“Can Home-Based High Intensity Interval Training Improve Post Exercise Glycaemic Control in People with Type 1 diabetes?”

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Abstract

Aims: The aims of this study were to investigate: the effects of home-HIIT and home-MICT completed in a postprandial state compared to a non-exercise control period on; i) hypoglycaemia ii) time in range (TIR), and iii) glycaemic variability (GV), for up to 48-hours post exercise in a free-living environment in adults with Type 1 diabetes. A secondary aim was to investigate whether acute changes following exercise influenced 14-day glycaemic control.

Methods: 11 adults with Type 1 diabetes (male n=4, female n=7, age 26 $\pm$ 7 years, BMI 25.43 $\pm$ 4.29 kg.m^2, Type 1 diabetes duration 10 $\pm$ 8 years) completed a randomised crossover study consisting of three 14-day interventions; 1) home-HIIT, 2) home-MICT and 3) non-exercise control (CON). During exercise intervention the effect of six exercise sessions on subsequent glycaemic control was assessed for up to 48-hours post exercise. CON data was time matched to home-HIIT. Glycaemic control was measured using an Abbot Freestyle Libre flash glucose monitor. Dietary intake and insulin dose were also assessed.

Results: Neither home-HIIT or home-MICT increased time spent in serious, clinically significant hypoglycaemia (< 3.0 mmol/L) compared to CON at any period during the 48 hours post exercise ($P > 0.05$). TIR in home-HIIT was significantly greater during the period immediately after exercise compared to CON (11% [0, 22], $P = 0.043$) and significantly greater compared to home-MICT during the awake periods on the day following (10% [2, 18], $P = 0.013$) and second day following exercise (11% [3, 20], $P = 0.014$). GV, assessed as coefficient of variation (CV) was increased during the nocturnal period on the second day following home-MICT compared to CON (CV = 4% [1, 7] $P = 0.008$) and home-HIIT (CV = -5% [-8, 2], $P = 0.005$). This increase in

GV translated into an increased nocturnal GV over the 14-day day intervention period in home-MICT compared to home-HIIT (CV = -4% [-8, 0], P = 0.034).

Conclusion: In conclusion, both home-HIIT and home-MICT are safe exercise modalities for people with Type 1 diabetes but Home-HIIT may provide more beneficial effects on glycaemic control compared to home-MICT. This study provides novel evidence that exercise affects glycaemic control for up to 48-hours post exercise in people with Type 1 diabetes.

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List of Abbreviations

PA	Physical Activity
MVPA	Moderate to Vigorous Physical Activity
FOH	Fear of Hypoglycaemia
HIIT	High intensity interval training
MICT	Moderate intensity continuous training
IHE	Intermittent High intensity exercise
HIIE	High intensity interval exercise
Lab-HIIT	Laboratory-based high intensity interval training
Lab-MICT	Laboratory-based continuous intensity training
Lab-IHE	Laboratory-based intermittent high intensity exercise
Home-HIIT	Home-based high intensity interval training
Home-MICT	Home-based moderate intensity interval training
CVD	Cardiovascular disease
ADA	American Diabetes Associations
CSSI	Continuous subcutaneous insulin infusion
MDI	Multiple daily injections
DKA	Diabetic ketoacidosis
DCCT	Diabetes control and complications trial
EDIC	Epidemiology of Diabetes Interventions and Complications
A1C	Glycosylated Haemoglobin
TBR	Time below range
TIR	Time in range
TAR	Time above range

GV	Glycaemic Variability
L1	Level 1
L2	Level 2
Gd	Glucose disappearance rate
Ga	Glucose appearance rate
GIR	Glucose infusion rate
TAG	Triacylglycerol
HSL	Hormone sensitive lipase
ATP	Adenosine triosphosphate
CA^{2+}	Calcium
PDH	Pyruvate dehydrogenase
FA	Fatty acid
G-1-P	Glucose-1-Phosphate
G-6-P	Glucose-6-Phosphate
HR	Heart rate
HR_{max}	Maximum heart rate
HR_{mean}	Mean heart rate
VO_{2max}	Maximal aerobic capacity
WR_{peak}	Peak work rate
HRR	Heart rate reserve
CGM	Continuous glucose monitoring
FGM	Flash glucose monitoring
CHO	Carbohydrate

Declaration

I declare that the work contained within this thesis is entirely my own.

Poster Communications

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1 - Chapter 1 – Literature Review

1.1 Type 1 diabetes overviews

Type 1 diabetes is a cellular-mediated autoimmune disease whereby autoreactive T-cells infiltrate and destroy the ß-cells in the pancreas which produce insulin, resulting in high blood glucose levels (American Diabetes, 2012, American Diabetes, 2017). Causes of Type 1 diabetes are still relatively unknown, but there is a strong genetic component, thought to be controlled by a number of susceptibility genes that require exposure to an environmental stressor such as a virus, environmental toxins or certain foods (Atkinson and Eisenbarth, 2001). Type 1 diabetes can be diagnosed at any age, although incidence of diagnosis is greatest during childhood and adolescence with Type 1 diabetes accounting for ≥ 85% of all diabetes cases in youth < 20 years of age worldwide (Rogers et al., 2017, Maahs et al., 2010). Incidence rates of Type 1 diabetes are highly variable between ethnic populations and geographical location with the lowest recorded incidence of 0.1/100,000 per year in China and Venezuela, with the highest incidence rate of 36.5/100,000 per year in Finland and 36.8/100,000 in Sardinia (Maahs et al., 2010). Type 1 diabetes can be regulated through diet and blood glucose management, using exogenous insulin via continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI) (Lascar et al., 2014). Type 1 diabetes provides challenges to maintain euglycaemia resulting in fluctuating blood glucose levels and has many acute and long-term complications, these being increased risk of developing diabetic ketoacidosis (DKA), foot ulcers resulting in amputation, retinopathy, neuropathy, nephropathy, cardiovascular disease (CVD) and all-cause mortality (Livingstone et al., 2020, Subramanian and Hirsch, 2018, de Ferranti et al., 2014, Secrest et al., 2010).

1.2 Blood glucose levels

1.2.1 Hyperglycaemia

Hyperglycaemia is defined as blood glucose >10 mmol/l and is split into 2 severity levels; Level 1 (L1) hyperglycaemia (10.1 – 13.9 mmol/l) and level 2 (L2) hyperglycaemia (>13.9 mmol/l) (Battelino et al., 2019). The international consensus on clinical targets recommend spending <25% of time in L1 hyperglycaemia and <5% of time in L2 hyperglycaemia (Battelino et al., 2019). Hyperglycaemia in combination with catecholamine presence and severe insulin deficiency can have a very serious effect, causing increased ketone bodies to be present, leading to DKA if not managed with insulin, which can be fatal without treatment (Umpierrez and Korytkowski, 2016). Furthermore, hyperglycaemia in the presence of low levels of circulating insulin can result in hyperglycaemic hyperosmolar state ensuing dehydration and plasma hyperosmolality which correlate with impaired levels of consciousness and can also be fatal (Umpierrez and Korytkowski, 2016). At a vascular level, hyperglycaemia causes an increased inflammatory response and oxidative stress which have been reported as the key mechanisms of hyperglycaemic induced vascular damage (Brownlee, 2005). It is important to note that DKA and hyperglycaemic hyperosmolar state do not occur every time a person experiences hyperglycaemia, often the participants feels only very mild symptoms. However, the physiological consequences of repeated and chronic exposure to hyperglycaemia can result in many diabetic complications.

The consequences of chronic and repeated exposure to hyperglycaemia in adults with Type 1 diabetes was first reported in the landmark Diabetes Control and Complications Trial (DCCT) (1993, 1995) which included 1441 patients with Type 1 diabetes and spanned over a 6.5-year period. This was the first study to show an

increased risk of microvascular complications, including retinopathy, neuropathy and nephropathy, with increased long-term mean glycosylated haemoglobin levels, known as HbA_{1c} (A1C) (a marker of mean blood glucose over the previous 8-12 weeks). However, no correlations with macrovascular disease were found, potentially due to the young nature of the participants. The Epidemiology of Diabetes Interventions and Complications (EDIC) study (2016) provided a 30 year follow up to the DCCT study and found that participants with higher A1C in the DCCT study had increased the subsequent risk of cardiovascular disease by 42%, even though the A1C levels at follow up had converged to similar levels. The potentially fatal conditions resulting from both acute hyperglycaemia and chronic hyperglycaemia suggest that strategies to avoid this level of dysglycaemia are needed.

1.2.2 Hypoglycaemia

Hypoglycaemia is defined as blood glucose levels $\leq$ 3.9mmol/l and is split into two severity dependent levels, L1 hypoglycaemia (blood glucose 3.0 to 3.9 mmol/l) and L2 (blood glucose < 3mmol/l), with an episode of hypoglycaemia requiring third party assistance being classed as severe hypoglycaemia (Danne et al., 2017, Battelino et al., 2019). International consensus guidelines for clinical targets recommended spending < 4% of time in L1 hypoglycaemia and < 1% of time in L2 hypoglycaemia, highlighting the danger of this blood glucose level (Battelino et al., 2019). Hypoglycaemia has many negative symptoms ranging from acute to long-term effects. Acute side effects disrupt everyday life by impairing work and social activities through cognitive impairment, mood change and a general malaise (Frier, 2014). Long term effects include developing fear of hypoglycaemia (FOH), reduced quality of life, weight gain, restrictions on employment, driving license restrictions, cognitive decline

(possibly accelerating dementia), possible worsening of diabetic and vascular complications and in extreme cases, death (Frier, 2014, Amiel et al., 2019). Nocturnal hypoglycaemia accounts for around 50% of all severe hypoglycaemic episodes in individuals with Type 1 diabetes (Frier, 2014). Which is of great importance as people with Type 1 diabetes have been reported to have gone to bed in good health and been found dead the next morning as a result of hypoglycaemia causing cardiac death, this is known as the 'dead-in-bed' syndrome which is a devastating complication of Type 1 diabetes (Hsieh and Twigg, 2014). The life-threatening side effects of hypoglycaemia clearly reinforce the reasoning for the presence of FOH in adults with Type 1 diabetes. Strategies to prevent hypoglycaemia are therefore required.

1.2.3 Euglycaemia ("In Range")

Euglycemia often referred to as "In range" is defined as a blood glucose of 4-10 mmol/L and has recently been recommended in the international consensus to be a focus point of clinical targets in people with Type 1 diabetes (Battelino et al., 2019). The guidelines suggest a target of >70% time in range (TIR) for people with Type 1 diabetes (Battelino et al., 2019). Using data from the DCCT study, Beck et al (2019b) found that the risk of retinopathy progression and the development of microalbuminuria was increased by 64% and 40% respectively for each 10% decrease in TIR, concluding that deceased TIR is associated with microvascular complications (Beck et al., 2019a). Associations between TIR and A1C have also been observed, with an increase in TIR of 10% being reported to correspond to a decrease in A1C of approximately 0.5% in a study using datasets from 4 randomised controlled trials including 545 participants (Beck et al., 2019a) and 0.8% in a study reviewing 22 studies including 1137 participants (Vigersky and McMahon, 2019). The evidence for

the benefits of increasing TIR support the notion to focus on TIR as an important metric of glycaemic control in adults with Type 1 diabetes, therefore strategies to increase TIR while not increasing hypoglycaemia are required for this population (Battelino et al., 2019)

1.2.4 Glycaemic Variability

Glycaemic variability (GV) can be defined as the degree to which a person's blood glucose levels fluctuate between low and high blood glucose (Hirsch, 2015), and is also an important metric for assessing glycaemia in people with Type 1 diabetes (Battelino et al., 2019, Danne et al., 2017). Glycaemic management for people with Type 1 diabetes is extremely tough due to the large range of factors affecting blood glucose levels. Low blood glucose level will often result in a large rebound in glucose levels causing a large fluctuation, incidentally, increasing GV. GV has been found to be positively associated with clinically significant hypoglycaemic events and hypoglycaemia alert events (Gomez et al., 2019). GV has also been reported to be positively associated with cardiovascular events, retinopathy, nephropathy and increased brain glucose levels in people with Type 1 diabetes (Gorst et al., 2015, Hwang et al., 2019). However, some studies find that there are no associations between GV and vascular health benefits in people with Type 1 diabetes (Smith-Palmer et al., 2014). Even-though there are disagreements surrounding the vascular benefits of improved GV in people with Type 1 diabetes, there is overwhelming evidence that GV is positively associated with hypoglycaemia in this population, therefore minimising GV is necessary to achieve glucose stability and decrease the risk of hypoglycaemia.

1.3.1 *Exercise guidelines*

A position statement from the American Diabetes Association (ADA) recommends that people with Type 1 diabetes complete 150 minutes of moderate to vigorous intensity physical activity (MVPA) per week, spread over at least three days, with no more than two consecutive days without activity (Colberg et al., 2016). Regular physical activity (PA) is recommended for this population due to it's associations with decreased risk factors for cardiovascular disease (CVD). CVD is reported as the leading cause of mortality in people with Type 1 diabetes and this population are at greater risk of CVD than healthy individuals (Orchard et al., 2015. Soedmah-Muthu et al., 2006). Regular PA has been found to improve vascular risk factors such as; blood lipid profiles, by increasing HDL-cholesterol levels and reducing LDL-cholesterol levels, endothelial function and insulin sensitivity, thereby reducing insulin resistance which is independently associated with developing micro and macrovascular complications (Chaturvedi et al., 2001, Fuchsjäger-Mayrl et al., 2002, Rigla et al., 2000, Laaksonen et al., 2000, Lehmann et al., 1997, Chimen et al., 2012). Furthermore, exercise has been found to improve aerobic capacity in people with Type 1 diabetes (Scott et al., 2019b). Aerobic capacity is reported to be the strongest indicator of cardiovascular mortality and improvements are associated with a reduction in all-cause mortality in people without Type 1 diabetes, however there are currently no studies reporting the effect of aerobic capacity on mortality in people with Type 1 diabetes (Lee et al., 2010, Myers et al., 2002). Furthermore a cohort study found that active men were three times less likely to die than sedentary men with Type 1 diabetes (Moy et al., 1993). The evidence for the benefits of regular PA and exercise are overwhelming and therefore adults with Type 1 diabetes should aim to achieve the PA guidelines.

Despite PA providing many health benefits, it is widely reported that the majority of people with Type 1 diabetes fail to meet these activity guidelines. Plotnikoff et al (2006) found that out of 682 Canadian adults with Type 1 diabetes, only 32% of the sample met the 150 minutes per week guidelines, when using self-report to assess PA. Bohn et al (2015) also used self-report methods to measure PA in 18,028 adults with Type 1 diabetes aged 18-80 from Germany and Austria and found that 63% of adults did not complete PA on at least one day per week. Furthermore, a UK based study using accelerometers found that adults recently diagnosed with Type 1 diabetes (< 3months) completed a quarter less MVPA per day than adults without Type 1 diabetes (Type 1 diabetes = 37.4±9.1 mins/day, healthy = 52.9±9.1 mins/day)(Matson et al., 2018). Brazeau et al. (2012) objectively measured PA in both adults with long-standing Type 1 diabetes (23.4 ± 10 years) and adults without diabetes using accelerometers and found no difference in PA levels between groups. The aforementioned studies suggesting that a high percentage of people with Type 1 diabetes are inactive and do not see the full benefits of PA, highlighting that there may be barriers to exercise.

1.3.2 *Barriers to exercise*

The large percentages of inactive people with Type 1 diabetes suggests there are many barriers preventing people from exercising. Several studies using questionnaires and semi-structured interviews have found that many of the barriers to exercise in people with Type 1 diabetes are also common to healthy individuals and other chronic diseases. These barriers being; lack of time caused by work, poor accessibility to facilities (e.g. travel to gyms and cost of memberships/ equipment), embarrassment of body image, lack of motivation, weather and low levels of fitness

(Brazeau et al., 2008, Lascar et al., 2014, Kime et al., 2018, Scott et al., 2019c). In addition to these common barriers, fear of hypoglycaemia (FOH) is a barrier specific to people with Type 1 diabetes. FOH was the most commonly reported barrier to exercise in a study using the Barriers to Physical Activity in Type 1 diabetes (BAPAD-1) scale in 103 people with Type 1 diabetes (Brazeau et al., 2008) as well as in a study using semi-structured interviews and a focus group in 15 adults with Type 1 diabetes (Kennedy et al., 2018). Furthermore, FOH is accompanied with a lack of knowledge and confidence in managing the effects of exercise on blood glucose profiles, suggesting that people with Type 1 diabetes and their health care professionals need education in diabetes management with exercise (Kennedy et al., 2018, Lascar et al., 2014). Individuals lack of knowledge results in a trial and error approach to managing the effects of exercise on their diabetes (Kime et al., 2018), often resulting in hypoglycaemia. Increased incidence of hypoglycaemia inevitably increases FOH (Brazeau et al., 2008), further reinforcing this barrier to exercise. The barriers to exercise in this population are outlined and strategies to relieve these barriers are required to increase PA in people with Type 1 diabetes.

1.4 Acute effects of Moderate Intensity Exercise

Moderate intensity continuous training (MICT; 50-70% heart rate maximum (HR_{max}) or $_{VO2\ maximum}$) can be completed in many forms, e.g. swimming, jogging, walking, cycling etc. MICT is the main exercise modality advised by the ADA for people with diabetes (Colberg et al., 2016). An international consensus statement by Riddell et al. (2017) providing exercise guidelines for people with Type 1 diabetes stated that MICT can commence if blood glucose levels are between 7-15 mmol/L and recommend a carbohydrate (CHO) intake of 10-30 grams/hour during an exercise bout >30 minutes, dependent on the level of circulating insulin (i.e. the greater the level of circulating

insulin, the greater the CHO requirement. If a meal is consumed 90-minutes prior to exercise commencing, guidelines suggest reducing bolus insulin dose by 50% for 30-minutes of MICT and 75% for 1 hour of MICT to reduce the risk of hypoglycaemia occurring (Riddell et al., 2017).

These guidelines are in place as MICT in people with Type 1 diabetes is associated with a decline in blood glucose and risks exercise-induced hypoglycaemia. A meta-analysis of 7 studies comparing the rate of change in glucose during a bout of MICT to a rest/control period presented an average hourly rate of change of -4.43mmol/L/h^{-1} (Garcia-Garcia et al., 2015). These findings have been replicated in a Scott et al. (2019b) which reported an average rate of change of -5.5mmol/L during laboratory based MICT (lab-MICT) ranging from 30-50 minutes duration, at 65% VO_2 peak in the postprandial state in 14 sedentary adults (8 females, 6 males, age = 26 $\pm$ 3 years, VO_{2peak} = 35.6 $\pm$ 2.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 $\pm$ 1.4 years). Studies using euglycaemic clamps also support these findings; McMahon et al (2007) completed a study in 9 adolescents (4 females, 5 males, age = 16 $\pm$ 1.8 years, VO_{2peak} = 37.99 $\pm$ 2.92 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 $\pm$ 4.1 years) where participants exercised for 45-mintues in the postprandial state at 95% lactate threshold (~55% VO_{2Max}). This study presented findings of an increased glucose infusion rate (GIR) for the 90 minutes post exercise compared with a sedentary control visit (McMahon et al., 2007). Similarly, Guelfi et al. (2007) reported the glucose disposal (Gd) rate to be greater during exercise (30 minutes MICT exercise at 40% VO_{2max}) than at baseline in 9 physically active adults (4 females, 5 males, MDI, n= 6, CSSI, n = 3, age = 22.6 $\pm$ 5.7 years, VO_{2peak} = 41.8 $\pm$ 4.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 5.6 $\pm$ 3.9 years). The increased Gd was greater than glucose appearance (Ga) rates, causing an imbalance

between utilisation and production, resulting in a decline in blood glucose (Guelfi et al., 2007). In summary, commencing MICT with blood glucose 7-15 mmol/L as stated in the guidelines (Riddell et al., 2017), risks hypoglycaemia if blood glucose decreases by the average rate of 4.43mmol/L/h^{-1} (Garcia-Garcia et al., 2015). Consequently, there is a need for an alternative exercise modality that prevents the decline in blood glucose seen with MICT.

1.5 Mechanisms Responsible for dop in blood glucose with MICT

1.5.1 *Glucose Responses in adults without Type 1 diabetes*

Exercise increases blood flow and capillary perfusion, increasing the delivery of glucose to the muscle (Wagenmakers et al., 2016, Sjøberg et al., 2017, Kjaer et al., 1991). Muscular contraction mediates GLUT-4 translocation to the sarcolemma due to increased Ca^{2+}, ATP turnover and mechanical stress, resulting in glucose uptake into the muscle (Jensen and Richter, 2012). Glucose uptake into the muscle causes a decline in blood glucose resulting in suppression of insulin to below resting levels which enables an increase in glucagon secretion and further sensitising the liver to glucagon (Chan and Sherwin, 2013, Wasserman et al., 1989a, Wasserman et al., 1989b). Glucagon travels to the liver via the portal vein to facilitate the production of hepatic glucose via gluconeogenesis to maintain glucose homeostasis and spare liver glycogen stores (Koyama et al., 2001, Wasserman et al., 1989a).

If glucose production cannot match glucose utilisation during exercise, then blood glucose concentrations will continue to decrease, thereby triggering a counter-regulatory response of increased epinephrine secretion from the adrenal medulla, resulting in increased glycogenolysis of liver glycogen stores (Cryer, 2008). As well as breakdown of muscle glycogen to further increase glucose availability and reduce

glucose uptake into the muscle (Cryer, 2008). Epinephrine is also an activator of hormone sensitive lipase (HSL) which has been described as the rate-limiting enzyme responsible for the lipolysis of triacyglycerol (TAG) stores in the adipose tissue, liver and muscle, thus increasing fatty acid (FA) availability (Watt and Spriet, 2004, Anthonsen et al., 1998, Watt et al., 2003). Exercise induces increased fat transporter protein (FATCD/36 and FABpm) translocation to the sarcolemma increasing uptake of plasma FA into the skeletal muscle ready to be oxidised (Bradley et al., 2012). Increased uptake of FA into the muscle is important during MICT as this leads to an increase in fat oxidation with plasma FA as the main fuel source (Watt et al., 2002, van Loon et al., 2003). Increased fat oxidation resulting in the reduction of CHO oxidation reduces the decrease in blood glucose seen during the earlier stages of an exercise bout (Watt et al., 2002, van Loon et al., 2003). The reduction in CHO oxidation is a result of activation of pyruvate dehydrogenase kinase which downregulates pyruvate dehydrogenase (PDH) and prevents the conversion of pyruvate to acetyl-CoA needed for CHO oxidation (Watt et al., 2002). Taken together, the suppression of insulin secretion alongside the increase in glucagon secretion resulting in hepatic glucose production, as well as the shift to increased fat oxidation, facilitates homeostasis of blood glucose concentrations during MICT in people without Type 1 diabetes.

1.5.2 *Glucose responses to MICT in adults with Type 1 diabetes*

People with Type 1 diabetes rely on exogenous insulin which has a much greater half-life compared to endogenous insulin. Consequently, circulating insulin levels are not reduced and potentially even increased during exercise, due to increased blood flow around subcutaneous tissue (Marliss and Vranic, 2002, Mallad et al., 2015). Exercise

Increases capillary perfusion which in-turn increases insulin delivery to the muscle (Frank et al., 2018, Wagenmakers et al., 2016). Insulin results in GLUT-4 translocation to the sarcolemma (Watson and Pessin, 2001), this alongside contraction mediated GLUT-4 translocation also seen in healthy individuals has been reported to produce an additive effect resulting in greater glucose uptake into the skeletal muscle in people with Type 1 diabetes (Bally et al., 2015, Frank et al., 2018). High levels of circulating insulin in Type 1 diabetes supresses the increase in glucagon secretion which is responsible for 60% of hepatic glucose production required for glucose homeostasis in healthy individuals (Mallad et al., 2015, Chan and Sherwin, 2013, Wasserman et al., 1989a, Wasserman et al., 1989b). Furthermore, hyperinsulinemia downregulates HSL, thereby inhibiting lipolysis of TAG's and intramuscular triglycerides which reduces the availability of fat as a fuel source and further increases the reliance on CHO as the fuel source (Horowitz et al., 1997).

It has been reported that at physiologically optimal insulin levels, the glucagon response to exercise is in-tact in people with Type 1 diabetes (Bally et al., 2016). However, some individuals with Type 1 diabetes have a blunted glucagon response which has been reported to be impaired as early as 12-months after diagnosis and completely lost as early as 5 years from diagnosis (Ertl and Davis, 2004). The loss of the glucagon response results in no gluconeogenesis in reaction to declining blood glucose values, reducing hepatic glucose production and therefore increasing the reliance on liver and muscle glycogen, consequently increasing the risk of hypoglycaemia with exercise.

Repeated exposure to hypoglycaemia can cause hypoglycaemic-associated autonomic failure (HHAF) which results in a blunted epinephrine response to hypoglycaemia, thus preventing hepatic glucose production and importantly causing

a lack of autonomic symptom generation to hypoglycaemia (hypoglycaemia unawareness) (Cryer, 2013, Cryer, 2004, Rickels, 2019). Hypoglycaemic unawareness has been reported to be present in ~20% of adults with Type 1 diabetes (Geddes et al., 2008). It is often suggested that “hypoglycaemia begets hypoglycaemia” and has been described as a “viscous circle” (Ertl and Davis, 2004). Epinephrine reduces glucose uptake into the muscle by increasing glycogenolysis of muscle glycogen, increasing Glucose-6-Phosphate (G-6-P) concentration in the muscle, decreasing phosphorylation of glucose which subsequently reduces the glucose gradient between the muscle and the blood, attenuating further glucose uptake into the muscle (Watt et al., 2001). Epinephrine also upregulates HSL to increase the availability of FA for oxidation, therefore the loss of the epinephrine response to declining blood glucose during MICT further adds to the declining blood glucose by not reducing glucose uptake into the muscle or increasing FA availability for oxidation, thus increasing the reliability on CHO metabolism. The combined inability to suppress insulin, secrete glucagon and potentially epinephrine, in response to declining blood glucose levels, results in decreasing plasma glucose concentrations which could potentially lead to hypoglycaemia. This shows the issues for people with Type 1 diabetes during exercise and provides physiological reasoning supporting FOH associated with MICT, thus, highlighting the need for a safer alternative exercise modality for people with Type 1 diabetes.

1.6 Acute effects of High Intensity Exercise

1.6.1 *Intermittent High Intensity Exercise (IHE)*

Intermittent high intensity exercise (IHE) consists of moderate intensity continuous exercise interspersed with supramaximal (>100% W_{max}) high intensity intervals (often

lasting 4-15 seconds). IHE has been commonly researched in adults with Type 1 diabetes and reduces the decline in blood glucose present during, and in the short period after exercise. Guelfi et al (2005) were one of the first to report that postprandial laboratory-based IHE (lab-IHE) (30 minutes cycling at 40% VO_{2max} with 4 second sprint intervals every 2 minutes) reduced blood glucose by 2.9 mmol/L compared to a 4.4 mmol/L decline with lab-MICT (30 minutes cycling at 40% VO_{2max}) in 7 healthy, physically active adults (3 females, 4 males on MDI, age = 21.6 $\pm$ 4 years, VO_{2peak} = 41.8 $\pm$ 4.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 8.6 $\pm$ 5 years). Furthermore, Bally et al (2016) using a euglycaemic clamp method reported a greater GIR with morning lab-MICT (90 minutes iso-cycling at 50% VO_{2max}) compared to lab-IHE (90 minutes iso-cycling at 50% VO_{2max} with 10 second sprints every 10 minutes) in the final 30 minutes of exercise in 15 physically active healthy males (MDI, n = 11, CSSI, n = 4, age = 26.1 $\pm$ 4.8 years, VO_{2peak} = 47 $\pm$ 9 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 13.3 $\pm$ 6.7 years). Maran et al (2010) reported a reduced decline in blood glucose with afternoon postprandial IHE (30 minutes cycling at 40% VO_{2max} + 5s sprint at 85% VO_{2max} every 2 minutes) compared to lab-MICT (30 minutes cycling at 40% VO_{2max}) in 8 healthy, physically active male adults on MDI (age = 34 $\pm$ 7 years, VO_{2max} = 33.7 $\pm$ 6.1 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 14.3 $\pm$ 8 years). However, Iscoe & Riddell (2011) following afternoon postprandial exercise reported a decrement of 5.0 mmol/L with lab-IHE (45 minutes cycling at 55% WR_{peak} with 15 seconds intervals at 100% WR_{peak} every 5 minutes) compared to lab-MICT (45 minutes cycling at 55% WR_{peak}) showing a decline of 5.1 mmol/L in 11 physically active adults (6 females, 5 males, CSSI, n = 6, MDI, n = 5, age = 35.1 $\pm$ 3.5 years, VO_{2max} = 42.4 $\pm$ 1.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 15.6 $\pm$ 5.6 years). The discrepancies in

results are potentially caused by the range of exercise protocols used in these studies or by the difference in time of day and prandial state that exercise was completed in as well as the variation in participant demographics. However, these studies show promise for IHE as a safer alternative to MICT for people with Type 1 diabetes. However, IHE does not alleviate the barriers; lack of time, access to facilities and lack of motivation. Therefore, a shorter exercise modality that requires no equipment and produces similar, if not greater acute blood glucose responses to exercise is needed.

1.6.2 *High Intensity Interval Training (HIIT)*

The popular exercise modality “HIIT” provides an alternative to IHE by potentially alleviating the barrier “lack of time”, with studies using a laboratory-based HIIT (lab-HIIT) protocol with a duration of 12-20 minutes, compared to laboratory-based MICT (lab-MICT) sessions which had a duration of 30-50 minutes (Scott et al., 2019b). HIIT is commonly defined as bouts of exercise > 80% of predicted maximal heart rate (HR_{max}) ($220\text{-}age_{(years)}$) interspersed by periods of lower intensity exercise or rest (Gibala, 2018). HIIT has been reported to elicit the same if not greater physiological benefits than traditional MICT (Gibala, 2018, Gibala et al., 2012), and Scott et al (2019b) found that 6 weeks of lab-HIIT resulted in similar increases in aerobic capacity to 6 weeks of lab-MICT in people with Type 1 diabetes. However, for this to be an effective and safer exercise modality for people with Type 1 diabetes, the effects it has on acute blood glucose would need to replicate or better the response seen with IHE, by reducing or attenuating the decline in blood glucose that is present in MICT in people with Type 1 diabetes.

Scott et al (2019b) found that postprandial lab-HIIT (6, 8 and 10 intervals of 1-minute cycling at 100% VO_{2max} interspersed with 1-minute rest) completed on a cycle ergometer resulted in an attenuated drop (-0.2 mmol/L) in blood glucose compared to lab-MICT (-5.5 mmol/l) (30-50 minutes cycling at 65% VO_{2max}) in 14 sedentary adults (8 females, 6 males, age = 26 $\pm$ 3 years, VO_{2peak} = 35.6 $\pm$ 2.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 $\pm$ 1.4 years). A study by Aronson et al. (2019) assessing the effects of morning fasted lab-HIIT in 17 physically active adults using (4 females, 13 males, MDI, n=17, age = 24.9 $\pm$ 10.1 years, VO_{2peak} = 40.3 $\pm$ 6.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 17 $\pm$ 11 years) found that a more demanding protocol (3x5-minute working intervals at >80% HR_{max} interspersed by 5 minutes rest mixing bodyweight and cycle ergometer exercise protocols) increased plasma glucose by an average of 3.8 mmol/L resulting in hyperglycaemia post exercise. However, this study was conducted after an overnight fast and a recent study by Scott et al. (2019a) reported that there were no detrimental effects on blood glucose with either lab-HIIT or lab-MICT when fasted (>10hours) in 14 sedentary adults (8 females, 6 males, age = 26 $\pm$ 3, VO_{2peak} = 30.8 $\pm$ 2.0 ml/kg^{-1}/ min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 $\pm$ 1.4 years).
In contrast, Lee et al. (2020) found afternoon postprandial lab-HIIT (-3.6 mmol/L) to decrease blood glucose greater than lab-MICT (-2.7 mmol/L) in 12 adults (9 females, 3 males, MDI = 9, CSSI = 3, age = 40.4 $\pm$ 9.9 years, VO_{2peak} = 28.2 $\pm$ 6.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 16.5 $\pm$ 9.8 years). Discrepancies in findings by Lee et al. (2020) compared to Scott et al. (2019b) could be a result of a more demanding lab-HIIT protocol (4x4-minute intervals at 85-95% HR_{peak} interspersed with 3-minute rest intervals at 50-70% HR_{peak} on a cycle ergometer). Furthermore, the discrepancies could be caused by Lee et al. (2020) having an older

sample with a greater duration of Type 1 diabetes (age = 40.4 ± 9.9 years, Type 1 duration = 16.5 ± 9.8 years) than Scott et al. (2019b) (age = 26 ± 3 years, Type 1 duration = 8.2 ± 1.4 years) which may affect the physiological responses to exercise. Age may affect acute blood glucose responses as Kohrt et al. (1993) found that older people without Type 1 diabetes had blunted catecholamine response to exercise compared with younger people. Also, residual ß-cell function is reduced with increased duration of Type 1 diabetes which also may affect acute blood glucose responses to exercise (Davis et al., 2015). Finally the differences in prior physical activity and fitness levels could also provide reasoning for different acute responses to exercise. The findings from this small body of literature show potential for HIIT as a time efficient exercise modality that might provide more desirable acute responses to exercise for people with Type 1 diabetes. However, these studies do not address the barriers to exercise in people with Type 1 diabetes of lack of motivation and access to facilities, as these studies were completed in a laboratory on a cycle ergometer. Therefore, to ensure HIIT is a safer alternative exercise modality to MICT, research into the effects of exercise in a free-living environment are required.

1.6.3 *Home-based HIIT*

To address accessibility and motivation, Scott et al. (2019c) investigated the feasibility of home-based bodyweight HIIT (6, 8 and 10 intervals of 1 minute working at 80% HR_{max} interspersed with 1 minute rest) in 11 adults (7 female, 4 male, age = 30 ± 3 years, VO_{2peak} = 2.5± 0.2 L/min^{-1}) with Type 1 diabetes (Type 1 duration = 10 ± 2 years) in a free-living environment over a 6-week period. This study found home-based HIIT (home-HIIT) increased VO_{2peak} and reduced insulin dose without reductions in blood glucose during or 1-hour post exercise (Scott et al., 2019c). The results also

indicate high levels of adherence to this exercise protocol when virtually supervised (Scott et al., 2019c). Qualitative data was collected from participants which identified three key themes, these being 1) *the flexibility of home-HIIT*; consisting of the stability of blood glucose in response to exercise, not requiring access to facilities and the freedom to exercise from home. 2) *increased motivation;* derived from the use of home-HIIT and virtual monitoring (monitored online by a member of the research team). 3) *the "HIIT experience"* resulting from having a range of exercise options, alleviating boredom (Scott et al., 2019c). This feasibility study shows the potential for home-HIIT to provide a safer, and more suitable alternative exercise modality to MICT for people with Type 1 diabetes. However, further investigation is needed to assess the effects of home-HIIIT on post exercise blood glucose profiles in people with Type 1 diabetes.

1.7 Mechanisms responsible for blood glucose response to high intensity exercise

1.7.1 *Glucose responses to high intensity exercise in adults without Type 1 diabetes*

The onset of High intensity intermittent exercise (HIIE) increases sympathetic nerve activation resulting in a 14-18 fold increase in catecholamines which are the primary regulators of hepatic glucose production (Marliss et al., 1992, Sigal et al., 1996, Marliss et al., 1991). HIIE causes a 7-8 fold increase in hepatic glucose production via glycogenolysis and a rise in plasma glucose during exercise (Marliss and Vranic, 2002). Muscle glucose uptake however, only increases by 3-4 fold during exercise, consequently glucose production is greater than uptake causing blood glucose to rise, risking hyperglycaemia (Marliss and Vranic, 2002). Reduced glucose uptake during exercise is reportedly a result of increased Ca^{2+} and catecholamine mediated

activation of muscle glycogenolysis increasing Glucose-1-Phosphate (G-1-P) and G-6-P concentrations in the muscle, reducing the need for plasma glucose uptake (Marliss and Vranic, 2002, Hargreaves and Spriet, 2020). To combat the rise in blood glucose with HIIE, insulin secretion post exercise increases. Insulin levels remain elevated for a sustained period to combat the potential for hyperglycaemia by increasing glucose uptake, through GLUT-4, into the muscle for glycogen resynthesis by glycogenosis (Marliss and Vranic, 2002).

1.7.2 *Glucose responses to high intensity exercise in adults with Type 1 diabetes*

In people with Type 1 diabetes, the inability to reduce insulin levels during HIIE does not cause the same issues as seen during MICT due to the dominance of the catecholamine response, contraction mediated glucose uptake and the reliance on muscle glycogen as the primary fuel at this intensity (Romijn et al., 1993, Marliss and Vranic, 2002, Sjøberg et al., 2017). In individuals with Type 1 diabetes and healthy individuals, the catecholamine and hepatic glucose response is comparable, with high intensity exercise often resulting in increases to plasma glucose concentrations and post exercise hyperglycaemia (Marliss and Vranic, 2002, Sigal et al., 1996, Potashner et al., 2019, Riddell et al., 2019). However, people with Type 1 diabetes cannot produce endogenous insulin to combat this rise in plasma glucose as seen in healthy individuals. Often resulting in individuals with Type 1 diabetes having to administer exogenous insulin and calculate the correct dose to maintain glucose homeostasis (Marliss and Vranic, 2002). The current guidelines do not provide any information regarding the post exercise insulin dose with HIIE, and for this reason speculation has suggested that HIIT may increase the risk of hypoglycaemia following exercise. However, a study by Aronson et al. (2019) found that both a typical (100% insulin

correction factor) and a greater (150% insulin correction factor) than usual insulin dose, calculated using a personalised insulin correction factor, increased TIR post exercise, without increasing the risk of hypoglycaemia. The physiological mechanisms described support the attenuation of the decrement in blood glucose during HIIE and support the potential for HIIT to provide a safer alternative avoiding hypoglycaemia during exercise. However, further research is needed into the effect of HIIT on blood glucose responses following exercise.

1.8.1 Post exercise glycaemia

So far, this literature review has provided evidence for home-HIIT be a safe alternative exercise modality compared to MICT due to the beneficial effects on acute blood glucose responses. However, for home-HIIT to be truly accepted as a safer alternative to MICT, it would have to elicit the same if not greater effects on post exercise glycaemic control. It is suggested in consensus and position statement's that there is an effect of exercise on glycaemia for at least 12 to 24 hours post exercise (Riddell et al., 2017) and even potentially up to 48 hours post exercise (Colberg et al., 2016). The physiological reasoning for exercise affecting glycaemia for a sustained period post exercise is the increased insulin sensitivity that exercise induces. Insulin sensitivity is increased for up to 48 hours post exercise (Hawley and Lessard, 2008), causing increased insulin stimulated translocation of GLUT-4 to the sarcolemma, increasing glucose uptake into the muscle. The increases in glucose uptake into the muscle results in a decrease in plasma glucose, consequently affecting glycaemic control by potentially altering time in ranges, resulting in blood glucose fluctuations. The development of continuous glucose monitoring (CGM) has allowed studies to assess

the effects of exercise on glycaemia post exercise by providing readings every 5-15 minutes, dependent on the monitor used.

1.8.2 Post exercise late-onset hypoglycaemia

1.8.2.1 MICT

Gomez et al (2015), using CGM in 33 adults with Type 1 diabetes (16 female, 17 male, age = 30.31 ± 12.66) with Type 1 diabetes (Type 1 duration = 13.67 ± 9.15 years), found that 60 minutes postprandial lab-MICT in the afternoon increased the incidence of hypoglycaemia compared to morning fasted lab-MICT, especially during nocturnal periods and between 15-24 hours post exercise. Scott et al. (2019a) found there to be no increased incidence of, or time spent in hypoglycaemia for up to 24 hours post exercise following 30 minutes fasted lab-MICT at 65% VO_{2max} compared to a sedentary control period in 14 sedentary adults (8 females, 6 males, age = 26 ± 3, VO_{2peak} = 30.8 ± 2.0 ml/kg^{-1}/ min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 ± 1.4 years) (Scott et al., 2019a). Findings by Scott et al (2019a) suggest that the fed state may be responsible for findings by Gomez et al (2015) between morning fasted exercise and afternoon postprandial exercise. There is evidence that exercise in a postprandial state increases the risk of hypoglycaemia as a study conducted under euglycaemic-insulin clamp conditions by McMahon et al. (2007) in 9 adolescents (4 females, 5 males, age = 16 ± 1.8 years, VO_{2peak} = 37.99 ± 2.92 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 ± 4.1 years) , found that a 45-minute lab-MICT session at 55% VO_{2max} commencing at 4pm required an increased GIR at 7-11 hours post exercise (11:45pm – 03:45am) compared to a sedentary control day. Iscoe and Riddell. (2011), using CGM, reinforced these findings by observing an increased number of hypoglycaemic

episodes in the night following postprandial, afternoon lab-MICT (45 minutes MICT at 55% WRpeak) compared to a sedentary control in in 11 physically active adults (6 females, 5 males, CSSI, n = 6, MDI, n = 5, age = 35.1 ± 3.5 years, VO_{2max} = 42.4 ± 1.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 15.6 ± 5.6 years).

In summary, laboratory-based studies have shown that postprandial MICT can increase the risk of post exercise hypoglycaemia especially when exercise is completed in the afternoon, with nocturnal periods providing the greatest risk period. Therefore, an alternative exercise modality reducing the risk of post exercise hypoglycaemia in people with Type 1 diabetes would be desirable. However, Riddell et al (2020) found no differences in time spent in hypoglycaemia in the 24 hours following home-MICT (30-minutes at 70-80% HR_{max}) performed under free-living conditions.

1.8.2.2 IHE

Two studies using CGM have compared overnight glucose profiles in adults with T1D following postprandial lab-MICT (Bally et al., 2016: 90 minutes iso-cycling at 50% VO_{2max}, Rempel et al., 2018: 45-minutes walking at 45-55% HRR) and lab-IHE (Bally et al., 2016; 90 minutes iso-cycling at 50% VO_{2max} with 10-second sprints every 10-minutes, Rempel et al., 2018: 45% HRR for 45-minutes with 60-second intervals at 70, 80 and 90% HRR every 4-minutess). These studies found no differences between training modes for incidence and time spent in hypoglycaemia (Bally et al., 2016, Rempel et al., 2018). In contrast, Maran et al (2010) found a significantly greater number of hypoglycaemic episodes following postprandial, afternoon lab-IHE (30 min at 40% VO_{2max} + 5s sprint at 85% VO_{2max} every 2 minutes) compared to lab-MICT (30 min at 40% VO_{2max}). Whereas, Iscoe and Riddell (2011) found that postprandial, afternoon lab-IHE (45-minutes at 55% WR_{peak} interspersed 15-second intervals at

100% WR^{peak} every 5-minutes) reduced the incidence of nocturnal hypoglycaemic episodes compared with lab-MICT (45-minutes at 55% WRpeak), but did increase nocturnal hypoglycaemia compared to a sedentary control period. The varying results could be a result of the range of exercise protocols included within these studies, making it difficult to determine the effect of lab-MICT compared to lab-IHE.

1.8.2.3 HIIT

Scott et al. (2019a) found there to be no difference in incidence or time spent in hypoglycaemia during the nocturnal and 24 hours periods following fasted (>10 hours) lab-MICT (30 minutes at 60-70% VO_{2max}) and lab-HIIT (6x1-minute working intervals at 100% VO_{2max} interspersed by 1-minute rest intervals) in 14 sedentary adults (8 females, 6 males, age = 26 $\pm$ 3, VO_{2peak} = 30.8 $\pm$ 2.0 ml/kg^{-1}/ min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 $\pm$ 1.4 years). These findings have been replicated by Lee et al (2020), who also found no differences in time spent in hypoglycaemia between lab-HIIT (4x4-minute intervals, at 85-95% HR_{max} interspersed with 3 minutes recovery at 50-70% HR_{max}), lab-MICT (33-minutes at 60-70% HR_{max}) and sedentary control in the nocturnal and 24-hour periods post exercise in 12 adults (9 females, 3 males, MDI = 9, CSSI = 3, age = 40.4 $\pm$ 9.9 years, VO_{2peak} = 28.2 $\pm$ 6.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 16.5 $\pm$ 9.8 years). A recent study by Riddell et al. (2020) has shown that the aforementioned studies are translatable to the real world in adults with Type 1 diabetes. Riddell et al. (2020) found that home-HIIT (30-minutes with intervals at 80-90% HR_{max}) did not increase time spent in hypoglycaemia compared to sedentary control days in 44 adults (MDI, n= 9, CSSI, n= 34, age = 35 $\pm$ 15 years) with Type 1 diabetes (Type 1 duration = median 16 (9, 24) years). In summary there may be no difference between MICT and HIIT for risk of late-onset hypoglycaemia post

exercise, further increasing the potential for home-HIIT to provide a safer and more effective alternative exercise modality to MICT, due to the acute blood glucose benefits and barrier reductions, for people with Type 1 diabetes. However, no study has yet investigated the effects of exercise on blood glucose for more than 36 hours post exercise, even though insulin sensitivity is increased for 48 hours post exercise. Therefore the effects of both home-HIIT and home-MICT on glycaemia should be investigated for 48 hours post exercise.

1.8.3 Post exercise time in range

TIR has now come to the forefront of assessing glycaemic control, with the aim being to increase TIR while not increasing time in hypoglycaemia (Battelino et al., 2019). Therefore, an exercise modality that increases TIR without increasing hypoglycaemia would be desirable. To date a limited number of studies have assessed TIR following exercise in people with Type 1 diabetes. Gomez et al (2015) found there to be an increased TIR on the days following (up to 36hours) 60-minutes of morning fasted lab-MICT compared to a non-exercise control day, but no difference was found following 60-minutes of postprandial, afternoon lab-MICT compared to control in 33 adults with Type 1 diabetes (16 female, 17 male, age = 30.31 $\pm$ 12.66) with Type 1 diabetes (Type 1 duration = 13.67 $\pm$ 9.15 years). However, this finding could be due to the difference in fed states that exercise was conducted in. Scott et al. (2019a) found there to be no difference in TIR between lab-HIIT (6x1-minute intervals 100% VO_{2peak} interspersed with 1 minute rest), lab-MICT (30-minutes at 65%VO_{2peak}) and a sedentary control day during the 24 hours post exercise when exercise was completed in a fasted state (>10 hours) in 14 sedentary adults (8 females, 6 males, age = 26 $\pm$ 3, VO_{2peak} = 30.8 $\pm$ 2.0 ml/kg^{-1}/ min^{-1}) with

Type 1 diabetes (Type 1 duration = 8.2 ± 1.4 years). Lee et al. (2020) found no TIR differences between postprandial lab-HIIT (4x4-minute intervals, at 85-95% HR_{max} interspersed with 3 minutes recovery at 50-70% HR_{max}), lab-MICT (33-minutes at 60-70% HR_{max}) and a sedentary control period during the nocturnal periods and 24 hours post exercise in 12 adults (9 females, 3 males, MDI = 9, CSSI = 3, age = 40.4 ± 9.9 years, VO_{2peak} = 28.2 ± 6.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 16.5 ± 9.8 years). In contrast under free-living condition Riddell et al. (2020) have recently shown that exercise, comprising a mixture of home-HIIT, home-MICT (30-minutes at 70-80% HRmax) or habitual exercise, resulted in improved TIR during the 24 hours post exercise compared to non-exercise control in 44 adults (MDI, n= 9, CSSI, n= 34, age = 35 ± 15 years) with Type 1 diabetes (Type 1 duration = median 16 (9, 24) years).The failure to observe differences in laboratory-based studies compared to the free-living environment may have been related to the small, and highly variable study samples as well as large glucose variability among the laboratory-based study participants. To the best of the authors knowledge, no study has yet assessed the effects of exercise on TIR for greater than 36 hours post exercise. Therefore, further investigation into the effects of home-HIIT and home-MICT for up to 48 hours post exercise is required.

1.8.4 Post exercise glycaemic variability

The interest in GV has recently grown due to the associations with increased hypoglycaemia and the potential vascular complications this could have in people with Type 1 diabetes. To ensure home-HIIT can provide a safer alternative to MICT, HIIT should elicit the same, if not greater GV responses than MICT. Iscoe & Riddell (2011) reported similar GV on the day of exercise between afternoon, postprandial

lab-IHE (45-minutes at 55% WR_{peak} interspersed 15-second intervals at 100% WR_{peak} every 5-minutes) and lab-MICT (45-minutes at 55% WR_{peak}) in 11 physically active adults (6 females, 5 males, CSSI, n = 6, MDI, n = 5, age = 35.1 $\pm$ 3.5 years, VO_{2max} = 42.4 $\pm$ 1.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 15.6 $\pm$ 5.6 years). However, these exercise conditions both had greater GV scores than a sedentary control day. A study by Scott et al. (2019a) in 14 sedentary adults (8 females, 6 males, age = 26 $\pm$ 3, VO_{2peak} = 30.8 $\pm$ 2.0 ml/kg^{-1}/ min^{-1}) with Type 1 diabetes (Type 1 duration = 8.2 $\pm$ 1.4 years) showed that GV was not different between lab-HIIT (6x1-minute intervals 100% VO_{2peak} interspersed with 1-minute rest), lab-MICT (30-minutes at 65%VO_{2peak}) and a sedentary control day during the 24-hours post exercise, when exercise was completed in a fasted state (>10 hours). However, GV was found to be increased in the nocturnal periods following lab-HIIT (CV = 28$\pm$5%) compared to lab-MICT (CV = 19$\pm$4%), with the control period being similar to lab-HIIT (CV = 25$\pm$4%) (Scott et al., 2019a). In contrast, Lee et al. (2020) found no difference in GV during the nocturnal and 24-hour periods following postprandial lab-HIIT (4x4-minute intervals, at 85-95% HR_{max} interspersed with 3 minutes recovery at 50-70% HR_{max}), lab-MICT (33-minutes at 60-70% HR_{max}) and a control period when post exercise insulin doses were reduced in 12 adults (9 females, 3 males, MDI = 9, CSSI = 3, age = 40.4 $\pm$ 9.9 years, VO_{2peak} = 28.2 $\pm$ 6.6 ml/kg^{-1}/min^{-1}) with Type 1 diabetes (Type 1 duration = 16.5 $\pm$ 9.8 years). Finally, Riddell et al (2020) found there to be no difference in GV during the 24 hours post exercise in home-HIIT and home-MICT compared to sedentary control periods, when performed in a free-living environment in 44 adults (MDI, n= 9, CSSI, n= 34, age = 35 $\pm$ 15 years) with Type 1 diabetes (Type 1 duration = median 16 (9, 24) years). To the best of the authors knowledge, no study has investigated the effects of

exercise on GV for greater than 24-hours post exercise. The aforementioned studies suggest that postprandial HIIT and MICT do not affect GV, however, the current body of evidence is limited and only one study has assessed home-based exercise in a free-living environment. Therefore, further investigation into the effects of home-based HIIT and MICT on GV for up to 48 hours post exercise is required.

1.9 Summary and Aims

This literature review has sought to provide an overview of the issues surrounding exercise in people with Type 1 diabetes. The overwhelming beneficial effects of exercise for people with Type 1 diabetes have been highlighted. However, it is clear that people with Type 1 diabetes face many barriers when exercising, consequently large numbers of this population are inactive. This literature review has highlighted the potential benefits of HIIT on acute blood glucose responses compared to traditional MICT. On the other hand, the effects of both HIIT and MICT on post exercise glycaemic control in people with Type 1 diabetes is less well understood with many studies not investigating greater than 24 hours post exercise. Furthermore, most of studies have been conducted under highly controlled laboratory conditions, with only one investigating exercise in a free-living environment (Riddle et al., 2019). This study had low levels of control on additional structured exercise, prandial state that exercise was completed in and intensity and duration of exercise sessions (Riddell et al., 2020). Therefore, the aims of this study were to investigate: the effects of home-HIIT and home-MICT completed in a postprandial state compared to a non-exercise control period on; i) hypoglycaemia ii) TIR, and iii) GV, for up to 48-hours post exercise in a free-living environment. A secondary aim was to investigate whether acute changes following exercise influenced 14-day glycaemic control.

2 - Chapter 2

“Can Home-Based High Intensity Interval Training Improve Post Exercise Glycaemic Control in People with Type 1 diabetes?”

2.1 Methods

2.1.1 Ethical approval

All participants provided written informed consent, the study was approved by the Liverpool John Moores University Research Ethics Committee (approval reference no. 19/SPS/061) and conformed to the Declaration of Helsinki (Rickham, 1964).

2..1.2 Participants

11 adults (n= 4 men, n= 7 women) with Type 1 diabetes (see **Table 2.1 for descriptive statistics**) on basal-bolus insulin treatment administered via multiple daily injections (MDI) (n = 6) or continuous subcutaneous insulin infusion (CSII) (n = 5) were recruited through adverts on Type 1 diabetes social media groups. Inclusion criteria were; aged between 18-55 years, diagnosed with Type 1 diabetes > 6 months and BMI $\leq$ 32 kg.m^2. Exclusion criteria were; pregnancy, disability preventing participation in an exercise regime, angina, autonomic neuropathy, medication that affects heart rate, major surgery planned within 6 weeks of the study, uncontrolled blood pressure, significant history of hyperglycaemia, history of severe hypoglycaemia requiring third party assistance within the last 3 months, severe non-proliferative and unstable proliferative retinopathy. Participant eligibility was confirmed during an initial meeting, which included a 12-lead resting electrocardiogram.

2.1.3 Study Design

Participants completed a randomised counterbalanced crossover experiment, consisting of three 14-day intervention periods: home-based high intensity interval training (home-HIIT), home-based moderate intensity continuous training (home-MICT) and a non-exercise control period (CON). Ten out of eleven participants

completed interventions consecutively, one participant had a 14-day period between intervention two and three. Free-living glycaemic control was assessed throughout the 14-day periods using an Abbott Freestyle Libre (Abbott Diabetes Care, CA, USA) flash glucose monitor (FGM), inserted subcutaneously into the interstitial fluid of the upper arm prior to each intervention. Participants were unblinded to the FGM, meaning they could see their glucose values by scanning the monitor. Participants also recorded insulin doses and dietary intake throughout the intervention periods.

During the CON period participants were instructed to perform no structured exercise (e.g. playing sport, going to the gym or running), but could continue any habitual physical activity (e.g. walking to work or shops). Exercise intervention periods were identical except for the exercise performed. During the two exercise periods (home-HIIT and home-MICT) the effect of 6 exercise sessions on subsequent glycaemic control was assessed. Exercise sessions were performed on days; 1, 3, 6, 8, 10 and 13 of the 14-day period, leaving at least 48 hours between sessions. The timing of exercise sessions was not controlled, but participants were asked to complete sessions at a similar time of day within and between interventions, and bouts were not performed after an overnight fast. Participants were asked to refrain from any form of structured exercise other than the prescribed sessions during the intervention periods.

2.1.3.1 *Exercise Session Monitoring*

To ensure exercise sessions were completed as prescribed participants were provided with a Polar H10 heart rate (HR) monitor (Polar, Kempele, Finland) and asked to wear this for each exercise session. During home-HIIT and home-MICT sessions participants were asked to attain specific HR targets, described below. Participants

received instant feedback on their HR during sessions, using the compatible polar application (Polar Beat, www.polar.com/beat/uk-en). Following exercise, HR data was automatically uploaded to a cloud storage site (www.flow.polar.com), allowing the research team to assess the number of exercise sessions completed and compliance with HR targets.

2.1.3.2 *Home-based High Intensity Interval Training (home-HIIT)*

Participants were instructed to complete a low intensity warm up for 3-minutes prior to starting each home-HIIT session. All home-HIIT sessions had a duration of 12 minutes, with participants completing six 1-minute high intensity intervals, interspersed with 1-minute rest intervals. Intervals used bodyweight exercises, with each interval divided into two different bodyweight exercises performed for 30 seconds with no rest between exercises. Participants were able to choose from a selection of 18 exercise pairs detailed in an exercise workbook (**appendix 10**). Participants were advised to achieve ≥80% of predicted HR_{max} (220-age) during the intervals. A session was deemed compliant if participants completed at least 1 interval with a heart rate ≥80% of predicted $HR_{max.}$

2.1.3.3 *Moderate Intensity Continuous Training (MICT)*

MICT sessions consisted of 30 minutes of continuous exercise of the participant's choosing (e.g. walking/jogging, cycling, swimming etc). Participants were asked to attain a HR of 60-70% of predicted HR_{max} during the exercise session and a session was deemed compliant if mean HR (HR_{mean}) was between 60 and 70% HR_{max}.

2.1.4 Measurements

2.1.4.1 Assessment of Glycaemic Control

Twelve metrics of glycaemia were assessed in line with the American Diabetes Association (ADA) guidelines (Danne et al., 2017, Battelino et al., 2019); mean glucose (mmol/L), glycaemic variability measured through standard deviation (SD) (mmol/L) and coefficient of variation (CV) (%), % time below range (TBR) ($\leq$ 3.9 mmol/L), % time above range (TAR) (> 10 mmol/L), % time in level 2 (L2) hypoglycaemia (< 3.0 mmol/L), % time in level 1 (L1) hypoglycaemia (3.0 – 3.9 mmol/L), % time in range (TIR) (4.0 – 10.0 mmol/L), % time in L1 hyperglycaemia (10.1 – 13.9 mmol/L), % time in L2 hyperglycaemia (> 13.9 mmol/L), number of hypoglycaemic episodes ($\geq$ 2 consecutive FGM values $\leq$ 3.9 mmol/L) and number of hyperglycaemic episodes ($\geq$ 2 consecutive FGM values > 10 mmol/L). Over the 14-day period, estimated glycated haemoglobin was also measured through use of the glucose management indicator (GMI) (mmol/L) (Bergenstal et al., 2018).

Glycaemic metrics recorded over the 14-day intervention period were assessed and reported at three time points in line with the current ADA guidelines (Battelino et al., 2019, Danne et al., 2017), i) full 14-day period, ii) nocturnal periods (00:00 – 06:00) during the 14-day period, iii) awake periods (06:00 – 00:00) during the 14-day period.

Glycaemic metrics were also assessed over five time points for up to 48 hours post exercise. Post exercise metrics are reported as an average of all 6 exercise sessions. A detailed description of the post exercise time points can be found in **Figure 2.1**, in brief the 5 time points were; 1) Awake 0 (A0), post exercise to 00:00 on the day of exercise, 2) Nocturnal 1 (N1) 00:00 to 06:00 the day following exercise (days begin at 00:00), 3) Awake 1 (A1), the awake period (06:00 – 00:00) the day following exercise, 4) Nocturnal 2 (N2), the nocturnal period (00:00 – 06:00) on the second day

following, 5) Awake 2 (A2), the awake period on the second day following exercise until 48 hours post exercise or the commencement of the next exercise session dependent on which occurred first. Post-exercise glucose data in the CON intervention was time and day matched with sessions from the home-HIIT intervention.

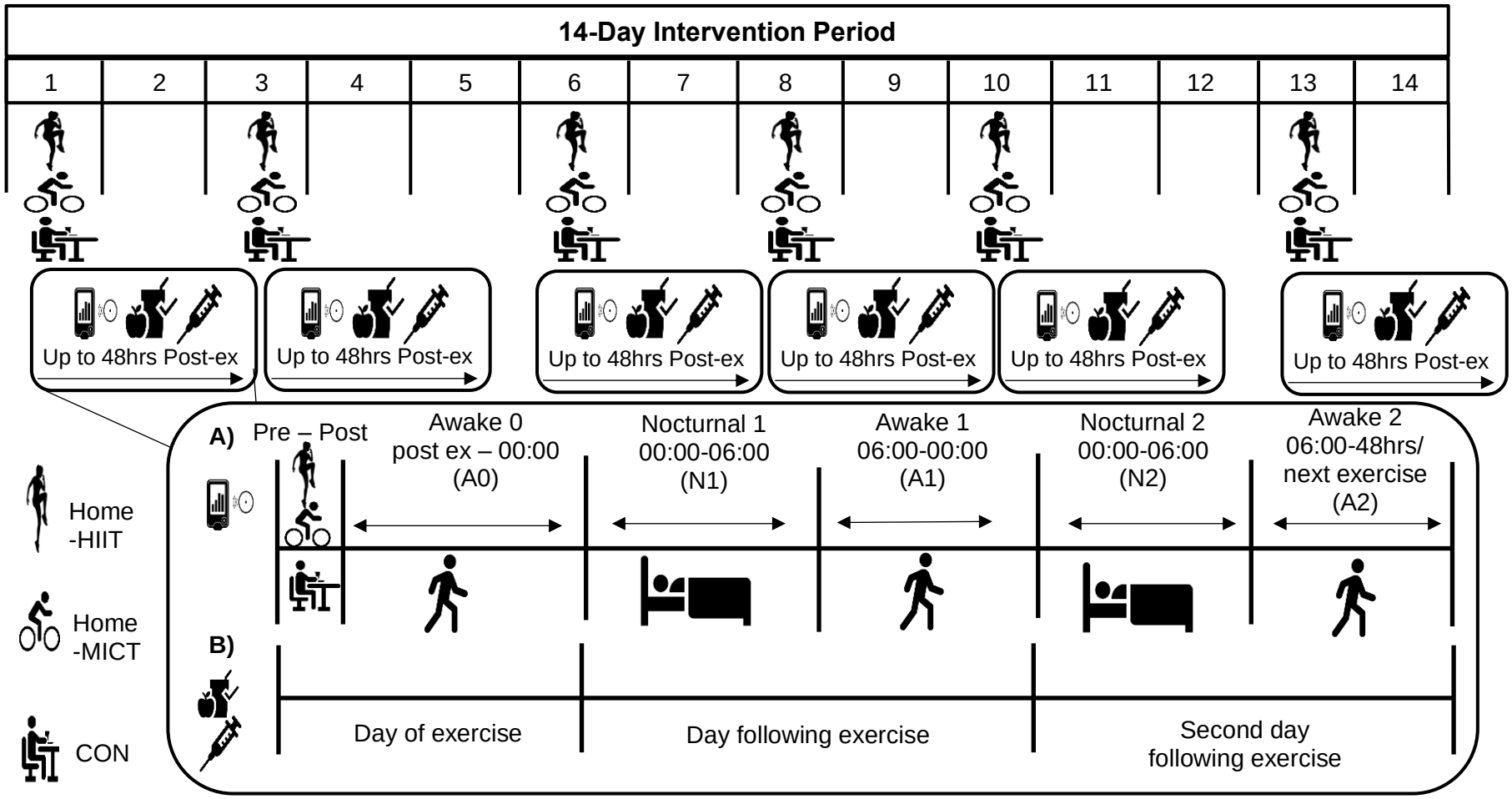

Figure 2.1. Assessment of glycaemic control within this study. Glycaemia metrics recorded over the 14-day intervention period were assessed at three time points; 1) Full 14-day period, 2) Nocturnal periods (00:00 – 06:00), 3) Awake periods (06:00-00:00). Exercise interventions consisted of 6 exercise bouts on days 1, 3, 6, 8, 10 and 13 of the intervention. A) FGM data following home-HIIT, home-MICT and CON was assessed over five time periods until 48 hours post exercise or until the next exercise bout commenced, dependent on which occurred first. B) Dietary intake and insulin dose data assessed for the day of exercise, day following exercise and the second day following exercise exercise with CON periods time matched to home-HIIT post exercise periods.

2.1.4.2 *Insulin dose*

Participants using MDI were asked to self-report insulin doses using either the smart phone application (LibreLink) or the reader linked to the FGM. This data was then automatically uploaded to the cloud system (LibreView) alongside the interstitial glucose data. Participants using CSSII were asked to provide information from their pump report online for the dates they were participating in the study. Basal and bolus (units) insulin were recorded and total daily dose relative to bodyweight (TDD/kg) was also calculated (basal dose + bolus dose / bodyweight(kg) = TDD/kg (units.kg)) for each 14-day intervention period and for the day of exercise, the day following exercise and the second day following exercise (see **Figure 2.1)**.

2.1.4.3 *Dietary Intake*

Dietary Intake was assessed using the MyFitnessPal application on smartphone (MyFitnessPal, CA, USA). Calorie (kcal) and carbohydrate (CHO) intake (grams) were assessed for each 14-day intervention period and for the day of exercise, the day following exercise and second day following exercise (see **Figure 2.1)**. Participants were asked to maintain their habitual diet and report their dietary intake as accurately as possible. A day was considered complete and valid if the calorie intake recorded was ≥ 500 kcal and ≤ 5000kcal (Carter et al., 2013). If participants recorded less than 50% valid days (< 7 days) in an intervention period, then their dietary data was excluded (Burke et al., 2011).

2.1.5 *Statistical analysis*

Statistical analysis was performed using SPSS 26 (IBM SPSS Statistics 26; Armork: IBM Corp). A linear mixed model was used to assess all variables at all time points

unless stated otherwise. Data for the interventions were converted to change from CON (home-HIIT = home-HIIT – CON; home-MICT = home-MICT – CON; CON = CON – CON) and are presented as adjusted change with values showing mean difference between interventions. The linear mixed model method assessed the statistical difference between home-HIIT and CON, home-MICT and CON, as well as between home-HIIT and home-MICT using LSD post hoc tests. Data are presented as mean differences and 95% Confidence Intervals (95% CI). A two factor repeated measures ANOVA was used to assess whether there was an acute change in interstitial glucose concentration following home-HIIT and home-MICT, with the within-subject factors 'training mode' and 'time point', data presented as mean ± SD. Paired-samples t-test's were used to analyse exercise session data (Sessions completed and compliance with the HR target), data presented as mean ± SD. Throughout all statistical tests, the alpha level was set at $P \leq 0.05$.

2.2 Results

Table 2.1 presents the participant characteristic of the eleven physically active adults with Type 1 diabetes in this study. Participants completed >150 minutes of MVPA per week and were physically active on at least 3 days per week.

Table 2.1 Descriptive statistics for participants. Data presented as means ± SD.

Variable	All	Female	Male
Participants (n=)	11	7	4
Age (years)	*26 ± 7*	26 ± 7	25 ± 6
Height (m)	1.68 ± 0.14	1.60 ± 0.05	1.82 ± 0.15
Mass (kg)	71.65 ± 13.14	67.20 ± 14.57	79.43 ± 4.88
BMI (kg/m^2)	25.43 ± 4.29	26.10 ± 4.90	24.25 ± 3.23
Type 1 diabetes Duration (years)	10 ± 8	10 ± 10	9 ± 4
CSSI (n=)	5	5	0
MDI (n=)	6	2	4

2.2.1 *Exercise Sessions & HR Data*

A total of 59 home-HIIT and 56 home-MICT sessions were completed. Participants completed 5±1 home-HIIT sessions (range = 4 to 6 sessions) and 5±1 home-MICT sessions (range = 2 to 6 sessions), with no difference in the number of sessions completed between home-HIIT or home-MICT (t_{10} = 0.61, P = 0.557). Compliance with the target HR was significantly greater (t_{10} = 3.26, P = 0.009) in home-HIIT than home-MICT (home-HIIT 100±0%, home-MICT 65±35% of sessions completed at the target HR). Lower compliance in home-MICT was due to 25±36.27% of sessions being completed above the HR target (HR_{mean} 60-70%HR_{max}) and 9±15% of sessions being completed below target. The average start time of the home-HIIT sessions was 17:36:44 ± 02:24:00 (hh:mm:ss) and the average start time of the home-MICT sessions was 16:29:33 ± 02:06:55 (hh:mm:ss).

2.2.2 *Glycaemic Control Assessed Over the 14-day Intervention Periods*

A total of 448 days were included in the analyses with an average of 41 ±3 days per participant included. On average, 914:20 ± 62:45 (hhh:mm) of FGM data per participant was included in the analyses, equating to 91 ± 6 % of the prescribed period.

Glycaemic control data from the FGMs assessed over the full 14 day, nocturnal and awake periods are presented in **Tables 2.2.1, 2.2.2.** and **2.23**. The data below is presented as change from CON, see **Appendix 1, 2 and 3** for raw data on the glycaemic metrics assessed over the full 14 day, nocturnal and awake periods, respectively (mean± SD). The effects of training modes on post exercise glycaemic control are presented in **Figure 2.3**

Compared to control neither home-HIIT or home-MICT altered mean glucose, TIR, TAR and TBR over the full 14 day, nocturnal or awake periods (P>0.05). The number of hypo- and hyperglycaemic episodes were also not different during home-HIIT or home-MICT compared to control over the full 14 day, nocturnal or awake periods (P>0.05). Glucose CV was not different during home-HIIT or home-MICT compared to control over the full 14 day or awake periods (P>0.05). Compared to control neither home-HIIT (P = 0.734) or home-MICT (P = 0.068) increased nocturnal glucose CV significantly. However, glucose CV was significantly greater following home-MICT compared to home-HIIT (P = 0.034).

Table 2.2.1. Glycaemic Metrics during the 14-day intervention periods in home-HIIT and home-MICT. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.2 (-0.8, 0.4)	0.496	0.0 (-0.6, 0.6)	0.996	-0.2 (-0.8, 0.4)	0.500
GMI (mmol/L)	-0.9 (-3.7, 1.8)	0.496	-0.0 (-2.8, 2.7)	0.996	-0.9 (-3.7, 1.8)	0.500
% TIR	4 (-12, 9)	0.170	-1 (-6., 5)	0.737	5 (-1, 10)	0.093
% TAR	-4 (-11, 2)	0.185	0 (-7, 7)	0.969	-5 (-11, 2)	0.173
% Time in L1 Hyperglycaemia	-4 (-9., 0)	0.072	-2 (-7, 3)	0.349	-2 (-7, 3)	0.357
% Time in L2 Hyperglycaemia	0 (-3, 3)	0.987	2 (-1, 6)	0.161	-2 (-6, 1.)	0.166
% TBR	1 (-2, 3)	0.575	1 (-1, 3)	0.449	0 (-2, 2)	0.841
% Time in L1 Hypoglycaemia	1 (-1, 2)	0.188	1 (-1, 2)	0.211	0 (-1, 2)	0.945
% Time in L2 Hypoglycaemia	0 (-1, 1)	0.411	0 (-1, 1)	0.803	0 (-1, 1)	0.563
Number of Hyperglycaemic episodes	-1 (-6, 4)	0.759	-3 (-8, 2)	0.165	3 (-2, 8)	0.272
Number of Hypoglycaemic episodes	1 (-3, 6)	0.498	1 (-3, 5)	0.556	0 (-4, 4)	0.928
SD (mmol/L)	0.1 (-0.2, 0.3)	0.676	0.2 (-0.1, 0.4)	0.137	-0.1 (-0.4, 0.1)	0.274
CV (%)	1 (-2, 4)	0.559	2 (-1, 5)	0.120	-1.3 (-4.0, 1.4)	0.315

Table 2.2.2. Glycaemic Metrics during nocturnal time periods throughout the home-HIIT and home-MICT 14-day intervention periods. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.0 (-0.8, 0.7)	0.926	-0.3 (-1.1, 0.4)	0.353	-0.3 (-0.4, 1.0)	0.401
% TIR	4 (-4, 12)	0.295	3 (-5, 11)	0.433	1 (-7, 9)	0.786
% TAR	-4 (-12, 4)	0.307	-4 (-13, 4)	0.272	0 (-8, 9)	0.938
% Time in L1 Hyperglycaemia	-6 (-13, 2.)	0.159	-5 (-13, 3)	0.207	0 (-8, 7)	0.875
% Time in L2 Hyperglycaemia	1 (-4, 7)	0.606	0 (-5, 6)	0.865	0.9 (-5, 6)	0.728
% TBR	0 (-4, 4)	0.978	1 (-3, 6)	0.505	-1 (-6, 3)	0.522
% Time in L1 Hypoglycaemia	2 (-1, 4)	0.198	2 (-1, 5)	0.129	0 (-3, 2)	0.805
% Time in L2 Hypoglycaemia	-2 (-4, 1)	0.255	-1 (-3, 2)	0.657	-1 (-4, 2)	0.432
Number of Hyperglycaemic episodes	-1 (-4, 2)	0.353	-2 (-4, 1)	0.262	0 (-3, 3)	0.841
Number of Hypoglycaemic episodes	0 (-1, 1)	0.444	0 (-1, 1)	0.565	0 (-1, 1)	0.847
SD (mmol/L)	-0.1 (-0.6, 0.5)	0.848	0.2 (-0.3, 0.7)	0.439	-0.2 (-0.8, 0.3)	0.337
CV (%)	-1 (-5, 3)	0.734	4 (0, 8)	0.068	-4 (-8, 0)	0.034

Table 2.2.3. Glycaemic Metrics during the awake time periods throughout the home-HIIT and home-MICT 14-day intervention periods. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.2 (-0.9, 0.5)	0.587	0.1 (--0.6, 0.8)	0.772	-0.3 (-1.0, 0.4)	0.407
% TIR	3 (-4, 9)	0.409	-2 (-9, 4)	0.509	5 (-2, 11)	0.145
% TAR	-4 (-11, 4)	0.341	2 (-6, 9)	0.681	5 (-13, 3)	0.179
% Time in L1 Hyperglycaemia	-4 (-8, 1)	0.098	-1.4 (-5.8, 3.0)	0.525	-2 (-7, 2)	0.289
% Time in L2 Hyperglycaemia	0 (-4, 5)	0.938	2.9 (-1.6, 7.4)	0.200	-3 (-7, 2)	0.227
% TBR	1 (-1, 3)	0.423	0.6 (-1.6, 2.8)	0.565	0 (-2, 2)	0.818
% Time in L1 Hypoglycaemia	1 (-1, 2)	0.302	0.5 (-0.9, 2.0)	0.455	0 (-1, 2)	0.769
% Time in L2 Hypoglycaemia	0 (-1, 1)	0.774	0.1 (-0.8, 1.0)	0.843	0 (-1, 1)	0.930
Number of Hyperglycaemic episodes	-1 (-7, 4)	0.586	-2.4 (-7.5, 2.8)	0.348	1 (-4, 6)	0.689
Number of Hypoglycaemic episodes	1 (-3, 5)	0.472	1.1 (-2.8, 5.0)	0.564	0 (-4, 4)	0.885
SD (mmol/L)	0.0 (-0.2, 0.3)	0.751	0.2 (--0.0, 0.4)	0.098	-0.2 (-0.4, 0.1)	0.172
CV (%)	1 (-2, 3)	0.666	1.8 (-0.9, 4.5)	0.175	-1 (-4, 1)	0.344

2.2.3 *Acute changes in interstitial glucose concentration during exercise*

There was a significant interaction effect between timepoint and training mode (P = 0.042) for mean interstitial glucose pre to post exercise. Post hoc analysis revealed that home-HIIT resulted in a stable mean interstitial glucose response from pre (9.5 ± 2.1 mmol/L) to post (9.0 ± 2.3 mmol/L) exercise (P = 0.139). However, home-MICT resulted in a significant decrease in mean interstitial glucose from pre (9.7 ± 1.8 mmol/L) to post (8.0 ± 1.9 mmol/L) exercise (P = 0.011).

2.2.4 *Glycaemic Control within 48h of Exercise*

Mean interstitial glucose profiles for the 48-hours post exercise for each intervention period are presented in **Figure 2.2**. **Figure 2.3** presents a summary of the data captured over the 5 time points. The data below is presented as change from CON, see **Appendix 4, 5, 6, 7 and 8** for raw data on the glycaemic metrics assessed over the five time points, respectively (mean± SD).

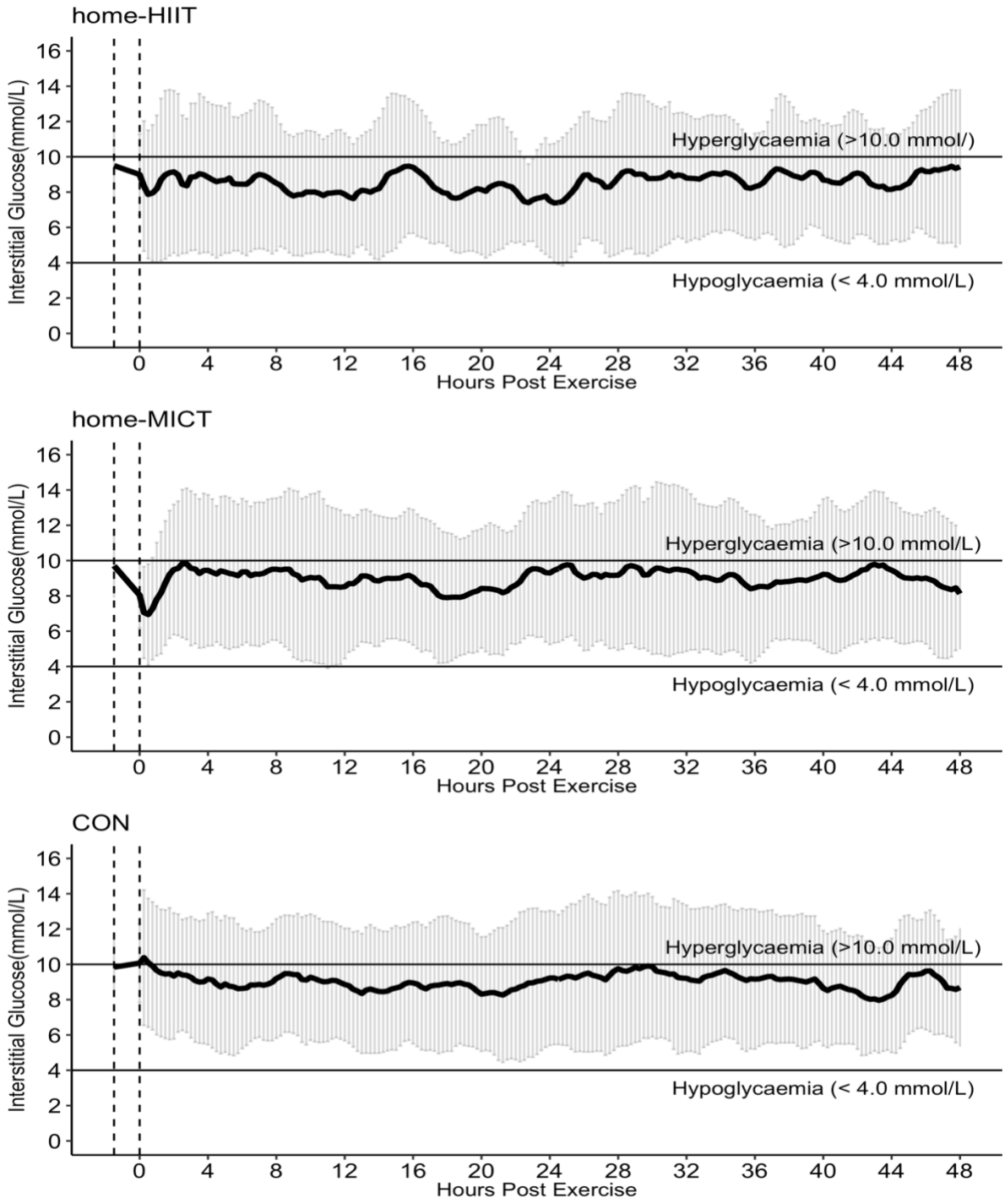

Figure 2.2. Mean interstitial glucose profiles for the 48-hour post exercise following home-HIIT, home-MICT and CON. Solid black line represents mean interstitial glucose values every 15-minutes post exercise; light grey error bars represent mean variance measured as SD at each timepoint. The vertical dashed lines represent the start and end of exercise and the solid horizontal lines represent hypoglycaemic and hyperglycaemic thresholds.

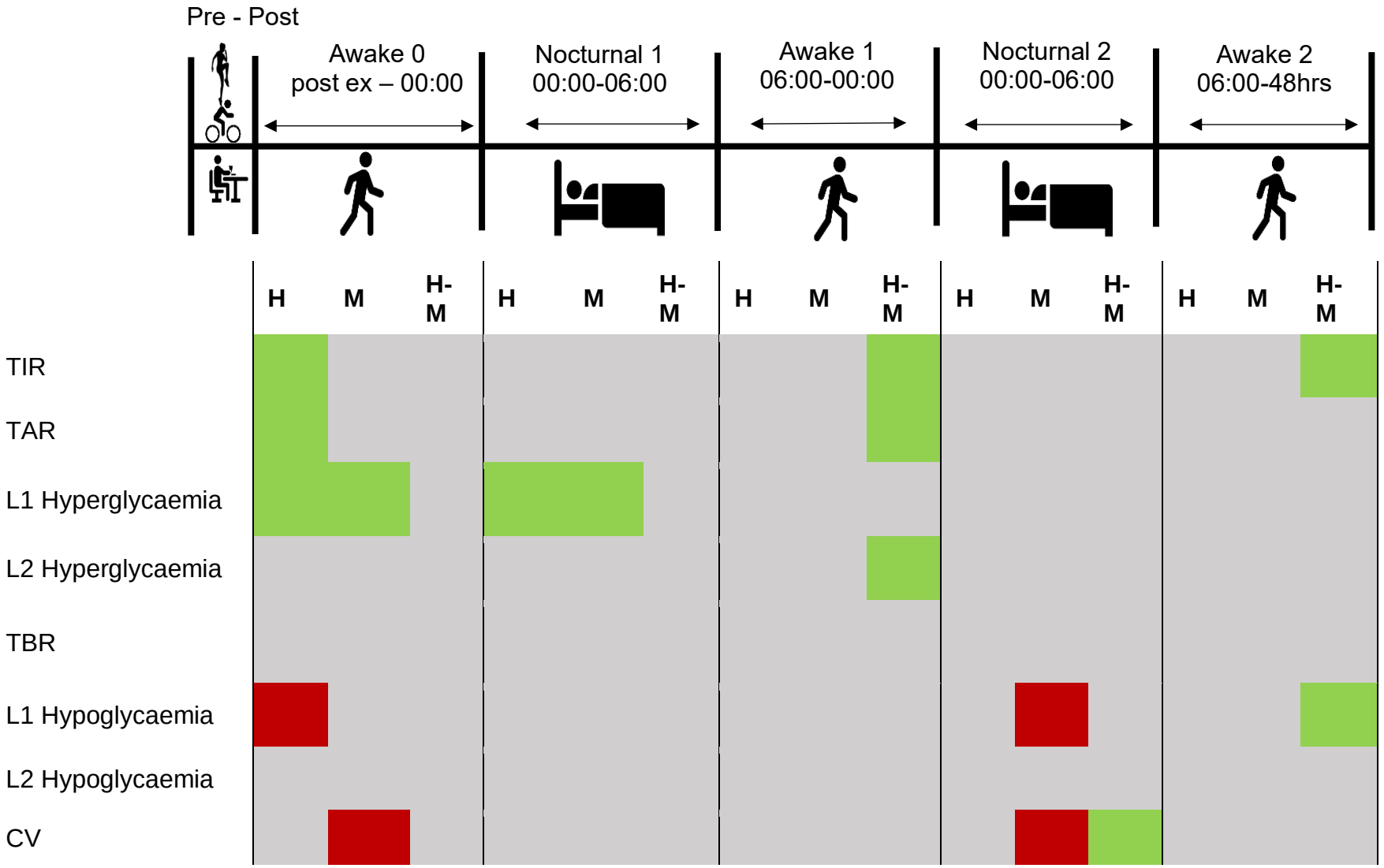

Figure 2.3. Schematic illustrating glycaemic control during five post exercise time points. H) Home-HIIT compared to CON, M) home-MICT compared to CON, H-M) home-HIIT compared to home-MICT. Grey = no change, red = significant negative effect ($P \leq 0.05$), green = significant positive effect ($P \leq 0.05$). Green at 'H-M' reflects home-HIIT as positive.

2.2.3.1 *Awake period on the day of exercise (A0)*

The awake period on the day of exercise had an average duration of 05:41:21 ± 02:17:51 (hh:mm:ss). FGM data for the awake period on the day of exercise is presented in **Table 2.3.1**. Compared to CON, mean glucose was not different following home-HIIT (P 0.256) or home-MICT (P = 0.488). Unlike home-MICT (P = 0.114) home-HIIT significantly increased TIR compared to CON (P = 0.043). There was no difference between training modes for TIR (P = 0.611). Increased TIR following home-HIIT compared to CON was accounted for by significantly reducing TAR in home-HIT compared to CON (P = 0.022). There were no differences, in TAR in home-MICT (P = 0.073) compared to CON or home-HIIT (P = 0.559). Specifically, time spent in L1 hyperglycaemia was reduced by both home-HIIT (P = 0.002) and home-MICT (P =0.002) compared to CON. Time spent in L2 hyperglycaemia and the number hyperglycaemic episodes were similar in all conditions (P>0.05). Compared to CON, TBR was not different following home-HIIT (P = 0.174) or home-MICT (P = 0.296). However, time spent in L1 hypoglycaemia was significantly increased following home-HIIT (P = 0.033) but not home-MICT (P = 0.070) compared to CON. No between training mode difference was observed (P = 0.708). Importantly, no differences in time spent in L2 hypoglycaemia or the number of hypoglycaemic episodes were observed between conditions (P>0.05). Home-HIIT did not alter either glucose CV or SD compared to control. However, home-MICT significantly increased glucose CV (P = 0.034) and SD (P = 0.014) compared to control, but no between training mode differences were observed (P > 0.05).

2.2.3.2 Nocturnal period on the day following exercise (N1)

FGM data for the nocturnal period the day following exercise is presented in **Table 2.3.2.** Compared to control mean glucose was not different following home-HIIT (P = 0.420) or home-MICT (P = 0.879). TIR, TAR, TBR and number of episodes of hypo- and hyperglycaemia were not different following home-HIIT or home-MICT compared to control (P>0.05). Although TIR and TAR were not different, time in L1 hyperglycaemia was reduced following both home-HIIT (P = 0.035) and home-MICT (P = 0.034). Neither home-HIIT nor home-MICT affected glucose CV or SD compared to control (P>0.05).

2.2.3.3 Awake period on the day following exercise (A1)

Table 2.3.3 presents the FGM data for the awake period on the day following exercise. Compared to control, mean glucose was not different following home-HIIT (P = 0.141) or home-MICT (P = 0.253). However, mean glucose was significantly lower following home-HIIT compared to home-MICT (P = 0.013). Compared to CON, TIR was not different following either home-HIIT (P = 0.209) or home-MICT (P = 0.173), but there was significantly more TIR in home-HIIT compared to home-MICT (P = 0.013). Compared to CON, there were no differences in TAR following home-HIIT (P=0.153) and home-MICT (P = 0.158). Increased TIR in home-HIIT compared to home-MICT was accounted for by significantly less TAR (P = 0.013). There were no differences in time spent in L1 hyperglycaemia following home-HIIT and home-MICT compared to CON, or between training modes (P > 0.05). However, significantly less time was spent in L2 hyperglycaemia following home-HIIT compared to home-MICT (P = 0.030). Compared to CON, there were no differences in time spent in L2 hyperglycaemia in home-HIIT or home-MICT. Compared to CON, TBR and the number of hypo- and

hyperglycaemic episodes were not different in home-HIIT or home-MICT and there were also no differences between training modes (P > 0.05). Neither home-HIIT nor home-MICT affected glucose CV or SD (P > 0.05)

2.2.3.4 *Nocturnal Period on the second day following exercise (N2)*

Table 2.3.4 presents the FGM data for the nocturnal period on the second day following exercise. Compared to CON, mean glucose was not different in home-HIIT (P = 0.477) or home-MICT (P = 0.204). TIR, TAR, TBR and the number of hypo- and hyperglycaemic episodes were not different in home-HIIT or home-MICT compared to CON (P > 0.05). Although, TBR was not different in home-HIIT compared to CON (P = 0.071), time spent in L1 hypoglycaemia was significantly greater in home-MICT compared to CON (P = 0.047). Home-HIIT did not alter either glucose CV or SD. However, home-MICT significantly increased both glucose CV (P = 0.024) and SD (P = 0.008) compared to CON. Furthermore, home-MICT increased glucose CV (P = 0.008) and SD (P = 0.019) compared to home-HIIT.

2.2.3.5 *Awake period on the second day following exercise (A2)*

The awake period on the second day following exercise had an average duration of 09:52:10 ± 02:10:09 (hh:mm:ss). **Table 2.3.5** presents the FGM data for the awake period on the second day following exercise. Compared to CON, mean glucose was not different following home-HIIT (P = 0.666) or home-MICT (P = 0.806). TIR, TAR, TBR and the number of hypo and hyperglycaemic episodes were not different following home-HIIT and home-MICT compared to CON (P > 0.05). Although there were no differences in TIR following home-HIIT or home-MICT compared to CON, there was significantly more TIR following home-HIIT compared to home-MICT (P = 0.034). This was accompanied by significantly less time spent in L1 hypoglycaemia

following home-HIIT compared to home-MICT ($P = 0.014$). Neither home-HIIT or home-MICT affected glucose CV and SD ($P > 0.05$) compared to CON ($P > 0.05$)

Table 2.3.1. Glycaemic Metrics during the period A0 for home-HIIT and home-MICT interventions. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.8 (-2.3, 0.7)	0.256	-0.5 (-2.0, 1.0)	0.488	-0.3 (-1.8, 1.2)	0.647
% TIR	11 (0, 22)	0.043	89 (-2, 20)	0.114	3 (-8, 14)	0.611
% TAR	-14 (-27, -2)	0.022	-11 (-23, 1)	0.073	-3 (-16, 9)	0.559
% Time in L1 Hyperglycaemia	-15 (-23, -7)	0.002	-14 (-23, -6)	0.002	-1 (-9, 8)	0.911
% Time in L2 Hyperglycaemia	1 (-10, 11)	0.929	3 (-7, 14)	0.503	-3 (-14, 8)	0.560
% TBR	3 (-2, 8)	0.174	2 (-2, 7)	0.296	0. (-4, 5)	0.737
% Time in L1 Hypoglycaemia	3 (0, 5)	0.033	2 (0., 5)	0.070	1 (-2, 3)	0.708
% Time in L2 Hypoglycaemia	0 (-2, 3)	0.833	0 (-3, 3)	0.996	0 (-2, 3)	0.830
Number of Hyperglycaemic episodes	-1 (-1, 0)	0.006	0 (-1, 0)	0.224	0 (-1, 0)	0.082
Number of Hypoglycaemic episodes	0 (0, 0)	0.722	0 (0, 0)	0.586	0 (0, 0)	0.849
SD (mmol/L)	0.1 (-0.2, 0.4)	0.539	0.4 (0.0, 0.7)	0.034	-0.3 (-0.6, 0.1)	0.112
CV (%)	3 (-1, 6)	0.125	4 (1, 8)	0.014	-2 (-5, 2)	0.285

Table 2.3.2. Glycaemic Metrics during the period N1 for home-HIIT, home-MICT. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.5 (-1.7, 0.7)	0.420	0 (-1, 1)	0.879	-0.6 (-1.8, 0.6)	0.340
% TIR	11 (-2, 24)	0.104	5 (-8, 18)	0.435	6 (-8, 19)	0.376
% TAR	-11 (-25, 4)	0.130	-5 (-19, 9)	0.484	-6 (-20, 8)	0.396
% Time in L1 Hyperglycaemia	-12 (-24, -1)	0.035	-13 (-24, -1)	0.034	0 (-11, 12)	0.986
% Time in L2 Hyperglycaemia	2 (-7, 10)	0.635	8 (0, 16)	0.052	-6 (-14, 2)	0.129
% TBR	0 (-7, 7)	0.974	0 (-7, 7)	0.946	0 (-7, 7)	0.972
% Time in L1 Hypoglycaemia	1 (-3, 5)	0.571	0 (-4, 3)	0.848	1 (-2, 5)	0.450
% Time in L2 Hypoglycaemia	-1 (-6, 4)	0.640	0 (-5, 5)	0.969	-1 (-6, 4)	0.613
Number of Hyperglycaemic episodes	0 (0, 0)	0.220	0 (0, 0)	0.713	0 (0, 0)	0.382
Number of Hypoglycaemic episodes	0 (0, 0)	0.629	0 (0, 0)	0.758	0 (0, 0)	0.860
SD (mmol/L)	0.1 (-0.2, 0.4)	0.539	0.4 (0.0, 0.7)	0.034	-0.3 (-0.6, 0.1)	0.112
CV (%)	3 (-2, 8)	0.273	2 (-4, 7)	0.539	1 (-4, 6)	0.622

Table 2.3.3. Glycaemic Metrics during the period A1 for home-HIIT and home-MICT. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.5 (-1.2, -0.2)	0.141	0.4 (-0.3, 1.1)	0.253	-0.9 (-1.6, -0.2)	0.013
% TIR	5 (-3, 12)	0.209	-5 (-13, 4)	0.173	10 (2, 18)	0.013
% TAR	-6 (-14, 2)	0.153	6 (-2, 13)	0.158	-11 (-19, -3)	0.008
% Time in L1 Hyperglycaemia	-3 (-9, 2)	0.204	2 (-4, 7)	0.494	-5 (-11, 0)	0.058
% Time in L2 Hyperglycaemia	-3 (-8, 3)	0.394	4 (-2, 9)	0.158	-6 (-12, -1)	0.030
% TBR	1 (-2, 4)	0.534	0 (-3, 3)	0.793	1 (2, 4)	0.379
% Time in L1 Hypoglycaemia	1 (-1, 3)	0.319	0 (-2, 2)	0.779	1 (-1, 3)	0.469
% Time in L2 Hypoglycaemia	0 (-1, 1)	0.730	-1 (-2, 0)	0.210	1 (-1, 2)	0.356
Number of Hyperglycaemic episodes	0 (0, 0)	0.859	-0 (-1, 0)	0.728	0 (0, 0)	0.865
Number of Hypoglycaemic episodes	0 (0, 0)	0.746	0 (0, 0)	0.837	0 (0, 1)	0.597
SD (mmol/L)	0.2 (-0.2, 0.5)	0.342	0.2 (-0.9, 0.6)	0.151	-0.1 (-0.4, 0.2)	0.609
CV (%)	3 (0, 6)	0.073	1 (-2, 5)	0.398	2 (-2, 5)	0.315

Table 2.3.4. Glycaemic Metrics during the period N2 for home-HIIT and home-MICT. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.3 (-1.1, 0.5)	0.477	-0.5 (-1.3, 0.3)	0.204	0.2 (-0.6, 1.0)	0.563
% TIR	1 (-14, 15)	0.922	-6 (-21, 8)	0.363	7 (-7, 22)	0.315
% TAR	-3 (-14, 8)	0.551	-0 (-11, 11)	0.966	-3 (-14, 8)	0.580
% Time in L1 Hyperglycaemia	-4 (-15, 7)	0.470	2 (-9, 14)	0.661	-6 (-17, 5)	0.251
% Time in L2 Hyperglycaemia	1 (-9, 11)	0.874	-3 (-12, 7)	0.575	3 (-7, 13)	0.474
% TBR	3 (-5, 10)	0.480	7 (-1, 14)	0.071	-4 (-11, 3)	0.248
% Time in L1 Hypoglycaemia	1 (-4, 6)	0.646	5 (0, 10)	0.047	-4 (-9, 1)	0.115
% Time in L2 Hypoglycaemia	1 (-4, 7)	0.565	2 (-3, 7)	0.483	-0 (-5, 5)	0.899
Number of Hyperglycaemic episodes	0 (0, 0)	0.988	0 (0, 0)	0.125	0 (-1, 0)	0.122
Number of Hypoglycaemic episodes	0 (0, 0)	0.195	0 (0, 0)	0.077	0 (0, 0)	0.604
SD (mmol/L)	0.0 (-0.3, 0.3)	0.914	0.4 (0.1, 0.7)	0.024	-0.4 (-0.7, 0.1)	0.019
CV (%)	0 (-3, 3)	0.869	4 (1, 7)	0.008	5 (-8, 2)	0.005

Table 2.3.5. Glycaemic Metrics during period A2 for home-HIIT and home-MICT. Values presented as mean change from CON (95% CI).

Variable	Home-HIIT (95%CI)	P Value (CON vs HIIT)	Home-MICT (95%CI)	P Value (CON vs MICT)	Between Groups (95%CI)	P Value (HIIT vs MICT)
Mean Glucose (mmol/L)	-0.1 (-0.8, 0.5)	0.666	0.1 (-0.6, 0.7)	0.806	-0.2 (-0.9, 0.4)	0.500
% TIR	6 (-3, 15)	0.180	-5 (-14, 3)	0.213	11 (3, 20)	0.014
% TAR	-5 (-15, 4)	0.222	3 (-6, 12)	0.551	-8 (-17, 1)	0.077
% Time in L1 Hyperglycaemia	-4 (-12, 4)	0.319	0 (-8, 8)	0.971	-4 (-12, 4)	0.302
% Time in L2 Hyperglycaemia	-2 (-9, 5)	0.559	3 (-5, 10)	0.367	-4 (-11, 3)	0.145
% TBR	0 (-4, 3)	0.801	3 (-1, 6)	0.105	-3 (-7, 0)	0.065
% Time in L1 Hypoglycaemia	0 (-2, 2)	0.739	2 (0, 4)	0.067	-2 (-4, 0)	0.034
% Time in L2 Hypoglycaemia	0 (-2, 2)	0.934	1 (-1, 3)	0.407	-1 (-3, 1)	0.363
Number of Hyperglycaemic episodes	0 (0, 0)	0.769	0 (-1, 0)	0.510	0 (0, 1)	0.345
Number of Hypoglycaemic episodes	0 (0, 0)	0.505	0 (-1, 0)	0.194	0 (-1, 0)	0.057
SD (mmol/L)	-0.1 (-0.6, 0.3)	0.535	0.1 (-0.3, 0.6)	0.617	-0.3 (-0.7, 0.2)	0.268
CV (%)	-1 (-7, 4)	0.592	2 (-3, 7)	0.444	-3 (-9, 2)	0.200

2.2.4 *Insulin Dose*

Insulin data is presented in Table 2.2.3. Compared to CON, neither home-HIIT or home-MICT effected bolus, basal or TDD/kg insulin dose during the 14-day intervention period or on the day of exercise, day following exercise and the second day following exercise ($P > 0.05$).

2.2.5 *Dietary intake*

Dietary intake data is presented in **Table 2.3.3.** Compared to CON, calorie and CHO intakes were not different on the day of exercise and the second day following exercise in home-HIIT or home-MICT ($P > 0.05$). On the day following exercise, there was no difference in calorie content in either home-HIIT ($P = 0.335$) or home-MICT ($P = 0.151$) compared to CON. There was also no difference in CHO intake on the day following exercise in home-HIIT compared to CON ($P = 0.535$). However, CHO intake on the day following exercise was significantly greater in home-MICT compare to CON ($P = 0.050$).

Table 2.3.3. Energy intake and insulin dose in home-HIIT and home-MICT interventions during the 14-day intervention period and the day of exercise, the day following exercise and the second day following exercise. Values presented as mean change from CON (95% CI).

Time period	Variable	Home-HIIT (95% CI)	P Value (CON vs HIIT)	Home-MICT (95% CI)	P Value (CON vs MICT)	Between Groups (95% CI)	P Value (HIIT vs MICT)
Intervention	Calorie Intake (Kcal)	114 (-9, 236)	0.067	17 (-105, 140)	0.767	96 (-26, 219)	0.116
	CHO Intake (grams)	14 (-1, 28)	0.064	9 (-6, 24)	0.217	5 (-10, 20)	0.488
	Bolus (units)	-2 (-5, 0)	0.078	-1 (-4, 2)	0.429	-1 (-4, 1)	0.290
	Basal (units)	0 (-1, 2)	0.676	-1 (-2, 1)	0.231	1 (0, 3)	0.117
	TDD/kg (unit.kg)	0 (-5, 1)	0.239	0 (-5, 2)	0.266	0 (-3, 3)	0.943
Day of exercise	Calorie Intake (Kcal)	65 (-47, 178)	0.237	47 (-65, 160)	0.387	18 (-95, 131)	0.738
	CHO Intake (grams)	12 (-7, 31)	0.190	8 (-11, 27)	0.371	4 (-15, 23)	0.659
	Bolus (units)	-2 (-6, 1)	0.132	-1 (-4, 2)	0.541	-1 (-4, 2)	0.346
	Basal (units)	0 (-1, 2)	0.490	-1 (-2, 1)	0.291	1 (0, 3)	0.092
	TDD/kg (unit.kg)	0 (-1, 0)	0.317	-0 (-1, 0)	0.342	0 (0, 0)	0.958
Day following exercise	Calorie Intake (Kcal)	109 (-123, 341)	0.335	165 (-67, 398)	0.151	-56 (-289, 176)	0.614
	CHO Intake (grams)	7 (-16, 30)	0.535	23 (0, 47)	0.050	-16 (-40, 7)	0.157
	Bolus (units)	0 (-4, 3)	0.838	-1 (-4, 2)	0.593	1 (-3, 4)	0.740
	Basal (units)	0 (-2, 2)	0.932	-1 (-2, 1)	0.414	1 (-1, 2)	0.369
	TDD/kg (unit.kg)	0 (0, 0)	0.824	0 (0, 0)	0.363	0 (0, 0)	0.487
Second day following exercise	Calorie Intake (Kcal)	274 (-52, 600)	0.094	146 (-180, 473)	0.335	128 (-199, 454)	0.420
	CHO Intake (grams)	34 (-8, 76)	0.104	21 (-21, 63)	0.305	13 (-29, 55)	0.514
	Bolus (units)	-2 (-7, 2)	0.317	0 (-4, 5)	0.867	-2 (-7, 2)	0.247
	Basal (units)	1 (-1, 2)	0.314	0 (-2, 1)	0.525	1 (0, 2)	0.112
	TDD/kg (unit.kg)	0 (0, 0)	0.593	0 (0, 0)	0.913	0 (0, 0)	0.521

2.3 Discussion

The aims of this study were to investigate the effects of home-HIIT and home-MICT completed in a postprandial state compared to a non-exercise control period on; i) hypoglycaemia ii) TIR, and iii) GV, for up to 48-hours post exercise in a free-living environment. A secondary aim was to investigate whether acute changes following exercise influenced 14-day glycaemic control. The most important novel findings of this study were that;1) neither home-HIIT or home-MICT increased time spent in serious, clinically significant hypoglycaemia (< 3.0 mmol/L) compared to non-exercise control at any period measured in the 48-hours following exercise. 2) That TIR compared to a non-exercise period was increased immediately following (post exercise to 00:00 on the day of exercise) home-HIIT but not home-MICT. After this initial period following exercise neither home-HIIT or home-MICT altered TIR compared to a non-exercise period, but TIR was significantly higher in the awake periods following home-HIIT compared to home-MICT. However, the differences observed following exercise did not translate to an improvement in TIR over the 14-day intervention period. 3) GV (SD and CV) was increased compared to CON immediately following home-MICT but not home-HIIT. GV (CV) was also increased in the nocturnal period on the second day following home-MICT. This increase in GV following home-MICT translated into an increased nocturnal GV over the 14-day intervention period in home-MICT compared to home-HIIT.

The findings of the current study add to a growing body of evidence that suggests HIIT does not increase the risk of serious, clinically significant hypoglycaemia compared to traditional MICT or non-exercise periods (Aronson et al.,

2019, Lee et al., 2020, Martín-San Agustín et al., 2020, Riddell et al., 2020, Scott et al., 2019a, Scott et al., 2019b). However, to date much of this work has been conducted following HIIT performed in an optimal laboratory environment (Aronson et al., 2019, Lee et al., 2020, Martín-San Agustín et al., 2020, Scott et al., 2019a, Scott et al., 2019b), with controlled glycaemic management strategies employed to minimise hypoglycaemia following exercise, including, insulin dose adjustment (Lee et al., 2020), carbohydrate intake and insulin dose adjustment (Aronson et al., 2019, Martín-San Agustín et al., 2020) or fasted exercise (Aronson et al., 2019, Scott et al., 2019a). As in the current study, Riddell et al. (2020) recently demonstrated that neither home-based vigorous intensity continuous training (30 minutes at an intended intensity of 70-80% HR_{max}) or home-HIIT (30 minutes of intervals at an intended intensity of 80-90% HR_{max}), performed under free living conditions, increased time spent in serious, clinically significant hypoglycaemia compared to on-exercise days. The current study adds important information, as the home-HIIT intervention investigated has previously been shown to be efficacious (increasing cardiorespiratory fitness and reducing insulin dose), time-efficient and practical, leading to high exercise adherence, in people with Type 1 diabetes (Scott et al., 2020).

Although serious, clinically significant hypoglycaemia was not increased, time spent in L1 hypoglycaemia was elevated, compared to CON, immediately following home-HIIT, but not home-MICT. This contrasts previous findings in the period immediately after HIIT, where interstitial glucose concentrations have been shown to be maintained (6-hours post exercise)(Martín-San Agustín et al., 2020) or elevated (3-hours post exercise)(Aronson et al., 2019). This difference may be due to differences in the HIIT protocol used. Martin-San Augustin et al. (2020) investigated a lab-HIIT strength program, where Thera-Bands were used to provide resistance during

intervals (8x 20 second intervals interspersed with 10s rest). While, Aronson et al (2019) used a more demanding lab-HIIT protocol (3x 5 minute bouts of HIIT interspersed with 5 minutes of rest, HIIT bouts involved 5x 30 second intervals at 100-130% of peak power output interspersed with 30 seconds of rest at 50% peak power output) where exercise was completed in a fasted state, which has been found to elicit more stable glucose responses to exercise compared to postprandial exercise in people with Type 1 diabetes (Scott et al., 2019a, Scott et al., 2019b). In addition, both Aronson et al. (2019) and Martin-San Augustin et al. (2020) implemented post exercise glycaemic management strategies through reduced insulin dose and standardised dietary intake to ensure hypoglycaemia was avoided. Therefore, practical post exercise glycaemic management guidelines may be needed to manage the drop in blood glucose immediately following home-HIIT.

Home-HIIT increased TIR by 11% in the awake period immediately following exercise compared to CON and ~10% on the day and second day following exercise compared to home-MICT. TIR increases appeared to be primarily influenced by decreases in time spent in L1 hyperglycaemia. Riddell et al. (2020) have recently shown that exercise, performed in a free-living environment, increases TIR compared to non-exercise control days. However, Riddell et al. (2020) were unable to show differences in TIR between home-HIIT and home-based vigorous intensity continuous exercise. The different responses to continuous exercise between the studies may be due to the increased exercise intensity investigated by Riddell et al. (2020) (30 minutes at 70-80% HRmax) compared to the current study (30 minutes at 60-70% HRmax). Two other studies have investigated TIR following laboratory-based exercise compared to a non-exercise control period, neither of these studies found a change in TIR following lab-HIIT (Lee et al. 4x 4-minute intervals at 86-95% HR_{max} interspersed

with 3 minutes rest at 50-70% HR_{max}; Scott et al. 6x 1-minute intervals at 100% VO_{2peak} interspersed with 1-minute rest) or lab-MICT (Lee et al. 33 minutes at 60-70% HR_{max}; Scott et al. 30 minutes at 65% VO_{2peak}). Importantly, Riddell et al. (2020) and the current study investigated the effect of exercise under free-living conditions, investigating multiple bouts of exercise in each participant, while the controlled laboratory studies investigated TIR following one bout of exercise. The increases in TIR following home-HIIT potentially have clinically significant implications. A chronic increase of 10% in TIR has been shown to reduce the risk of retinopathy progression and development of microalbuminuria by 64% and 40%, respectively, and is associated with reductions in HbA1c values between 0.5 and 0.8% (Beck et al., 2019a, Beck et al., 2019b, Vigersky and McMahon, 2019).

Home-HIIT had no deleterious effects on GV compared to CON and had beneficial effects when compared to home-MICT. Compared to home-HIIT, home-MICT was found to increase glucose CV in the nocturnal period over the 14-day intervention period (4%), which appeared to be primarily a result of increased GV in the nocturnal period on second day following exercise (CV = 4%, SD = 0.35 mmol/L). GV was also increased compared to CON immediately after home-MICT but not home-HIIT. Riddell et al. (2020) found there to be no difference in glucose CV during the 24 hours following both home-HIIT and home-MICT compared to sedentary control days. However, this study only assessed glucose for up to 24 hours post exercise and therefore did not assess the nocturnal period on the second day following exercise. To the best of the authors knowledge, no study has yet investigated the effect of HIIT or MICT during the nocturnal period on the second day following exercise in adults with Type 1 diabetes, therefore this study provides important novel information. These findings could have implications for people with T1D, as glucose CV >36% has been

found to be associated with increased incidence of clinically significant hypoglycaemia (Gomez et al., 2019). Furthermore, GV is positively associated with cardiovascular events, retinopathy, nephropathy and increased brain glucose levels in people with Type 1 diabetes (Gorst et al., 2015, Hwang et al., 2019). As such, the current findings add to the potential of home-HIIT as a more effective exercise modality compared to traditional MICT for people with Type 1 diabetes. In addition, this finding provides further evidence for the effect of exercise at time points greater than 24-hours post exercise.

The key strength of this study is the robust assessment of the effects of home-HIIT and home-MICT on glycaemia in a free-living environment, and the extensive methods used to assess interstitial glucose data in line with current international consensus guidelines from the ADA (Battelino et al., 2019, Danne et al., 2017). Importantly, unlike previous free-living exercise studies in people with Type 1 diabetes which used self-reported exercise information, exercise intensity and timing were device derived, via heart rate monitoring, allowing adherence and compliance with exercise prescriptions and specific exercise timings to be objectively assessed. Furthermore, this is the first study to assess the effects of exercise on glycaemia for up to 48 hours post exercise, providing novel findings within the field of exercise and Type 1 diabetes.

The changes in glycaemia observed following exercise are likely due to a combination of physiological and behavioural factors. The current study was not designed to explore the physiological mechanism responsible for the differences in glycaemic control observed following home-HIIT and home-MICT. However, an aim of was to investigate differences in glycaemic management through diet and insulin dose following exercise. The only difference in glycaemic management behaviour observed

was an increase in CHO intake the day following home-MICT compared to CON, which may have contributed to the decreased TIR the day following home-MICT compared to home-HIIT. However, it is possible that the use of self-reported dietary intake, and insulin dose data for participants using MDI, may be a limitation in the approach of the current study. The use of MyFitnessPal to self-report energy intake has been found to under-report energy intake by 127 to 445 kcal/per day(Chen et al., 2019). MyFitnessPal also did not allow for data to be time stamped, meaning diet data could not be assessed using the same time points as glycaemic control. Finally, anecdotal reports suggest that the majority of participants did not include corrective fast-acting CHO intake following exercise in their food diary. The omission of corrective CHO doses may be important as previous work has suggested that fast-acting CHO was used to prevent or treat episodes of hypoglycaemia more often during MICT than HIIT (Scott et al., 2019b). Participants using MDI were also asked to self-report insulin dose using the FGM application/reader, this could have also resulted in an underestimation of insulin dose. Moreover, although insulin data was time stamped, participants tended to input insulin doses at the end of the day meaning that insulin doses post exercise could not be distinguished. Despite the limitations with self-reporting of glycaemic management behaviours outlined above, these methods were used consistently across all three interventions; therefore, findings should be comparable.

The accuracy of the Abbot libre freestyle FGM used in the current study has been found to be reduced when blood glucose is in a hypoglycaemic range as well as during exercise, with a mean absolute relative difference (MARD) of 31.6% and 29.8% respectively (Moser et al., 2019). However, these monitors have been found to be accurate when not exercising and not in hypoglycaemic range by several studies reporting MARD scores between 13.2% and 14.3% respectively (Aberer et

al., 2017, Moser et al., 2019, Boscari et al., 2018). Furthermore, in the current study, participants were unblinded to their FGM which may have resulted in improved glycaemic control (Tyndall et al., 2019). However, the Abbot libre freestyle FGM is commonly used in clinical practice within the United Kingdom and Europe by people with Type 1 diabetes, therefore being unblinded to the monitors represents a free-living environment for this population. Also, participants were unblinded in all 3 interventions, limiting any effect.

The sample within the current study were young adults (26 $\pm$ 7 years) with an average BMI close to healthy range (25.43 $\pm$ 4.29 kg/m^2) and had a female bias (female n = 7, male = 4). Therefore, the sample within the current study is not representative of the entire Type 1 diabetes population. A different demographic of participants may have yielded different physiological and behavioural responses to home-HIIT and home-MICT that would have affected post exercise glycaemia. Therefore caution should be taken when generalising the findings of this study to the whole Type 1 diabetes population. However, the findings from the current study are suitable for generalisation to otherwise healthy young adults with Type 1 diabetes.

The current study used an age dependent formula (220-age) to calculate predicted HR_{max} to set HR goals for participants during the exercise sessions in line with recommendations from the ADA. This method has its own limitations as factors such as smoking status, gender and fitness levels can affect HR_{max} (Zavorsky, 2000, Papathanasiou et al., 2013). However, Nes et al. (2013) could not find evidence of interaction with gender, self-reported PA, smoking status, VO_{2peak} or BMI and found that age alone is the best predictor of $HR_{max.}$

Finally, this study did not control for menstrual cycle within female participants. This was due to the demanding nature of the study protocol and difficulties recruiting

people with Type 1 diabetes. Brown et al. (2015) found decreased insulin sensitivity during the luteal phase in people with Type 1 diabetes. This was associated with an increased risk of hyperglycaemia during the periovulation and early luteal phases compared to the early follicular phase. It was common for participants in the current study to complete intervention periods consecutively, meaning the second 14-day intervention period was completed in a different phase to the first and third interventions (Brown et al., 2015). However, intervention order was randomised minimising any potential influence.

2.3.1 *Future Directions*

Future studies should aim to assess the effects of differing exercise modalities at a mechanistic level for up to 48 hours post exercise in adults with Type 1 diabetes by assessing Gd and Ga rate using a euglycaemic insulinemic method. A greater understanding of the effects of HIIT and MICT on glucose uptake and production for up to 48 hours post exercise would allow for improved post exercise glycaemic management strategies for people with Type 1 diabetes. Given that the effects of exercise on glycaemia are likely a combination of both physiological and behavioural factors, further investigation into the effects of exercise on post exercise glycaemic management is required. The current study and Riddell et al (2020) are the only studies to assess the effects of HIIT and MICT in free-living environments in people with Type 1 diabetes, and both of these studies failed to identify differences in the glycaemic management behaviours between interventions. Therefore, thought must be given to the methods used to assess dietary intake and insulin dosages post exercise to ensure this pivotal data is not missed.

Future research should also consider residual ß-cell function in participants with Type 1 diabetes as previous work has assumed absolute insulin deficiency (American

Diabetes, 2012). However, more recently studies have found that high proportions (80%) of people with Type 1 diabetes are insulin microsecretors, with people diagnosed with Type 1 diabetes over the age of 18 years having greater residual ß-cell function for longer post diagnosis than patients diagnosed under the age of 18 years(Oram et al., 2015, Davis et al., 2015). Patients under18 years of age often had residual ß-cell function at 3-5 years from diagnosis, but this was lost 10 years post diagnosis (Davis et al., 2015). Residual ß-cell function has been shown to increase TIR following exercise in adults with Type 1 diabetes(Taylor et al., 2020). The effects of interindividual differences in ß-cell function are likely to effect results and should be considered in future studies investigating the effects of exercise in people with Type 1 diabetes as well as within exercise prescriptions for people in this population.

Finally, future research and exercise prescriptions in people with Type 1 diabetes should consider prior PA levels, especially involving HIIT. The home-HIIT protocol used in this study included 6-minutes of working intervals which may leave patients with high prior PA levels feeling underwhelmed following exercise and even lose motivation to exercise (Scott et al., 2019c). A recent home-HIIT feasibility study included bi-weekly increases of two working intervals into a six-week exercise intervention and found that motivation was maintained. Therefore to maintain motivation, sense of achievement and exercise benefits with HIIT, a different number of exercise intervals may need to be prescribed for patients dependent on prior PA levels. However, consideration must be provided to the minimum volume of exercise required to gain the physiological benefits of HIIT.

2.3.2 *Conclusions*

In conclusion, this study provides evidence that both home-HIIT and home-MICT are safe exercise modalities for people with Type 1 diabetes, as time spent in serious,

clinically significant hypoglycaemia was not increased by either exercise mode compared to a non-exercise control. However, home-HIIT may result in more desirable effects on TIR and GV following exercise than home-MICT, which may have clinically significant implications for people with Type 1 diabetes. Finally, the study provides novel evidence that exercise has the potential to influence glycaemic control for up to 48 hours in people with Type 1 diabetes.

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Appendix 1.

Raw glycaemic data during the 14-day intervention periods. Data presented as means ±SD.

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	8.8 ± 1.5	9.0 ± 1.7	9.0 ± 1.2
GMI (mmol/L)	7.1 ± 0.7	7.2 ± 0.7	7.2 ± 0.5
% TIR	64.4 ± 18.8	59.7 ± 18.6	60.6 ± 17.3
% TAR	30.4 ± 18.0	34.8 ± 19.8	34.7 ± 16.4
% Time in L1 Hyperglycaemia	20.4 ± 10.7	22.6 ± 11.0	24.8 ± 10.5
% Time in L2 Hyperglycaemia	9.9 ± 10.0	12.2 ± 11.0	9.9 ± 7.2
% TBR	5.3 ± 4.0	5.5 ± 5.0	4.7 ± 3.5
% Time in L1 Hypoglycaemia	4.0 ± 2.7	3.9 ± 3.2	3.0 ± 1.8
% Time in L2 Hypoglycaemia	1.3 ± 1.5	1.6 ± 2.1	1.7 ± 1.9
Number of Hyperglycaemic episodes	28.9 ± 10.9	26.3 ± 10.9	29.6 ± 9.5
Number of Hypoglycaemic episodes	11.2 ± 7.4	11.0 ± 9.2	9.8 ± 5.3
SD (mmol/L)	3.3 ± 1.2	3.5 ± 1.0	3.3 ± 0.8
CV (%)	36.7 ± 8.2	38.1 ± 7.3	36.0 ± 6.1

Appendix 2.

Raw glycaemic data during the nocturnal periods of the 14-day intervention periods. Data presented as means ±SD.

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	9.3 ± 2.5	9.0 ± 2.1	9.3 ± 1.8
% TIR	58 ± 27	57 ± 21	54 ± 24
% TAR	36 ± 27	36 ± 24	40 ± 24
% Time in L1 Hyperglycaemia	23 ± 14	24 ± 14	28 ± 15
% Time in L2 Hyperglycaemia	13 ± 18	12 ± 13	12 ± 12
% TBR	6 ± 6	7 ± 9	5 ± 6
% Time in L1 Hyperglycaemia	4 ± 4	4 ± 5	2 ± 3
% Time in L2 Hyperglycaemia	2 ± 2	3 ± 5	3 ± 4
Number of Hyperglycaemic episodes	8 ± 4	8 ± 4	10 ± 3
Number of Hypoglycaemic episodes	2 ± 2	2 ± 2	2 ± 1
SD (mmol/L)	3.2 ± 1.1	3.4 ± 1.1	3.2 ± 1.0
CV (%)	34 ± 7	38 ± 9	34 ± 10

Appendix 3.

Raw glycaemic data during the awake periods of 14-day intervention periods.
Data presented as means ±SD.

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	8.7 ± 1.5	9.0 ± 1.7	8.9 ± 1.1
% TIR	65 ± 19	61 ± 19	62.6 ± 15.3
% TAR	30 ± 17	35 ± 19	33.0 ± 14.5
% Time in L1 Hyperglycaemia	20 ± 10	22 ± 11	23.7 ± 9.1
% Time in L2 Hyperglycaemia	10 ± 10	12 ± 11	9.3 ± 6.5
% TBR	5 ± 4	5 ± 4	4.4 ± 3.9
% Time in L1 Hyperglycaemia	20 ± 10	22 ± 11	23.7 ± 9.1
% Time in L2 Hyperglycaemia	9 ± 10	12 ± 11	9.3 ± 6.5
Number of Hyperglycaemic episodes	26 ± 11	25 ± 11	27.7 ± 12.7
Number of Hypoglycaemic episodes	10 ± 7	10 ± 8	8.8 ± 5.2
SD (mmol/L)	3.3 ± 1.2	3.4 ± 1.0	3.2 ± 0.8
CV (%)	37 ± 8	38 ± 7	36.0 ± 6.2

Appendix 4.

Raw glycaemic data during period A0. Data presented as mean ±SD

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	8.8 ± 3.2	9.3 ± 2.9	9.6 ± 1.8
% TIR	65 ± 26	61 ± 24	54 ± 24
% TAR	29 ± 27	34 ± 26	43 ± 23
% Time in L1 Hyperglycaemia	16 ± 14	19 ± 12	30 ± 15
% Time in L2 Hyperglycaemia	13 ± 23	16 ± 19	13 ± 15
% TBR	6 ± 8	5 ± 5	3 ± 4
% Time in L1 Hypoglycaemia	4 ± 5	3 ± 3	1 ± 2
% Time in L2 Hypoglycaemia	2 ± 4	1 ± 2	2 ± 3
Number of Hyperglycaemic episodes	0 ± 0	1 ± 1	1 ± 1
Number of Hypoglycaemic episodes	0 ± 0	0 ± 0	0 ± 0
SD (mmol/L)	2.1 ± 0.8	2.4 ± 0.7	2.0 ± 0.6
CV (%)	25 ± 8	26 ± 6	22 ± 5

Appendix 5.

Raw glycaemic data during the period N1. Data presented as mean ±SD

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	8.7 ± 1.9	9.3 ± 2.9	9.2 ± 2.1
% TIR	62 ± 1	56 ± 23	51 ± 27
% TAR	31 ± 9	37 ± 27	42 ± 29
% Time in L1 Hyperglycaemia	20 ± 14	20 ± 16	32 ± 23
% Time in L2 Hyperglycaemia	11 ± 23	17 ± 21	9 ± 8
% TBR	7 ± 9	7 ± 11	7 ± 12
% Time in L1 Hypoglycaemia	5 ± 6	3 ± 5	4 ± 5
% Time in L2 Hypoglycaemia	3 ± 23	4 ± 8	4 ± 8
Number of Hyperglycaemic episodes	1 ± 16	1 ± 0	1 ± 0
Number of Hypoglycaemic episodes	0 ± 13	0 ± 0	0 ± 0
SD (mmol/L)	1.5 ± 0.3	1.5 ± 0.5	1.4 ± 0.8
CV (%)	19 ± 0	18 ± 6	16 ±9

Appendix 6.

Raw glycaemic data during the period A1. Data presented as mean ±SD

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	8.2 ± 1.1	9.1 ± 1.6	8.7 ± 1.3
% TIR	70 ± 15	60 ± 18	65 ± 16
% TAR	24 ± 13	36 ± 18	30 ± 16
% Time in L1 Hyperglycaemia	18 ± 9	23 ± 12	21 ± 11
% Time in L2 Hyperglycaemia	7 ± 7	13 ± 11	9 ± 7
% TBR	6 ± 5	5 ± 4	5 ± 5
% Time in L1 Hypoglycaemia	5 ± 4	4 ± 4	4 ± 3
% Time in L2 Hypoglycaemia	1 ± 1	0 ± 1	1 ± 2
Number of Hyperglycaemic episodes	2 ± 1	2 ± 1	2 ± 1
Number of Hypoglycaemic episodes	1 ± 1	1 ± 1	1 ± 1
SD (mmol/L)	2.9 ± 1.0	3.0 ± 1	2.8 ± 0.7
CV (%)	35 ± 8	33 ± 9	32 ± 5

Appendix 7.

Raw glycaemic data during the period N2. Data presented as mean ±SD

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	9.2 ± 2.5	-0.5 ± 2.2	9.5 ± 2.5
% TIR	58 ± 29	-6 ± 24	57 ± 33
% TAR	35 ± 30	-0 ± 23	38 ± 31
% Time in L1 Hyperglycaemia	20 ± 18	2 ± 14	24 ± 18
% Time in L2 Hyperglycaemia	15 ± 18	-3 ± 13	14 ± 19
% TBR	7 ± 10	7 ± 13	5 ± 6
% Time in L1 Hypoglycaemia	4 ± 4	5 ± 10	3 ± 4
% Time in L2 Hypoglycaemia	3 ± 7	2 ± 6	2 ± 4
Number of Hyperglycaemic episodes	1 ± 0	0 ± 0	1 ± 0
Number of Hypoglycaemic episodes	0 ± 0	0 ± 0	0 ± 0
SD (mmol/L)	1.2 ± 0.6	0.4 ± 1	1.2 ± 0.4
CV (%)	14 ± 5	4 ± 5	14 ± 4

Appendix 8.

Raw glycaemic data during the period A2. Data presented as mean ±SD

	Home-HIIT	Home-MICT	CON
Mean Glucose (mmol/L)	8.8 ± 1.3	9.0 ± 1.8	8.9 ± 1
% TIR	69 ± 21	58 ± 21	63 ± 20
% TAR	27 ± 19	35 ± 22	33 ± 18
% Time in L1 Hyperglycaemia	20 ± 14	23 ± 12	23 ± 12.
% Time in L2 Hyperglycaemia	8 ± 9	12 ± 12	10 ± 8
% TBR	4 ± 5	7 ± 6	4 ± 4
% Time in L1 Hypoglycaemia	3 ± 3	5 ± 4	3 ± 3
% Time in L2 Hypoglycaemia	1 ± 3	2 ± 4	1 ± 2
Number of Hyperglycaemic episodes	1 ± 1	1 ± 1	1 ± 1
Number of Hypoglycaemic episodes	0 ± 1	1 ± 1	0 ± 0
SD (mmol/L)	2 ± 1	2.7 ± 0.7	2.6 ± 0.9
CV (%)	28 ± 112	31 ± 8	29 ± 8

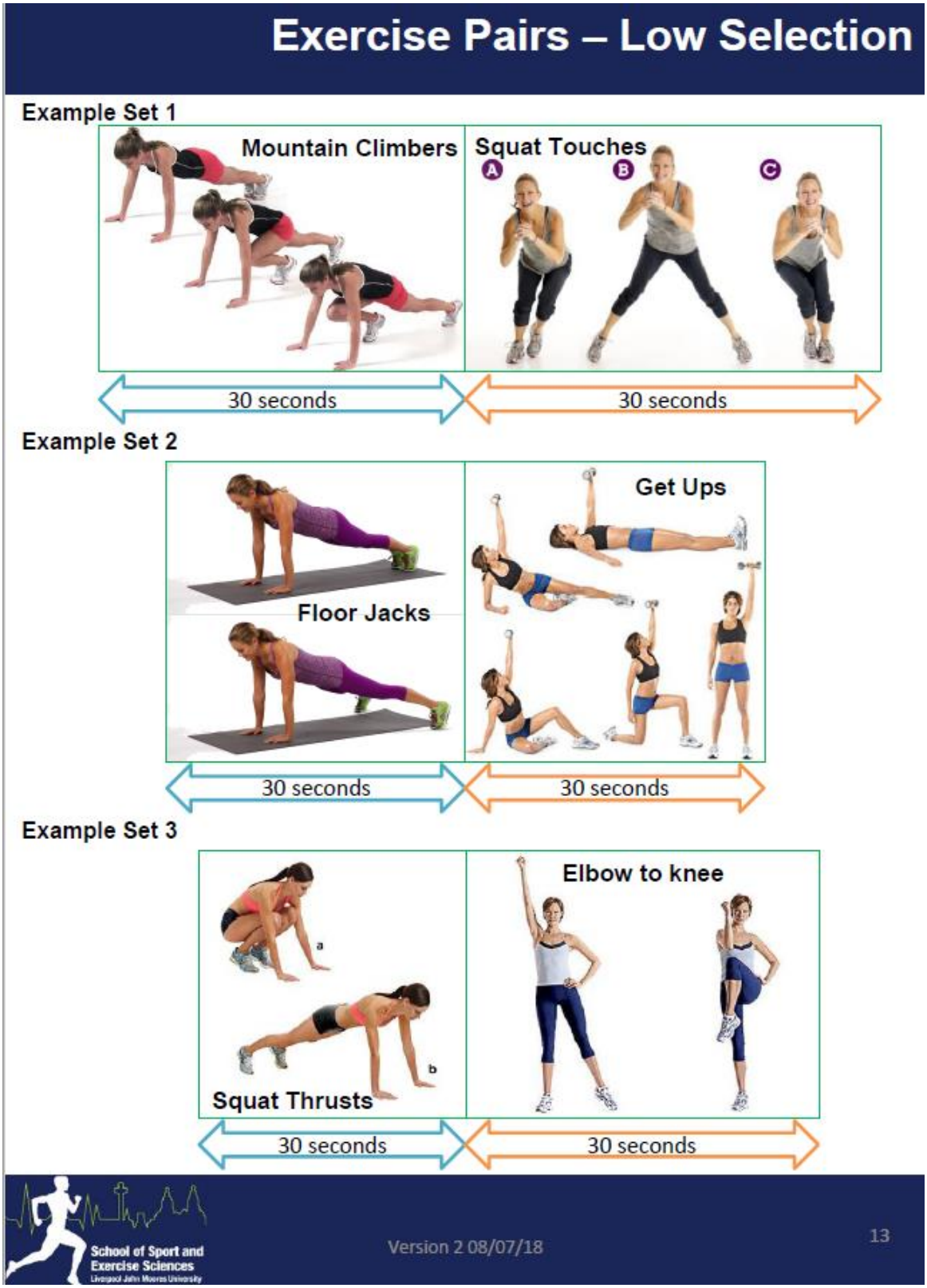
Appendix 9.

Raw dietary intake and insulin data during the 14-day intervention period, the day of exercise, the day following exercise and the second day following exercise. Data presented as mean ± SD

Time-point	Variable	home-HIIT	home-MICT	CON
Intervention	Calorie intake (Kcal)	1487 ± 460	1761 ± 647	1633 ± 789
	CHO intake (grams)	155 ± 69	189 ± 75	176 ± 71
	Bolus Insulin (Units)	19 ± 6	16 ± 6	19 ± 8
	Basal Insulin (Units)	19 ± 5	20 ± 6	18 ± 5
	TDD/kg (Units.kg)	0 ± 0	0 ± 0	0 ± 0
Day of exercise	Calorie intake (Kcal)	1552 ± 317	1534 ± 438	1486 ± 378
	CHO intake (grams)	174 ± 47	170 ± 44	162 ± 55
	Bolus Insulin (Units)	17 ± 6	18 ± 7	20 ± 7
	Basal Insulin (Units)	20 ± 6	18 ± 5	19 ± 5
	TDD/kg (Units.kg)	0 ± 0	0 ± 0	1 ± 0
Day following exercise	Calorie intake (Kcal)	1563 ± 429	1619 ± 412	1454 ± 460
	CHO intake (grams)	166 ± 45	182 ± 49	159 ± 69
	Bolus Insulin (Units)	20 ± 5	19 ± 5	20 ± 6
	Basal Insulin (Units)	19 ± 7	18 ± 5	19 ± 5
	TDD/kg (Units.kg)	1 ± 0	0 ± 0	1 ± 0
Second day following exercise	Calorie intake (Kcal)	1761 ± 647	1633 ± 789	1487 ± 460
	CHO intake (grams)	189 ± 75	176 ± 71	155 ± 69
	Bolus Insulin (Units)	16 ± 6	19 ± 8	19 ± 6
	Basal Insulin (Units)	20 ± 6	18 ± 5	19 ± 5
	TDD/kg (Units.kg)	0 ± 0	0 ± 0	0 ± 0

Appendix 10.

Images below show the home-HIIT workbooks that participants received upon commencing the study

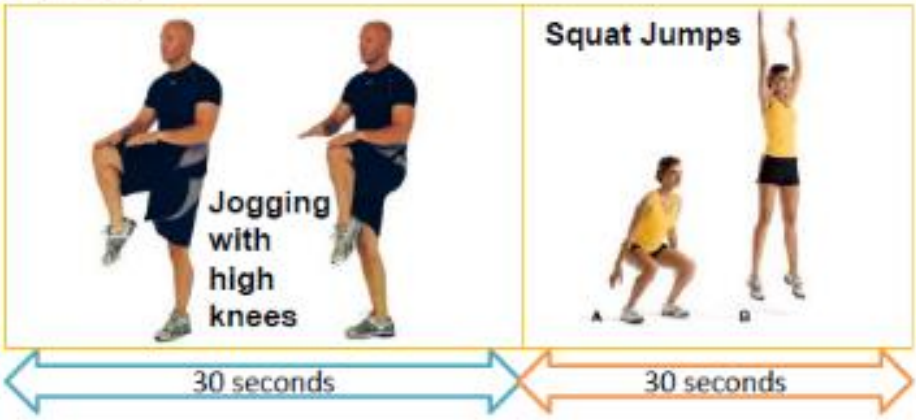


Exercise Pairs – Medium Selection

Example Set 4

Example Set 5

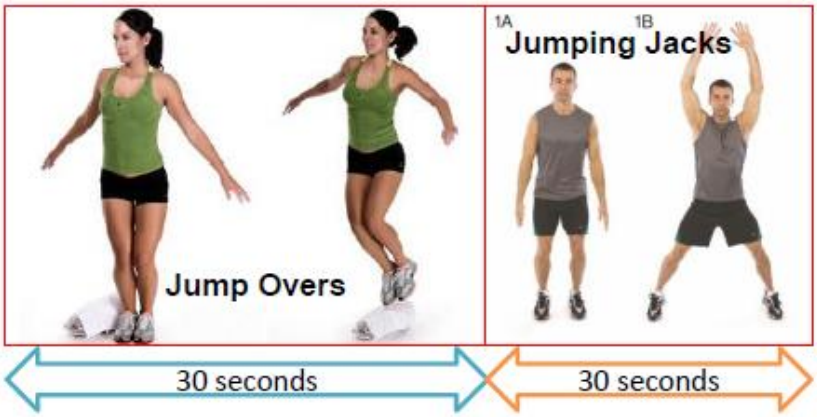
Example Set 6



Exercise Pairs – High Selection

Example Set 7

Example Set 8



Example Set 9