a consequence of reduced hyperglycaemia (TAR <10.1 mmol/L: SIT 26.5 ± 27.5 vs. SIT-LESS 8.6 ± 18.3%, $p = .005$; Table 1); exposure to hypoglycaemia remained comparable across conditions, irrespective of pre-treatment HbA1c, with similar TBR (<3.9 mmol/L: SIT 2.7 ± 8.4

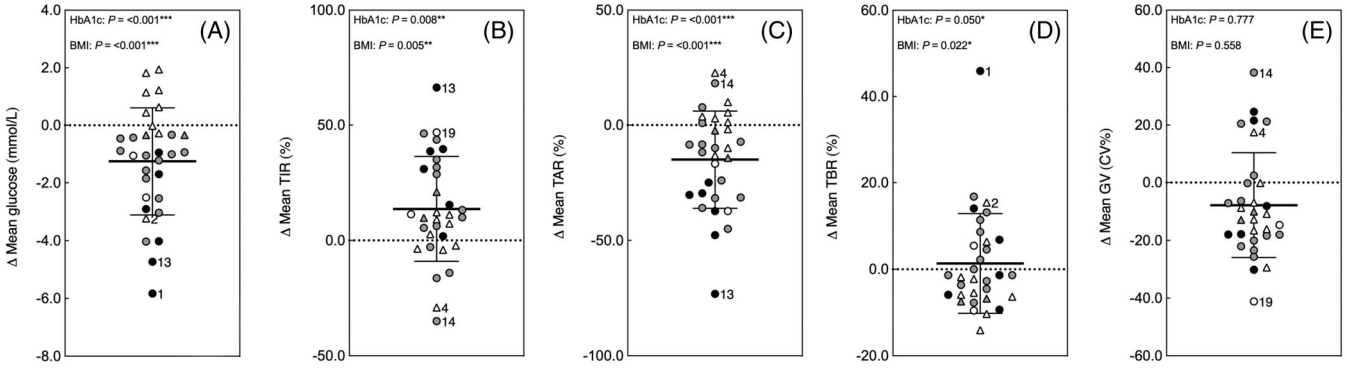

FIGURE 2 Individualised magnitude of change in treatment response between SIT and SIT-LESS across: (A) mean glucose, (B) mean TIR, (C) mean TAR, (D) mean TBR, (E) mean GV. Circles = pre-treatment HbA1c ≥7.5 mmol/mol; triangles = pre-treatment HbA1c <7.5 mmol/mol. White data points = normal weight (<25 kg/m^2); grey data points = overweight (25-29.9 kg/m^2); black data points = obese (>29.9 kg/m^2). Numbers represent individually annotated participant data points. Treatment response calculated by subtracting mean SIT-LESS responses from mean SIT responses. BMI, body mass index; GV, glycaemic variability (coefficient of variation %); HbA1c, glycated haemoglobin; SIT, uninterrupted sitting; SIT-LESS, interrupted sitting with 3-min bouts of self-paced light-intensity walking at 30-min intervals; TAR, time above range (>10 mmol/L); TBR, time below range (<3.9 mmol/L); TIR, time in range (3.9-10.0 mmol/L). Statistically significant association with magnitude of treatment response at: *$p < .05$; **$p < .01$; ***$p < 0$.

TABLE 2 Association between pre-treatment clinical characteristics and treatment response

	HbA1c	BMI
Experimental and free-living phase response		
Mean change in mean glucose, mmol/L	β = −0.801 (−1.39 to −0.78); $p < .001$***	β = −0.773 (−0.53 to −0.283); $p = <.001$***
Mean change in % TIR 3.9-10.0 mmol/L (70-180 mg/dl)	β = 0.462 (2.18 to 13.14); $p = .008$**	β = 0.481 (0.97 to 5.22); $p = .005$**
Mean change in % TAB >10.0 mmol/L (>180 mg/dl)	β = −0.686 (−14.72 to −6.37); $p < .001$***	β = −0.740 (−5.94 to −2.93); $p < .001$***
Mean change in % TBR <3.9 mmol/L (<70 mg/dl)	β = 0.343 (−0.064 to −5.84); $p = .049$*	β = − 0.404 (−0.208 to −2.45); $p = .022$*
Mean change in glycaemic variability, CV%	β = 0.052 (−4.241 to 5.624); $p = .777$	β = 0.108 (−1.36 to 2.47); $p = .558$

Note: Data presented as unstandardised β-coefficients (95% confidence interval).
Abbreviations: BMI, body mass index; CV, coefficient of variation; HbA1c, glycated haemoglobin; TAB, time above range; TBR, time below range; TIR, time in range.
*Statistically significant association at $p < .05$; **Statistically significant association at $p < .01$; ***Statistically significant association at $p < .001$.

vs. SIT-LESS 3.34 ± 10.2%, $p = .795$; Table 1) and total number of hypoglycaemic episodes at a threshold of 3.9 mmol/L (SIT 4 vs. SIT-LESS 5).

The glycaemic lowering impact of SIT-LESS continued into the free-living period (Figure 1 and Table 1), with lower subsequent 48-h mean glucose under SIT-LESS (SIT 8.1 ± 1.3 vs. SIT-LESS 6.9 ± 1.5 mmol/L, $p = .001$) and increased TIR by 13.0% (SIT 71.6 ± 19.3 vs. SIT-LESS 84.6 ± 14.8%, $p = .004$). TAR (>10.0 mmol/L) was reduced by 14.4% under SIT-LESS (SIT 23.8 ± 18.6 vs. SIT-LESS 9.4 ± 11.6%, $p = .001$), with TBR (<3.9 mmol/L) comparable across conditions (SIT 4.6 ± 5.0 vs. SIT-LESS 6.0 ± 9.9%, $p = .529$). SIT-LESS reduced 48-h glycaemic variability (CV%) by 7.2% ($p = .035$). These findings were consistent when assessing discrete time periods with SIT-LESS improving postprandial, whole-day and night-time TIR ($p < .05$; Figure 1 and Table 1). Dietary intake, insulin administration and objectively assessed physical activity levels were similar across conditions during the subsequent 48-h free-living period ($p < .05$; Table S2).

A significant HbA1c-by-condition interaction effect ($p = .007$, $F = 8.635$, $\eta^2 = 0.249$, $\beta = -0.801$), and BMI-by-condition interaction effect ($p = .030$, $F = 5.293$, $\eta^2 = 0.169$, β- $= -0.773$) were observed for the magnitude of change between SIT and SIT-LESS in mean glucose. Higher pre-treatment HbA1c and BMI were associated with greater improvements across mean glucose, TIR, TAR, and TBR, but not glycaemic variability (Figure 2; Table 2). Age, sex, diabetes duration, residual C-peptide and treatment regimen (CSII vs. MDI), did not significantly mediate any of the responses observed ($p > .05$).

4 | DISCUSSION

To our knowledge, this study is the first to evaluate the impact of interrupting prolonged sitting with frequent short bouts of light-intensity activity on glucose control in people with T1D. This intervention improved acute postprandial glucose control, reducing mean glucose concentrations, improving TIR while reducing glycaemic variability without increasing exposure to hypoglycaemia. Glycaemic improvement was sustained for at least 48-h under free-living conditions. Overall, these findings build on previous experimental work in people with or at risk of type 2 diabetes, and support the extension of current physical activity guidelines[2] to individuals with T1D, specifically regarding the interruption of prolonged sitting with frequent, short-duration, light-intensity activity breaks.

In people with diabetes, prolonged uninterrupted sitting is associated with worsening glucose control and increased weight,[4,23] which collectively and independently predict both macro- and microvascular complications.[24,25] In the present study, we show that simply interrupting prolonged sitting with regular light-intensity activity breaks results in a net glucose-lowering effect of ~1.3 mmol/L, with the greatest level of improvements in those with higher pre-treatment HbA1c and BMI. This clinically relevant margin, which if maintained over the long-term, has previously been shown to result in a reduction of HbA1c of ~2%,[26] translating to a 38% reduced risk of a macrovascular event, 40% reduced risk of a microvascular event and 38% reduced risk of premature mortality at a HbA1c threshold of ≥7%[27]; this is substantial given recent data indicating that fewer than 30% of people with T1D achieve the HbA1c treatment target of <7.5%.[28]

Importantly, glucose lowering was achieved without increasing the risk of hypoglycaemia. We, and others, have previously shown that moderate-vigorous physical activity predisposes to an increased risk of hypoglycaemia during, immediately following and late after moderate-vigorous intensity exercise,[1] and, that fear of exercise-induced hypoglycaemia is a major barrier to regular participation in physical activity.[14] Whereas exercise is often viewed as daunting and unachievable by many patients, translation of our data into clinical practice and patient education may help to reduce fear of hypoglycaemia surrounding physical activity and enable better glycaemic control when adopting lower-intensity activities. In addition, it is probable that the adoption of our strategy to target sedentary time with short-duration light-intensity activity breaks may serve as a logical starting point for inactive individuals with T1D to develop and build upon achievable and positive behavioural routines that increase overall physical activity levels.

The assessment of acute postprandial glucose control provides novel insightful data. We observed ~17% improvement in TIR under SIT-LESS, resulting almost exclusively from a reduction in hyperglycaemia. Moreover, 75% of patients under SIT-LESS achieved TIR >80% and 56% achieved TIR 100% during their laboratory stay, compared with 38% and 6% under SIT, respectively. During this time, glycaemic variability was reduced by 6% with all patients achieving the target CV% of <36%[29] while concurrently avoiding increased exposure to hypoglycaemia. Furthermore, this effect persisted over the course of the subsequent 48-h free-living observation window with an improvement in daytime TIR of ~12%, with 66% of patients under SIT-LESS achieving TIR >80%, which was double that achieved under SIT. Given that no differences were observed in dietary intake, insulin administration, or objectively assessed physical activity levels during this period, it is probable that persistence in glycaemic improvement under SIT is because of the residual effect from the interrupted sitting intervention rather than secondary to a change in behaviour. As such, our data showed that the majority of patients adopting our strategy are able to achieve and exceed current mealtime glycaemic targets.[29] This a major finding given the inherent complexity and difficulty associated with optimising postprandial glucose management in T1D and that controlling postprandial glucose excursions is a key component of achieving recommended HbA1c levels and minimising disease burden. In reality, many patients are exposed to increased glycaemic variability and hypoglycaemia during mealtimes, both of which are significant sources of frustration for patients, and factors that increase the risk of cardiovascular events and premature mortality independent of HbA1c.[30]

A remarkable finding of the present study was that the magnitude of glycaemic improvement across our chosen CGM metrics (mean glucose, TIR, glycaemic variability) persisted beyond our controlled experimental observation window for up to a further 48 h under free-living conditions. Importantly, time spent in nocturnal hyperglycaemia was on average 16% lower under SIT-LESS with minimal exposure to

hypoglycaemia. Whereas our data highlight the detrimental and persistent effects of high levels of prolonged sitting in T1D, they also showed the glycaemic benefits of interrupting prolonged sitting and offer a strategy for incorporating more physical activity throughout the day while avoiding increased exposure to potentially dangerous hypoglycaemia. It remains unknown, however, whether adopting a SIT-LESS protocol on consecutive days, or on multiple days per week results in further glucose lowering. Future work should assess the impact and safety of sustained adoption of SIT-LESS to establish whether combining activity days has continued or increased glucose-lowering power.

Within our study, we also examined the potential impact of pre-treatment clinical characteristics on the magnitude of treatment response. Our data show that baseline HbA1c and BMI status are important clinical characteristics that strongly associate with the magnitude of glucose lowering, with patients presenting with poorer glucose control and increased BMI showing, on average, the largest degree of glucose lowering. The measures employed within this study do not enable an exploration into the putative mechanisms underpinning the improvements in glycaemic control observed under SIT-LESS, nor the interaction between HbA1c and BMI with treatment response. However, the standardisation of insulin administration and dietary intake across conditions, is suggestive of enhanced contraction-induced and/or energy deficit-induced insulin sensitivity,[31] and/or a greater reliance on insulin-independent contraction-mediated glucose disposal.[32] As such, interrupting sitting may present an opportunity not only to tackle suboptimal glucose control, but also increase insulin sensitivity in those presenting with insulin resistance. Overweight, obesity and insulin resistance have recently been shown to be highly prevalent within the T1D population and strongly associated with the risk of micro- and macrovascular complications independent of HbA1c.[24] Therefore, future studies are warranted that explore the longer-term impacts of interrupted sitting on insulin resistance in T1D. Furthermore, it would be beneficial to explore whether the additive effects of exercise and diet-induced energy deficit on glycaemic improvement extend to physical activities at the lowest end of the physical activity continuum, to optimise lifestyle change prescription.

Strengths of this study include the rigorous well-controlled randomised crossover study design allowing for within and between participant comparisons, increasing internal validity and reliability of the data collected, and permitting a smaller sample size while ensuring adequate statistical power. We standardised condition run-in periods with strict but pragmatic assessment and replication of confounding variables including: diet, physical activity, fasting metabolic and glycaemic status, and experimental start time; comprehensive and blinded glucose profiling under controlled and extended free-living conditions with negligible data loss (<0.1%); full retention of study participants that reflect a relatively broad and representative demographic; and, the simple and practical nature of the intervention, which enables widespread promotion and adoption. Key study limitations are that this is a single centre study with a conservative sample size, which prevented subgroup analyses. Furthermore, we assessed physical activity volume using total step count and were unable to assess other dimensions of physical activity and therefore cannot rule out the possibility that undetected changes in physical activity could have impacted glucose outcomes during the free-living period. Future research is needed to determine whether such an intervention can be optimised (frequency, intensity and duration of walking breaks), and tailored specifically to accommodate patients with mobility issues, functional limitations, the presence of overt diabetes complications and other comorbidities, as well as those with insulin resistance. In addition, future studies should establish if such a strategy can be maintained by patients in free-living environments over the long-term and whether this translates to reduced risk of long-term complications and improved quality of life.

5 | CONCLUSION

To the best of our knowledge, we show for the first time that interrupting prolonged sitting with frequent short bouts of light-intensity activity improves acute postprandial glucose control resulting in glucose lowering, improved TIR and reduced glycaemic variability without increased risk of hypoglycaemia, with sustained improvement for up to a further 48 h. Although longer-term efficacy needs to be established, our findings provide the first experimental evidence for the value of frequent low intensity physical activity for improving glycaemia in individuals with T1D. This simple and acceptable approach may help to enable inactive individuals to incorporate more physical activity into the day and improve diabetes management. Interruption of sitting with light activities could be particularly useful for those who are unable or unwilling to engage in structured exercise, and this approach can be seen as an important 'stepping-stone' toward regular participation in structured moderate-vigorous physical activity or exercise. It should be emphasised that, unlike moderate-vigorous exercise, the improvement in glycaemia with our simple intervention did not result in increased hypoglycaemia and therefore we propose that health care professionals consider advising patients to interrupt prolonged sitting regularly. Large-scale studies are warranted to evaluate fully both the short- and long-term impact of this simple intervention in the management of individuals with T1D.

AUTHOR CONTRIBUTIONS

MDC performed the conceptualisation, funding acquisition, investigation, methodology, resources, supervision, visualisation, writing (original draft, review and editing); AMA carried out the investigation, visualisation, writing (review and editing); MH performed the investigation, visualisation, writing (review and editing); PCD carried out the conceptualisation, funding acquisition, investigation, methodology, resources, supervision, visualisation, writing (review and editing); SMP performed the investigation, visualisation, writing (review and editing); NK carried out the investigation, visualisation, writing (review and editing); RC performed the investigation, visualisation, writing (review and editing); RAA carried out the conceptualisation, funding acquisition, investigation, methodology, resources, supervision, visualisation,

writing (review and editing). All authors had access to the data, approved the final version, and accept responsibility to submit for publication. This study was funded by Diabetes UK (20/0006154). The funder was not involved in the design of the study, data collection, analysis, or interpretation.

ACKNOWLEDGMENTS

We thank the study participants for their time and commitment to the study protocol; this research would not have been possible without them.

FUNDING INFORMATION

This study was funded by Diabetes UK (project grant: 20/0006154).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15254.

DATA AVAILABILITY STATEMENT

Deidentified participant data collected during the trial alongside the study protocol and statistical analysis plan will be made available beginning 3 months and ending 36 months following article publication for investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals may be submitted up to 36 months following article publication and should be directed to matthew.campbell@sunderland.ac.uk to gain access, data requestors will need to sign a data access agreement. After 36 months the data will be available in our university's data warehouse but without investigator support other than deposited metadata.

ORCID

Matthew D. Campbell https://orcid.org/0000-0001-5883-5041
Sam M. Pearson https://orcid.org/0000-0002-4943-6759
Noppadol Kietsiriroje https://orcid.org/0000-0002-5076-4450

REFERENCES

1. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2016;39(11):2065-2079.
2. Dempsey PC, Friedenreich CM, Leitzmann MF, et al. Global public health guidelines on physical activity and sedentary behavior for people living with chronic conditions: a call to action. *J Phys Act Health*. 2020;18(1):76-85.
3. Patterson R, McNamara E, Tainio M, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol*. 2018;33:811-829.
4. Cooper AJ, Brage S, Ekelund U, Wareham NJ, Griffin SJ, Simmons RK. Association between objectively assessed sedentary time and physical activity with metabolic risk factors among people with recently diagnosed type 2 diabetes. *Diabetologia*. 2014;57:73-82.
5. Dempsey PC, Larsen RN, Sethi P, et al. Benefits for type 2 diabetes of interrupting prolonged sitting with brief bouts of light walking or simple resistance activities. *Diabetes Care*. 2016;39(6):964-972.
6. Dempsey PC, Owen N, Yates TE, Kingwell BA, Dunstan DW. Sitting less and moving more: improved glycaemic control for type 2 diabetes prevention and management. *Curr Diab Rep*. 2016;16:1-15.
7. Dempsey PC, Blankenship JM, Larsen RN, et al. Interrupting prolonged sitting in type 2 diabetes: nocturnal persistence of improved glycaemic control. *Diabetologia*. 2017;60:499-507.
8. Dempsey PC, Sacre JW, Larsen RN, et al. Interrupting prolonged sitting with brief bouts of light walking or simple resistance activities reduces resting blood pressure and plasma noradrenaline in type 2 diabetes. *J Hypertens*. 2016;34(12):2376-2382.
9. Dunstan DW, Kingwell BA, Larsen R, et al. Breaking up prolonged sitting reduces postprandial glucose and insulin responses. *Diabetes Care*. 2012;35(5):976-983.
10. Bohn B, Herbst A, Pfeifer M, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: a cross-sectional multicenter study of 18,028 patients. *Diabetes Care*. 2015;38(8):1536-1543.
11. Czenczek-Lewandowska E, Leszczak J, Weres A, et al. Sedentary behaviors in children and adolescents with type 1 diabetes, depending on the insulin therapy used. *Medicine*. 2019;98(19):e15625.
12. Matson RI, Leary SD, Cooper AR, Thompson C, Narendran P, Andrews RC. Objective measurement of physical activity in adults with newly diagnosed type 1 diabetes and healthy individuals. *Front Public Health*. 2018;6:360.
13. Wadén J, Forsblom C, Thorn LM, et al. Physical activity and diabetes complications in patients with type 1 diabetes: the Finnish diabetic nephropathy (FinnDiane) study. *Diabetes Care*. 2008;31(2):230-232.
14. Alobaid AM, Zulyniak MA, Ajjan RA, Brož J, Hopkins M, Campbell MD. Barriers to exercise in adults with type 1 diabetes and insulin resistance. *Can J Diabetes*. 2023;S1499-2671(26):97.
15. Brazeau A, Leroux C, Mircescu H, Rabasa-Lhoret R. Physical activity level and body composition among adults with type 1 diabetes. *Diabet Med*. 2012;29(11):e402-e408.
16. Campbell MD, Kime N, McKenna J. Exercise and physical activity in patients with type 1 diabetes. *Lancet Diabetes Endocrinol*. 2017;5(7):493.
17. Yardley JE, Campbell MD. Moving toward precision medicine with diabetes, exercise and physical activity. *Can J Diabetes*. 2020;44(8):679.
18. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care*. 1995;18(4):517-522.
19. Cleland CL, Hunter RF, Kee F, Cupples ME, Sallis JF, Tully MA. Validity of the global physical activity questionnaire (GPAQ) in assessing levels and change in moderate-vigorous physical activity and sedentary behaviour. *BMC Public Health*. 2014;14:1-11.
20. Timmons JG, Boyle JG, Petrie JR. Time in range as a research outcome measure. *Diabetes Spectr*. 2021;34(2):133-138.
21. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care*. 2017;40(12):1631-1640.
22. Brouns F, Bjorck I, Frayn K, et al. Glycaemic index methodology. *Nutr Res Rev*. 2005;18(1):145-171.
23. Huerta-Uribe N, Ramírez-Vélez R, Izquierdo M, García-hermoso A. Association between physical activity, sedentary behavior and physical fitness and glycated hemoglobin in youth with type 1 diabetes: a systematic review and meta-analysis. *Sports Med*. 2023;53(1):111-123.
24. Helliwell R, Warnes H, Kietsiriroje N, et al. Body mass index, estimated glucose disposal rate and vascular complications in type 1 diabetes: beyond glycated haemoglobin. *Diabet Med*. 2021;38(5):e14529.
25. Group DER. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. *Diabetes Care*. 2016;39(5):686-693.

26. Association AD. 6. Glycemic targets: standards of medical care in diabetes—2019. *Diabetes Care*. 2019;42:S61-S70.
27. Zoungas S, Chalmers J, Ninomiya T, et al. Association of HbA 1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. *Diabetologia*. 2012;55:636-643.
28. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the US: updated data from the T1D exchange clinic registry. *Diabetes Care*. 2015;38(6):971-978.
29. Holt RI, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2021;44(11):2589-2625.
30. Amiel SA, Aschner P, Childs B, et al. Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. *Lancet Diabetes Endocrinol*. 2019;7(5):385-396.
31. Gaitan JM, Weltman A, Malin SK. Enhancing exercise responsiveness across prediabetes phenotypes by targeting insulin sensitivity with nutrition. *J Diabetes Res*. 2017;2017:1-8.
32. Bergouignan A, Latouche C, Heywood S, et al. Frequent interruptions of sedentary time modulates contraction-and insulin-stimulated glucose uptake pathways in muscle: ancillary analysis from randomised clinical trials. *Sci Rep*. 2016;6(1):1-13.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Campbell MD, Alobaid AM, Hopkins M, et al. Interrupting prolonged sitting with frequent short bouts of light-intensity activity in people with type 1 diabetes improves glycaemic control without increasing hypoglycaemia: The SIT-LESS randomised controlled trial. *Diabetes Obes Metab*. 2023;25(12):3589-3598. doi:10.1111/dom.15254