A comparison of the health benefits of reduced-exertion high-intensity interval training (REHIT) and moderate-intensity walking in type 2 diabetes patients

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Running Title: Health benefits of REHIT and walking in T2D patients

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ABSTRACT

Background/Aim: Reduced-exertion high-intensity interval training (REHIT) is a genuinely time-efficient intervention that can improve aerobic capacity ($\dot{V}O_2max$) and insulin sensitivity in sedentary individuals. The present study compared the effects of REHIT and moderate-intensity walking on health markers in patients with type 2 diabetes (T2D) in a counter-balanced crossover study.

Methods: Sixteen men with T2D (mean±SD age: 55±5 y, BMI: 30.6±2.8 kg·m^{-2}, $\dot{V}O_2max$: 27±4 mL·kg^{-1}·min^{-1}) completed 8 weeks of REHIT (three 10-min low-intensity cycling sessions/week with two 'all-out' 10-20-s sprints) and 8 weeks of moderate-intensity walking (five 30-min sessions/week at an intensity corresponding to 40-55% of heart-rate reserve), with a 2-month wash-out period between interventions. Before and after each intervention, participants underwent an incremental fitness test, an oral glucose tolerance test (OGTT), a whole body dual-energy X-ray absorptiometry (DXA) scan, and continuous glucose monitoring.

Results: REHIT was associated with a significantly larger increase in $\dot{V}O_2max$ compared to walking (7% vs. 1%; time x intervention interaction effect: $p<0.05$). Both REHIT and walking decreased resting mean arterial pressure (MAP, -4%; main effect of time: $p<0.05$) and plasma fructosamine (-5%; main effect of time: $p<0.05$). Neither intervention significantly improved OGTT-derived measures of insulin sensitivity, glycaemic control measured using continuous glucose monitors, blood lipid profile or body composition.

Conclusions: We conclude that REHIT is superior to a five-fold larger volume of moderate-intensity walking in improving aerobic fitness, but similar to walking REHIT is not an effective intervention for improving insulin sensitivity or glycaemic control in T2D patients in the short term.

KEYWORDS

INTRODUCTION

With an estimated 422 million people worldwide suffering from type 2 diabetes (T2D) in 2014 (NCD Risk Factor Collaboration, 2016), and a predicted increase to 592 million by 2035 (Guariguata et al., 2014), T2D represents an increasingly serious burden on global health. A clear link between a sedentary lifestyle and the development of T2D has been demonstrated in prospective studies (Albright et al., 2000), and exercise can be used as an effective treatment modality (Colberg et al., 2010). The primary objectives of exercise interventions in T2D are to improve insulin sensitivity and glycaemic control, but considering the substantial burden of comorbidities in T2D patients, improving aerobic fitness, blood pressure, blood lipid profile, and body composition are important secondary objectives. For example, low $\dot{V}O_2max$ is a strong predictor of mortality in T2D (Wei et al., 2000), and it has been suggested that besides encouraging reductions in sedentary time and increases in overall physical activity levels, improving $\dot{V}O_2max$ should also be a key objective (Bouchard et al., 2015; Lee et al., 2011). Similarly, although T2D patients are at increased risk of cardiovascular disease (Colberg et al., 2010), even small decreases in blood pressure (2.1/0.9 mm Hg systolic/diastolic) can reduce major cardiovascular events by 10% (Turnbull et al., 2005).

Although the physical activity recommendations for patients with T2D (Colberg et al., 2010) and the general population (Garber et al., 2011) are essentially the same, adherence to these recommendations by T2D patients is even lower than in the general population (Morrato et al., 2007). As lack of time has been identified as one of the key barriers to performing sufficient physical activity in T2D patients (Korkiakangas et al., 2009), there is a need for effective interventions that are more time-efficient. High-intensity interval training (HIT) has been proposed to represent a promising, time-efficient alternative/adjunct to aerobic exercise (Earnest, 2008). Meta-analyses have demonstrated that, compared to aerobic exercise, HIT is more effective at improving insulin resistance (Jelleyman et al., 2015) and $\dot{V}O_2max$ (Milanovic

et al., 2015) in healthy sedentary individuals. In T2D patients, HIT has been shown to be associated with improvements in insulin sensitivity (Karstoft et al., 2014), glycaemic control (Little et al., 2011), and endothelial function (Madsen et al., 2015). However, due to the required recovery periods in between high-intensity bouts, most available HIT protocols are not as time-efficient as often claimed (Gillen & Gibala, 2014), and even in submaximal HIT protocols the high number of high-intensity bouts per training session results in high perceived exertion (Little et al., 2011). Moreover, repeating sprints more than ~4 times has a negative impact on the affective response to HIT (Frazão et al., 2016).

Based on the hypothesis that the mechanisms for the beneficial effects of HIT may be linked to the rapid glycogen depletion associated with supramaximal exercise (Metcalfe et al., 2012; Metcalfe et al., 2015; Metcalfe et al., 2016), and the observation that glycogen depletion during supramaximal exercise is limited to the first ~15 seconds of the first bouts of repeated 'all-out' sprints (Parolin et al., 1999), we have developed a shorter and more manageable version of HIT, termed reduced-exertion HIT (REHIT) (Metcalfe et al., 2012; Metcalfe et al., 2016). The REHIT protocol, which involves two brief 'all-out' cycle sprints within a 10-min exercise session, is associated with improved insulin sensitivity and $\dot{V}O_2max$ in sedentary individuals (Metcalfe et al., 2012; Metcalfe et al., 2016). Similar results have been obtained with a REHIT protocol modified by Martin Gibala's group to include three sprints instead of two (Gillen et al., 2016; Gillen et al., 2014). Recently, Revdal et al. (2016) studied the effects of a treadmill-based version of REHIT on cardiometabolic risk factors in T2D patients, and observed improved $\dot{V}O_2max$ and diastolic blood pressure following 12 weeks of training, but no changes in glycaemic control or body composition. However, peak power output data were not reported, and it is unclear whether this treadmill-based protocol is comparable to our cycling-based (Wingate) protocol in the exercise intensities achieved, or the associated adaptations. Furthermore, there are conflicting data on whether patients with T2D will have enhanced

(Jenkins & Hagberg, 2011), or impaired (Layne et al., 2011; Sriwijitkamol et al., 2007) responses to exercise training in general, and therefore it remains unknown whether cycling-based REHIT can be used to improve insulin sensitivity and $\dot{V}O_2max$ in T2D patients, and whether it may be effective at improving other important health markers such as blood pressure, blood lipid profile, and body composition. Moreover, in order for any intervention to be recommended to patients with T2D, the effects of the intervention should be at least as good as those associated with current physical activity recommendations. Considering the high interindividual variability in response to standardised supervised training interventions for important cardiometabolic risk factors such as $\dot{V}O_2max$, insulin sensitivity, blood lipid profile, blood pressure and body composition (Bouchard & Rankinen, 2001; Metcalfe et al., 2016; Vollaard et al., 2009), it is clear that randomised controlled trials that compare HIT vs. aerobic exercise require large sample sizes in order to avoid being affected by random inclusion of more low or high responders in one of the groups. An alternative approach is to perform studies with a cross-over design, allowing comparison of differences in the efficacy between interventions *within* individuals. Thus, the aim of the present study was to compare the effects of an 8-week REHIT intervention vs. 8 weeks of moderate-intensity aerobic exercise on $\dot{V}O_2max$, OGTT-derived insulin sensitivity, glycaemic control measured using continuous glucose monitoring, blood lipid profile, blood pressure and body composition in patients with T2D using a cross-over design. Based on our previous findings in sedentary but healthy individuals (Metcalfe et al., 2012; Metcalfe et al., 2016) we hypothesised that REHIT would be associated with improvements in these cardiometabolic risk factors, and that the improvements would be comparable to those with moderate-intensity aerobic exercise.

MATERIALS AND METHODS

Participants

Twenty-one men with T2D were recruited through the local UK South West Primary Care Research Network and local advertisement. Volunteers were eligible for participation if they were diagnosed with T2D by a clinician at least 6 months prior to the start of the study according to standard criteria (fasting blood glucose $\geq$7.0 mmol·l^{-1} and/or 2-h oral glucose tolerance test blood glucose $\geq$11.1 mmol·l^{-1}), were not on exogenous insulin therapy or more than two anti-diabetic drugs, and had no contraindications to exercise, including cardiac disease, impaired liver or renal function, or uncontrolled hypertension. Further exclusion criteria were BMI>35 kg·m^{-2}, age <40 y or >60 y, any abnormalities on a resting ECG, and classification as highly physically active on the International Physical Activity Questionnaire (IPAQ). Participants were informed of the experimental protocol both verbally and in writing before providing informed consent. Ethical approval was obtained from the NHS National Research Ethics Service (South West England REC; 13/SW/0298). Five participants dropped out during the study (**Figure 1**); participant characteristics for the remaining sixteen participants are shown in **Table 1**. No participants reported changes in their medication during the study.

Pre-experimental procedures

An overview of the experimental procedures is shown in **Figure 2**. Seven days prior to the first testing day, participants performed a familiarisation session for the maximal incremental cycling test to volitional exhaustion. Intensity was increased by 1 W every 4 s following a 5-min warm-up at 50 W (Excalibur, Lode, Groningen, the Netherlands). $\dot{V}O_2$max was determined as the highest 15-breath rolling average for $\dot{V}O_2$ measured using an online gas analysis system (TrueOne 2400, Parvo Medics, Sandy, UT, US). Values for $\dot{V}O_2$max were accepted if two or

more of the following criteria were met: 1) volitional exhaustion, 2) RER>1.10, and 3) maximal heart rate within 10 beats of the age-predicted maximum (i.e. 220-age). This was the case for all tests performed.

Testing procedures

Testing days were scheduled before each intervention, and 3 days after the last training session of each intervention. Seven days prior to each of the testing days, participants were fitted with a combined heart-rate monitor / accelerometer (Actiheart, CamNtech, Oxford, UK), which was worn up to and including the testing day, and used to calculate the participants' mean physical activity level (PAL) (Loney et al., 2011). A diet record was completed for the 3 days prior to the pre-training testing day and analysed using dietary analysis software (Nutritics v3.74, Dublin, Ireland). Participants abstained from their anti-diabetic medication the day before and the day of testing. For each participant, a meal was provided by the research team for the evening before testing (chosen by the participant from a number of options; total energy: 3321±660 kJ; 16±4% protein, 46±9% carbohydrate, 38±10% fat). Participants received the same evening meal before each of the four testing days in order to control for variation in results associated with diet. On the testing day, participants reported to the lab in the morning after an overnight fast for measurement of body composition using a whole body dual-energy X-ray absorptiometry (DXA) scan (Hologic Discovery W, Waltham, MA, USA). Following the scan a continuous subcutaneous glucose monitor (CGM; iPro, Medtronic, Northridge, California, USA) was fitted to the abdomen for measurement of glucose levels over the subsequent ~20 hrs. The CGM device was calibrated through capillary blood sampling at regular intervals during the day when blood glucose levels were expected to be stable (FreeStyle Freedom Lite, Abbott Diagnostics, Maidenhead, UK). A cannula was then inserted into a superficial forearm vein for use during an oral glucose tolerance test (OGTT). Participants then sat at rest for 30 minutes before three consecutive measurements of systolic

(SBP) and diastolic (DBP) blood pressure (Alvita MC101). Mean arterial pressure (MAP) was calculated as 2/3 DBP + 1/3 SBP. The OGTT started 30 min later with the collection of a baseline blood sample in a 4-ml EDTA-tube before drinking 113 mL of Polycal (Nutricia Clinical Care, UK) dissolved in 87 mL of water (equivalent to a 75 g glucose load). Further blood samples were taken 30, 60, 90 and 120 min later. Samples were kept on ice before centrifugation to obtain plasma for storage at -80°C, and subsequent analysis for glucose (Randox RX Daytona, Co. Antrim, UK) and insulin (ELISA, Dako, Ely, UK). Area under the curve (AUC) for the glucose and insulin responses was calculated using the trapezoid model, and peripheral insulin sensitivity was determined using the Cederholm Index (Cederholm & Wibell, 1990). Baseline (t=0) plasma samples were also analysed for triglycerides, LDL, HDL, fructosamine, and alanine transaminase (Randox RX Daytona, Co. Antrim, UK). For the remainder of the day, diet was standardised by providing the participants with set meals and snacks at set times (total energy: 8797±1327 kJ; 14±2% protein, 53±5% carbohydrate, 34±5% fat). As with the evening meal prior to the testing day, the same food items were provided for each of the four testing days. Participants returned to the lab the following day for removal of the glucose monitor. A maximal incremental cycling test to volitional exhaustion was repeated as described above.

Exercise interventions

Participants completed two 8-week supervised exercise interventions (REHIT and walking), spaced 2 months apart (range: 7-10 weeks) in a randomised counter-balanced crossover design (**Figure 2**). Eight participants performed the REHIT intervention first, which involved three 10-min sessions per week consisting of cycling at 25 W (Corival, Lode, Groningen, the Netherlands) interspersed with one (first session) or two (all remaining sessions) Wingate-type cycle-sprints against a constant torque of 0.65 Nm·kg lean mass[-1]. Sprints lasted 10 s in sessions 1-4, 15 s in sessions 5-12, and 20 s in the remaining 12 sessions. The peak power output (PPO),

mean power output (MPO), and the power output at the end of the sprint (EPO), as well as heart rate (Polar RS400, Polar, Kempele, Finland) were recorded for all sessions. The walking intervention was based on guidelines provided by the American College of Sports Medicine and the American Diabetes Association (Colberg et al., 2010), and involved five 30-min walking sessions per week at an intensity corresponding to 40%, 50% and 55% of heart-rate reserve (HRR) in weeks 1 and 2, weeks 3 and 4, and weeks 5-8 respectively. In order to keep the number of visits to the lab the same between the two interventions, three of the five weekly walking sessions were performed in the lab, and the remaining two sessions were performed at a place of the participant's choice, with a heart rate monitor (Polar RS400) to monitor the exercise intensity. Rating of perceived exertion (RPE) was recorded using a standard 6-20 scale during the final session of each training week. Training characteristics for both interventions are summarised in **Table 2**. In order to be included in the main data analysis, participants were not allowed to miss more than 20% of the training sessions in total, 3 consecutive sessions, or the final session before post-intervention testing sessions for either intervention. None of the participants failed to meet these requirements. The importance of returning to their usual lifestyle during the break in between the first and second exercise intervention was explained to the participants. After completing the study, but prior to receiving their individual results, participants were asked which of the two interventions would have their preference if they were asked to continue one of them.

Statistical Analysis

Data are presented as mean±SD. A power analysis (β=0.80, α=0.05) based on the primary outcome measure (change in OGTT-derived insulin sensitivity (Cederholm Index)) indicated that ≥16 participants were required to be able to detect significant differences between the two interventions with an effect size (Cohen's *d*) of 0.75. The effects of the interventions on the measured variables were analysed using two-way repeated-measures ANOVA (intervention

[REHIT / WALK] x time [pre-training / post-training]), with the intervention x time interaction effect as the main statistic of interest. Potential temporal effects were also analysed using two-way repeated-measures ANOVA (intervention [first / second] x time [pre-training / post-training]). Alpha was set at 0.05.

RESULTS

Training characteristics

On average the participants completed 99% of the REHIT sessions and 97% of the walking sessions. The training sessions were well-tolerated and no adverse events were observed, or reported by the participants. Mean RPE scores for the REHIT intervention (13.6±1.1; 'somewhat hard') were significantly higher than for the walking intervention (11.7±1.2; 'light'; $p<0.001$; **Table 2**). Peak power output (PPO), mean power output (MPO) and end power output (EPO) were all significantly lower in the second sprint compared to the first sprint ($p<0.001$), and MPO and EPO decreased during the intervention as sprint duration increased ($p<0.001$; **Table 2**). Mean total energy intake, and energy contribution from carbohydrates, fats and protein for the 3 days prior to the testing days were not significantly different between the 4 trials (data not shown). There was a significant time x intervention interaction effect for ActiHeart-derived mean physical activity level (PAL) for the 7 days prior to the testing days ($p<0.05$), reflecting a slight increase in physical activity energy expenditure during the final week of the walking intervention compared to pre-training (mean±SD 24-h activity level: 1.44±0.12 vs. 1.45±0.13 METs), and a slight decrease during the final week of the REHIT intervention (1.45±0.09 vs 1.38±0.10 METs). Twelve out of sixteen participants indicated a preference for REHIT as their intervention of choice.

Training effects on cardiometabolic health markers

Mean pre- and post-intervention values for the measured parameters are shown in **Table 3**. There was a significant time x intervention interaction effect for $\dot{V}O_2max$ ($p<0.05$) with a 7% increase following REHIT and a 1% increase following the walking intervention. MAP, SBP and DBP improved following exercise (main effect of time: $p<0.05$), but there were no significant time x intervention interaction effects for these parameters. There was a significant

positive correlation between the percentage change scores for MAP following the REHIT and walking interventions (R^2=0.32, p<0.05), but no such correlation was observed for $\dot{V}O_2max$ (R^2=0.06, NS). OGTT-derived measures of insulin sensitivity, glycaemic control as measured by CGM, blood measures, and body composition were not significantly affected by either REHIT or walking, except for a small training-induced decrease in plasma fructosamine levels (main effect of time: p<0.05).

Effectiveness of the wash-out period and order effects

The 2-month wash-out period between the two interventions was effective, as demonstrated by the lack of any significant differences between the first and second intervention for the baseline (pre-intervention) mean values for any of the measured parameters. Furthermore, the significant interaction effect for $\dot{V}O_2max$ could not be explained by potential superior effects during the first or second intervention as there were no intervention x time interaction effects for $\dot{V}O_2max$ for the first and second intervention (data not shown).

DISCUSSION

Using a cross-over design, the present study compared the effects of the genuinely time-efficient REHIT intervention and moderate-intensity aerobic exercise on health markers in patients with T2D. Although following 8 weeks of training neither intervention significantly improved glycaemic control as determined using CGM or OGTT-derived insulin sensitivity, both interventions reduced blood pressure to a similar extent, and REHIT was superior to moderate-intensity walking in improving $\dot{V}O_2$max. This was despite the fact that the total training time-commitment for the REHIT intervention was 80% lower than for the walking intervention (30 min per week vs. 150 min per week). This is the first study to compare the health benefits of two exercise interventions in a sample of T2D patients using a cross-over design. This provides a more powerful approach than the more commonly used randomised controlled trial approach, which to achieve the same power to detect a difference between two interventions would have required 56 participants compared to the sample of n=16 used in the present study.

In previous studies we (Metcalfe et al., 2012) and others (Gillen et al., 2016; Gillen et al., 2014) have demonstrated that very low volumes of sprint exercise are sufficient to significantly improve measures of insulin sensitivity in sedentary people on average, but with large interindividual variability in response (Metcalfe et al., 2016). Conversely, with a similar protocol and a longer intervention duration (8 weeks vs. 6 weeks), in the present study we did not observe improvements in glycaemic control as measured using a continuous glucose monitor, or OGTT-derived measures of insulin sensitivity in T2D patients. This is in line with the recent findings by Revdal et al. (2016) who observed improvements in $\dot{V}O_2$max but not glycaemic control following 12 weeks of a running-based REHIT intervention. Interestingly, in contrast to data presented by Little et al. (2011), a HIT protocol consisting of 10 x 1 min at 90% of maximal heart rate was also found to be ineffective at improving glycaemic control in

the study by Revdal et al. (2016). This highlights the fact that the results of studies investigating the effects of exercise interventions on insulin sensitivity have been conflicting. Whereas some studies have reported greater benefits of exercise in people with poorer baseline insulin sensitivity (Jenkins & Hagberg, 2011), others have reported impaired responses to exercise in patients with T2D or metabolic syndrome (Layne et al., 2011; Sriwijitkamol et al., 2007), and longer T2D disease duration is associated with poorer improvements in insulin sensitivity and glycaemic control following aerobic exercise training (Solomon et al., 2013). In addition, it has been suggested that low response to exercise for important risk factors such as $\dot{V}O_2max$ or insulin sensitivity may result in increased risk of developing cardiometabolic disease (Lessard et al., 2013). If this is indeed the case, then it could be expected that low response to exercise is more prevalent in patient populations compared to healthy individuals. Thus, patients with T2D may require a larger dose and/or intensity of exercise training in order to improve insulin sensitivity. The present study suggests that neither 150 min of moderate-intensity walking nor 30 min of REHIT per week provide a sufficient training stimulus to improve OGTT-derived insulin sensitivity and glycaemic control in this patient group within an 8-week intervention duration.

An alternative explanation for the lack of effect for insulin sensitivity in patients with T2D is the potential interfering effect of medication. It has been demonstrated that metformin may attenuate the beneficial effects of exercise on glucose regulation, blood pressure, and blood lipid profile (Malin & Braun, 2016). Similarly, studies suggest that statins may attenuate exercise-induced adaptations as well (Mikus et al., 2013; Murlasits & Radak, 2014), although the opposite effect has also been observed (Meex et al., 2010). As our study was not sufficiently powered for a between-participant statistical comparison of the training adaptations in participants who were taking statins and/or metformin (n=12) vs. the participants who were not

(n=4), we cannot determine whether the use of medication may have affected the response to training in the present study.

In contrast to the lack of effect for OGTT-derived insulin sensitivity, REHIT significantly improved $\dot{V}O_2$max and MAP. Considering the strong association between an increase in $\dot{V}O_2$max and reduced all-cause and cardiovascular disease mortality (Barlow et al., 2012; Lee et al., 2011), this is an important finding. Similarly, the 5, 2 and 4 mm Hg reductions in systolic, diastolic and mean arterial pressure, respectively, following 8 weeks of REHIT favourably compare to the effects of blood pressure-lowering medication in T2D patients and can be expected to lead to a reduction in cardiovascular morbidity and mortality in the longer term (Turnbull et al., 2005). Thus we demonstrate that cardiovascular risk in a patient population at increased risk can be reduced with an exercise intervention which only requires 30 min of total training time per week. Although based on these findings alone it is too early to advise patients to perform REHIT rather than moderate-intensity aerobic exercise, they provide initial support for the use of REHIT in patients who feel they do not have sufficient time to follow current exercise recommendations. As the majority of participants in our study preferred the REHIT intervention over the walking intervention, and no adverse events occurred, further research into the effects of very low volumes of HIT in patient populations is warranted.

Neither of the interventions resulted in changes in body composition. This is not entirely surprising because the participants were informed that the objective of the study was not weight loss and they were encouraged to keep their diet and lifestyle habits stable for the duration of the study. Furthermore, previous larger studies have also demonstrated that 150 min per week of moderate intensity exercise is insufficient for weight loss (Church et al., 2007). Considering previous findings of superior weight loss with HIT vs. moderate intensity aerobic exercise (Trapp et al., 2008), and indications that an acute REHIT session affects appetite-regulating hormones (Metcalfe et al., 2015), it will be worthwhile to investigate in future studies whether

a combination of REHIT with a calorie-restricted diet may provide an effective means of adiposity management.

The safety of HIT interventions in patients remains a contentious issue. Despite the fact that there are no data to suggest that HIT is inherently less safe to perform by patients than aerobic or resistance exercise, opponents of the use of HIT in patients maintain the argument that the high exercise intensities must make HIT less safe (Biddle & Batterham, 2015; Holloway & Spriet, 2015). It remains unknown whether the short-term increase in heart rate associated with high-intensity exercise (reaching ~90% of maximal heart rate in our study) is more or less of a risk compared to the more sustained longer-term increase in heart rate during aerobic exercise. However, in our opinion the expected increase in blood flow and blood pressure during sprints presents the main *potential* risk of HIT. Only limited data is currently available on the acute responses for these parameters during and directly after HIT (Hussain et al., 1996), and this should be the focus of more detailed future studies. Nonetheless, in the present study we observed no adverse events associated with performing 'all-out' cycle sprints (mean±SD peak power output: ~350±50% of $\dot{V}O_2max$) in sixteen overweight/obese, middle-aged (43-60 y) patients with T2D. Although this does not 'prove' that REHIT is safe for T2D patients ('safety' is a difficult concept to demonstrate experimentally), our study at a minimum provides additional support for the safety of REHIT as an intervention for sedentary individuals in the general population.

It has been proposed that caution is needed before advocating HIT interventions to the general population because the high exercise intensities will decrease motivation and may evoke a high degree of negative affect (Hardcastle et al., 2014). This may (Frazão et al., 2016; Saanijoki et al., 2015), or may not (Freese et al., 2014; Jung et al., 2014) be the case for HIT protocols that rely on many (4-10) longer (30-60 s) sprints, but the ratings of perceived exertion in response to two 20-s sprints as used in the REHIT protocol in the present study appear to be manageable,

and the majority of participants (12 out of 16) stated a preference for performing REHIT rather than the walking intervention based on current physical activity recommendations. There is therefore an urgent need to perform further studies examining the efficacy, acceptability, and longer-term adherence to REHIT as a practical 'real-life' intervention.

In conclusion, we demonstrate that brief bouts of REHIT are well-tolerated by middle-aged men with T2D, and that this type of training is superior to a five-times larger total volume of moderate-intensity walking in improving $\dot{V}O_2max$. Furthermore, 8 weeks of both REHIT and walking are associated with a significant decrease in blood pressure in T2D patients, but the reasons why these patients do not respond to either intervention, on average, for glycaemic control and OGTT-derived insulin sensitivity needs to be investigated further.

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CONFLICT OF INTEREST DISCLAIMER

The authors report no conflicts of interest associated with this manuscript.

REFERENCES

Albright, A., Franz, M., Hornsby, G., Kriska, A., Marrero, D., Ullrich, I., et al. 2000. American College of Sports Medicine position stand. Exercise and type 2 diabetes. *Med. Sci. Sports Exerc., 32*(7), 1345-1360.

Barlow, C. E., Defina, L. F., Radford, N. B., Berry, J. D., Cooper, K. H., Haskell, W. L., et al. 2012. Cardiorespiratory fitness and long-term survival in "low-risk" adults. *J. Am. Heart Assoc., 1*(4), e001354. doi:10.1161/JAHA.112.001354

Biddle, S. J., & Batterham, A. M. 2015. High-intensity interval exercise training for public health: a big HIT or shall we HIT it on the head? *Int. J. Behav. Nutr. Phys. Act., 12*(1), 95. doi:10.1186/s12966-015-0254-9

Bouchard, C., Blair, S. N., & Katzmarzyk, P. T. 2015. Less Sitting, More Physical Activity, or Higher Fitness? *Mayo Clin. Proc., 90*(11), 1533-1540. doi:10.1016/j.mayocp.2015.08.005

Bouchard, C., & Rankinen, T. 2001. Individual differences in response to regular physical activity. *Med. Sci. Sports Exerc., 33*(6 Suppl), S446-451; discussion S452-443.

Cederholm, J., & Wibell, L. 1990. Insulin release and peripheral sensitivity at the oral glucose tolerance test. *Diabetes Res. Clin. Pract., 10*(2), 167-175.

Church, T. S., Earnest, C. P., Skinner, J. S., & Blair, S. N. 2007. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA, 297*(19), 2081-2091. doi:10.1001/jama.297.19.2081

Colberg, S. R., Albright, A. L., Blissmer, B. J., Braun, B., Chasan-Taber, L., Fernhall, B., et al. 2010. Exercise and type 2 diabetes: American College of Sports Medicine and the American Diabetes Association: joint position statement. Exercise and type 2 diabetes. *Med. Sci. Sports Exerc., 42*(12), 2282-2303. doi:10.1249/MSS.0b013e3181eeb61c

Earnest, C. P. 2008. Exercise interval training: an improved stimulus for improving the physiology of pre-diabetes. *Med. Hypotheses, 71*(5), 752-761. doi:10.1016/j.mehy.2008.06.024

Frazão, D. T., de Farias Junior, L. F., Dantas, T. C., Krinski, K., Elsangedy, H. M., Prestes, J., et al. 2016. Feeling of Pleasure to High-Intensity Interval Exercise Is Dependent of the Number of Work Bouts and Physical Activity Status. *PLoS One, 11*(3), e0152752. doi:10.1371/journal.pone.0152752

Freese, E. C., Acitelli, R. M., Gist, N. H., Cureton, K. J., Evans, E. M., & O'Connor, P. J. 2014. Effect of six weeks of sprint interval training on mood and perceived health in women at risk for metabolic syndrome. *J. Sport Exerc. Psychol., 36*(6), 610-618. doi:10.1123/jsep.2014-0083

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., et al. 2011. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med. Sci. Sports Exerc., 43*(7), 1334-1359. doi:10.1249/MSS.0b013e318213fefb

Gillen, J. B., & Gibala, M. J. 2014. Is high-intensity interval training a time-efficient exercise strategy to improve health and fitness? *Appl. Physiol. Nutr. Metab., 39*(3), 409-412. doi:10.1139/apnm-2013-0187

Gillen, J. B., Martin, B. J., MacInnis, M. J., Skelly, L. E., Tarnopolsky, M. A., & Gibala, M. J. 2016. Twelve Weeks of Sprint Interval Training Improves Indices of Cardiometabolic Health Similar to Traditional Endurance Training despite a Five-Fold Lower Exercise Volume and Time Commitment. *PLoS One, 11*(4), e0154075. doi:10.1371/journal.pone.0154075

Gillen, J. B., Percival, M. E., Skelly, L. E., Martin, B. J., Tan, R. B., Tarnopolsky, M. A., et al. 2014. Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. *PLoS One, 9*(11), e111489. doi:10.1371/journal.pone.0111489

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U., & Shaw, J. E. 2014. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res. Clin. Pract., 103*(2), 137-149. doi:10.1016/j.diabres.2013.11.002

Hardcastle, S. J., Ray, H., Beale, L., & Hagger, M. S. 2014. Why sprint interval training is inappropriate for a largely sedentary population. *Front. Psychol., 5*, 1505. doi:10.3389/fpsyg.2014.01505

Holloway, T. M., & Spriet, L. L. 2015. CrossTalk opposing view: High intensity interval training does not have a role in risk reduction or treatment of disease. *J. Physiol., 593*(24), 5219-5221. doi:10.1113/JP271039

Hussain, S. T., Smith, R. E., Medbak, S., Wood, R. F., & Whipp, B. J. 1996. Haemodynamic and metabolic responses of the lower limb after high intensity exercise in humans. *Exp. Physiol., 81*(2), 173-187.

Jelleyman, C., Yates, T., O'Donovan, G., Gray, L. J., King, J. A., Khunti, K., et al. 2015. The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. *Obes. Rev., 16*(11), 942-961. doi:10.1111/obr.12317

Jenkins, N. T., & Hagberg, J. M. 2011. Aerobic training effects on glucose tolerance in prediabetic and normoglycemic humans. *Med. Sci. Sports Exerc., 43*(12), 2231-2240. doi:10.1249/MSS.0b013e318223b5f9

Jung, M. E., Bourne, J. E., & Little, J. P. 2014. Where does HIT fit? An examination of the affective response to high-intensity intervals in comparison to continuous moderate- and continuous vigorous-intensity exercise in the exercise intensity-affect continuum. *PLoS One, 9*(12), e114541. doi:10.1371/journal.pone.0114541

Karstoft, K., Winding, K., Knudsen, S. H., James, N. G., Scheel, M. M., Olesen, J., et al. 2014. Mechanisms behind the superior effects of interval vs continuous training on glycaemic control in individuals with type 2 diabetes: a randomised controlled trial. *Diabetologia, 57*(10), 2081-2093. doi:10.1007/s00125-014-3334-5

Korkiakangas, E. E., Alahuhta, M. A., & Laitinen, J. H. 2009. Barriers to regular exercise among adults at high risk or diagnosed with type 2 diabetes: a systematic review. *Health Promot. Int., 24*(4), 416-427. doi:10.1093/heapro/dap031

Layne, A. S., Nasrallah, S., South, M. A., Howell, M. E., McCurry, M. P., Ramsey, M. W., et al. 2011. Impaired muscle AMPK activation in the metabolic syndrome may attenuate improved insulin action after exercise training. *J. Clin. Endocrinol. Metab., 96*(6), 1815-1826. doi:10.1210/jc.2010-2532

Lee, D. C., Sui, X., Artero, E. G., Lee, I. M., Church, T. S., McAuley, P. A., et al. 2011. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation, 124*(23), 2483-2490. doi:10.1161/CIRCULATIONAHA.111.038422

Lessard, S. J., Rivas, D. A., Alves-Wagner, A. B., Hirshman, M. F., Gallagher, I. J., Constantin-Teodosiu, D., et al. 2013. Resistance to aerobic exercise training causes metabolic dysfunction and reveals novel exercise-regulated signaling networks. *Diabetes, 62*(8), 2717-2727. doi:10.2337/db13-0062

Little, J. P., Gillen, J. B., Percival, M. E., Safdar, A., Tarnopolsky, M. A., Punthakee, Z., et al. 2011. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J. Appl. Physiol. (1985), 111*(6), 1554-1560. doi:10.1152/japplphysiol.00921.2011

Loney, T., Standage, M., Thompson, D., Sebire, S. J., & Cumming, S. 2011. Self-report vs. objectively assessed physical activity: which is right for public health? *J. Phys. Act. Health, 8*(1), 62-70.

Madsen, S. M., Thorup, A. C., Overgaard, K., Bjerre, M., & Jeppesen, P. B. 2015. Functional and structural vascular adaptations following 8 weeks of low volume high intensity interval training in lower leg of type 2 diabetes patients and individuals at high risk of metabolic syndrome. *Arch. Physiol. Biochem., 121*(5), 178-186. doi:10.3109/13813455.2015.1087033

Malin, S. K., & Braun, B. 2016. Impact of Metformin on Exercise-Induced Metabolic Adaptations to Lower Type 2 Diabetes Risk. *Exerc. Sport. Sci. Rev., 44*(1), 4-11. doi:10.1249/JES.0000000000000070

Meex, R. C., Phielix, E., Schrauwen-Hinderling, V. B., Moonen-Kornips, E., Schaart, G., Schrauwen, P., et al. 2010. The use of statins potentiates the insulin-sensitizing effect of exercise training in obese males with and without Type 2 diabetes. *Clin. Sci. (Lond), 119*(7), 293-301. doi:10.1042/CS20100153

Metcalfe, R. S., Babraj, J. A., Fawkner, S. G., & Vollaard, N. B. 2012. Towards the minimal amount of exercise for improving metabolic health: beneficial effects of reduced-exertion high-intensity interval training. *Eur. J. Appl. Physiol., 112*(7), 2767-2775. doi:10.1007/s00421-011-2254-z

Metcalfe, R. S., Koumanov, F., Ruffino, J. S., Stokes, K. A., Holman, G. D., Thompson, D., et al. 2015. Physiological and molecular responses to an acute bout of reduced-exertion high-intensity interval training (REHIT). *Eur. J. Appl. Physiol., 115*(11), 2321-2334. doi:10.1007/s00421-015-3217-6

Metcalfe, R. S., Tardif, N., Thompson, D., & Vollaard, N. B. J. 2016. Changes in aerobic capacity and glycaemic control in response to reduced-exertion high-intensity interval training (REHIT) are not different between sedentary men and women. *Appl. Physiol. Nutr. Metab.* doi:10.1139/apnm-2016-0253

Mikus, C. R., Boyle, L. J., Borengasser, S. J., Oberlin, D. J., Naples, S. P., Fletcher, J., et al. 2013. Simvastatin impairs exercise training adaptations. *J. Am. Coll. Cardiol., 62*(8), 709-714. doi:10.1016/j.jacc.2013.02.074

Milanovic, Z., Sporis, G., & Weston, M. 2015. Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. *Sports Med., 45*(10), 1469-1481. doi:10.1007/s40279-015-0365-0

Morrato, E. H., Hill, J. O., Wyatt, H. R., Ghushchyan, V., & Sullivan, P. W. 2007. Physical activity in U.S. adults with diabetes and at risk for developing diabetes, 2003. *Diabetes Care, 30*(2), 203-209. doi:10.2337/dc06-1128

Murlasits, Z., & Radak, Z. 2014. The effects of statin medications on aerobic exercise capacity and training adaptations. *Sports Med., 44*(11), 1519-1530. doi:10.1007/s40279-014-0224-4

NCD Risk Factor Collaboration. 2016. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. *Lancet, 387*(10027), 1513-1530.

Parolin, M. L., Chesley, A., Matsos, M. P., Spriet, L. L., Jones, N. L., & Heigenhauser, G. J. 1999. Regulation of skeletal muscle glycogen phosphorylase and PDH during maximal intermittent exercise. *Am. J. Physiol., 277*(5 Pt 1), E890-900.

Revdal, A., Hollekim-Strand, S. M., & Ingul, C. B. 2016. Can Time Efficient Exercise Improve Cardiometabolic Risk Factors in Type 2 Diabetes? A Pilot Study. *J. Sports. Sci. Med., 15*(2), 308-313.

Saanijoki, T., Nummenmaa, L., Eskelinen, J. J., Savolainen, A. M., Vahlberg, T., Kalliokoski, K. K., et al. 2015. Affective Responses to Repeated Sessions of High-Intensity Interval Training. *Med. Sci. Sports Exerc., 47*(12), 2604-2611. doi:10.1249/MSS.0000000000000721

Solomon, T. P., Malin, S. K., Karstoft, K., Kashyap, S. R., Haus, J. M., & Kirwan, J. P. 2013. Pancreatic beta-cell function is a stronger predictor of changes in glycemic control after an aerobic exercise intervention than insulin sensitivity. *J. Clin. Endocrinol. Metab., 98*(10), 4176-4186. doi:10.1210/jc.2013-2232

Sriwijitkamol, A., Coletta, D. K., Wajcberg, E., Balbontin, G. B., Reyna, S. M., Barrientes, J., et al. 2007. Effect of acute exercise on AMPK signaling in skeletal muscle of subjects with type 2 diabetes: a time-course and dose-response study. *Diabetes, 56*(3), 836-848. doi:10.2337/db06-1119

Trapp, E. G., Chisholm, D. J., Freund, J., & Boutcher, S. H. 2008. The effects of high-intensity intermittent exercise training on fat loss and fasting insulin levels of young women. *Int. J. Obes. (Lond), 32*(4), 684-691. doi:10.1038/sj.ijo.0803781

Turnbull, F., Neal, B., Algert, C., Chalmers, J., Chapman, N., Cutler, J., et al. 2005. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch. Intern. Med., 165*(12), 1410-1419. doi:10.1001/archinte.165.12.1410

Vollaard, N. B., Constantin-Teodosiu, D., Fredriksson, K., Rooyackers, O., Jansson, E., Greenhaff, P. L., et al. 2009. Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance. *J. Appl. Physiol. (1985), 106*(5), 1479-1486. doi:10.1152/japplphysiol.91453.2008

Wei, M., Gibbons, L. W., Kampert, J. B., Nichaman, M. Z., & Blair, S. N. 2000. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann. Intern. Med., 132*(8), 605-611.

Table 1   Participant characteristics (n=16)

Age (y)	55±5 (43-60)
Duration of T2D (y since diagnosis)	4±4 (1-11)
Body mass (kg)	96.7±11.1 (72.4-113.6)
Height (m)	1.78±0.06 (1.68-1.87)
BMI (kg·m^{-2})	30.6±2.8 (25.1-34.5)
$\dot{V}O_2$max (mL·kg^{-1}·min^{-1})	27.5±4.3 (21.3-34.1)
Systolic blood pressure (mm Hg)	132±12 (118-157)
Diastolic blood pressure (mm Hg)	82±7 (67-95)
Mean arterial pressure	99±8 (86-116)
Medication:	
None (n)	3
Metformin (n)	9
Sulfonylurea (n)	3
Blood pressure lowering (n)	4
Statins (n)	10
Anti-depressant (n)	1

Values shown are mean±SD (range)

Table 2   Training characteristics

	REHIT			Walking		
	Sessions 1-4	**Sessions 5-12**	**Sessions 13-24**	**Sessions 1-10**	**Sessions 11-20**	**Sessions 21-40**
RPE	13±1	14±1	14±2	11±1	12±2	12±1
HRpeak (% of HRmax)	86±6	87±6	88±6	-	-	-
Target vs. achieved HR (bpm)	-	-	-	110±10 / 111±10	120±10 / 121±10	126±11 / 125±12
PPO (sprint 1/sprint 2; W)	784±129 / 759±115	778±149 / 769±127	765±137 / 757±151	-	-	-
MPO (sprint 1/sprint 2; W)	626±105 / 618±105	602±105 / 589±103	564±96 / 532±89	-	-	-
EPO (sprint 1/sprint 2; W)	505±100 / 500±99	451±73 / 421±90	393±92 / 342±78	-	-	-

RPE: rating of perceived exertion; HR: heart rate; HRR: heart rate reserve; PPO: peak power output; MPO: mean power output; EPO: end power output

Table 3   Effects of the two training interventions (n=16)

	Pre-REHIT	Post-REHIT	Pre-Walking	Post-Walking
Body mass (kg)	96.8±11.7	97.1±12.0	97.0±11.6	97.2±11.9
Total body fat (%)	31.0±4.3	30.7±4.3	30.9±4.4	30.9±4.5
Android fat (%)	37.9±5.3	37.5±5.3	37.8±5.1	37.6±5.8
Gynoid fat (%)	28.0±5.1	27.3±5.1 *	28.1±5.4	27.7±5.4 *
$\dot{V}O_2max$ (L·min^{-1})	2.60±0.44	2.79±0.47 †	2.64±0.45	2.66±0.49 †
Systolic blood pressure (mm Hg)	132±13	127±10 *	132±11	130±17 *
Diastolic blood pressure (mm Hg)	81±8	78±6 *	82±8	78±6 *
Mean arterial pressure (mm Hg)	98±9	94±7 *	99±8	95±9 *
CGM average glucose (mM)	9.5±2.9	9.5±3.2	9.7±3.4	9.7±2.8
Fasted plasma glucose (mmol·L^{-1})	9.9±3.0	9.2±2.2	9.9±2.8	9.7±2.3
Fasted plasma insulin (mU·L^{-1})	16.0±11.6	16.1±13.6	13.7±10.1	17.7±13.9
HOMA-IR	7.1±5.2	6.6±5.4	6.2±4.8	7.5±5.3
OGTT plasma glucose AUC (mmol·min·L^{-1})	1848±543	1758±396	1893±483	1848±435
OGTT plasma insulin AUC (mU·min·L^{-1})	3395±679	3579±987	3563±612	3584±947
Cederholm index (mg·L^2·mmol^{-1}·mU^{-1}·min^{-1})	23.3±12.1	24.7±14.0	21.6±11.0	22.5±10.3
Triglycerides (mM)	1.5±0.8	1.4±0.7	1.5±0.9	1.4±0.7
Plasma LDL (mM)	2.9±1.7	3.2±1.8	2.8±1.4	2.6±1.5
Plasma HDL (mM)	1.0±0.2	1.1±0.2	1.1±0.2	1.1±0.2
Plasma fructosamine (μM)	387±65	376±56 *	396±54	366±69 *
Plasma ALT (U/L)	36±8	36±9	37±12	38±13

*Values shown are mean±SD. $\dot{V}O_2max$: maximal aerobic capacity, CGM: continuous glucose monitor HOMA-IR: homeostatic model assessment - insulin resistance, OGTT: oral glucose tolerance test, AUC: area-under-the-curve, NEFA: non-esterified fatty acids, LDL: low-density lipoprotein, HDL: high-density lipoprotein, ALT: alanine aminotransferase. Main effect of time: * p<0.05; trial x time interaction effect: † p<0.05*

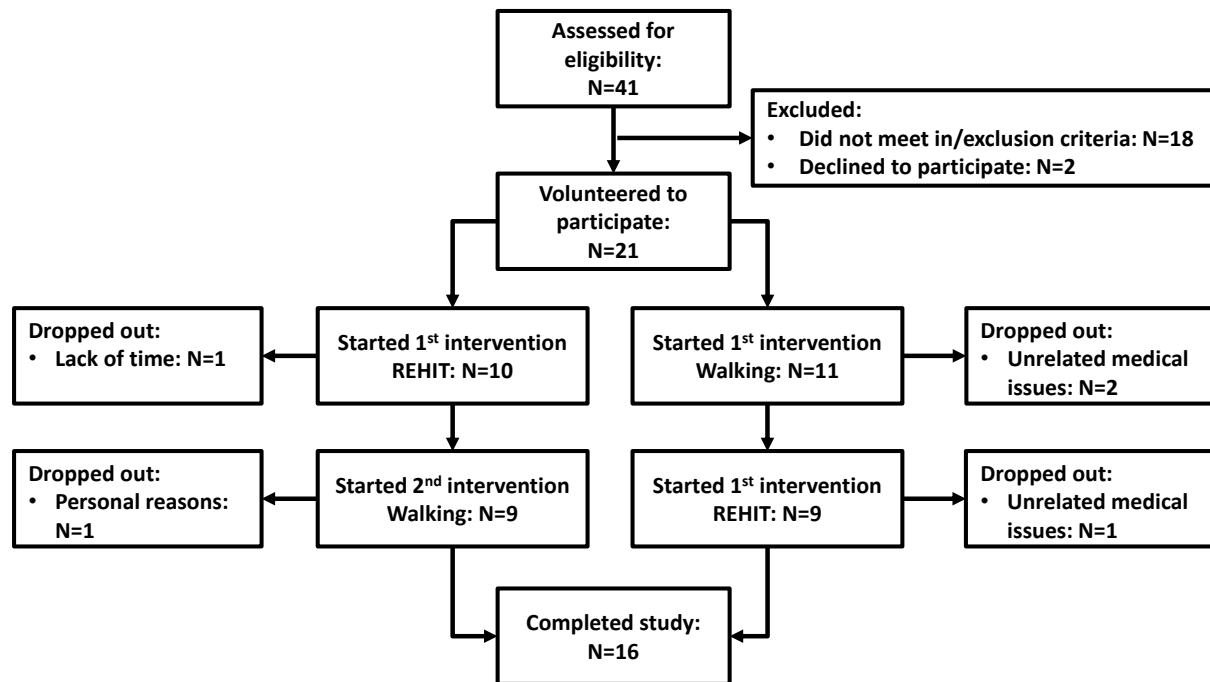**Figure 1**   Flow of participants through the study

Figure 2 Study diagram. ActiHeart devices were worn for 7 days prior to testing. Food diaries were kept for 3 days prior to testing. Abbreviations: BP: blood pressure, DEXA: dual-energy X-ray absorptiometry, FAM: familiarisation V̇O₂max test, MAX: V̇O₂max test, OGTT: oral glucose tolerance test, REHIT: reduced-exertion high-intensity interval training, WALK: walking intervention.