High-intensity physical activity for improving glucose regulation: can science justify IT?

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Abstract

High-intensity exercise for improving glucose regulation: can science justify IT?

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Background
Interest in high-intensity interval training (HIIT) has recently resurfaced as a way to improve adherence to physical activity by addressing the common barrier of a “lack of time”. The benefit HIIT and vigorous-intensity physical activity (VPA) have on cardiorespiratory fitness is well established however, the effects on glucose regulation and insulin sensitivity in individuals at high risk of type 2 diabetes (T2DM) are less clear.

Aims
The aims of this thesis were: to pool the available evidence regarding the effects of HIIT on markers of glycaemic control and insulin sensitivity, conduct observational analyses investigating the relationship between A) continuously and intermittently (≥10 minutes and <10 minutes, respectively) accumulated physical activity and B) increasing exercise intensity with markers of insulin sensitivity, and finally, to design and undertake an acute experimental study comparing the effect of high-intensity interval and moderate-intensity continuous exercise with sitting on post-challenge glucose and insulin responses.

Key findings
In individuals at high risk of T2DM, HIIT improves HbA1c and insulin sensitivity to a similar extent as moderate-intensity continuous training, despite a lower overall workload. Continuously, but not sporadically, accumulated physical activity is positively associated with insulin sensitivity, and increasing physical activity intensity is associated with increasingly greater benefits in glucose regulation and insulin sensitivity. High-intensity interval exercise significantly improves the postprandial insulin response to a greater extent than moderate-intensity continuous exercise and sitting. Both forms of exercise are effective at reducing glycaemic variability.

Conclusions
This thesis demonstrates that VPA is more effective than moderate-intensity physical activity at improving insulin sensitivity for a given unit of time. It shows that these benefits of vigorous-intensity physical activity can be achieved by performing HIIT, which may be a viable option for individuals at high risk of T2DM. HIIT could therefore be incorporated into the physical activity guidelines as a recommended health tool for improving diabetes outcomes.
It was always for you, Grandad.
Acknowledgements

My experiences of physical exertion in extreme environments have been far more within my comfort zone than completing this PhD has turned out to be. Thank you to those who supported me through it and helped me grow as a researcher and a person.

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Heartfelt thanks go to those who helped me set up and run the GO for IT study. This has been the most challenging part of my PhD and I would like to thank the following people for their on-going support and for keeping me afloat: To Ros Downing, Jill Clanchy and Nicola Tynan for their help with lab-related matters. To Chris Brough, Priti Odedra and Steve Hartshorn for their dedication to patient care and data collection despite not using the results themselves. A special mention must go to Priti whose ability, understanding, motivation and attitude was invaluable. Without you, I would not have been able to carry out this study. Thanks to Joe Henson and Jack Sargeant for taking my place when I couldn’t be there. To Tim Skelton, for trusting me to conduct this project. Thank you to the participants who took part. Your commitment and willingness to endure the study procedures was humbling. Thank you for your interest, engagement and trust. You are why I am inspired to work in this field.

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Contributions

Each chapter begins with my contribution to the study however, I would like to credit the following people for their input, without them the work would not have been possible.

Chapter 2

I would like to thank Dr. Laura Gray for helping to teach me how to perform a meta-analysis using Stata. Without the loan of several text books, sign-posting to relevant lectures and checking over my numerous incorrect attempts at coding, I would not hold the skills I do, nor have produced such a high-impact piece of work. I would like to thank Gary O’Donovan for bringing to my attention the PRISMA guidelines and for his thorough independent data extraction.

Chapter 3

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Chapter 4

James King offered intellectual input into the study design and running. Chris Brough conducted thorough screening of participants, ensuring they were safe to take part. Priti Odedra and Steve Hartshorn collected blood and cared for the participants at times I could not be present. Without them, I would have no participants and no samples. Jack Sargeant also ran several study days in exchange for samples.
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<td>Free 8-iso prostaglandin 2α</td>
</tr>
<tr>
<td>ACSM</td>
<td>American College of Sports Medicine</td>
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<tr>
<td>AIT</td>
<td>Aerobic interval training</td>
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<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>AMPK</td>
<td>Adenosine monophosphate-activated protein kinase</td>
</tr>
<tr>
<td>(i)AUC</td>
<td>(incremental) Area under the curve</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CGM</td>
<td>Continuous glucose monitoring</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CON</td>
<td>Non-exercising control</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DPP-4</td>
<td>Dipeptidylpeptidase-4</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eNOS</td>
<td>Endogenous nitric oxide synthase</td>
</tr>
<tr>
<td>FFA</td>
<td>Free fatty acid</td>
</tr>
<tr>
<td>GEE</td>
<td>General estimating equation</td>
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<tr>
<td>GLUT-4</td>
<td>Glucose transporter type 4</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
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<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
</tr>
<tr>
<td>HIIE</td>
<td>High-intensity interval exercise (single bout)</td>
</tr>
<tr>
<td>HIIT</td>
<td>High-intensity interval training (several sessions over a period of time)</td>
</tr>
<tr>
<td>HOMA-IS</td>
<td>Homeostatic model assessment of insulin sensitivity</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin-6</td>
</tr>
<tr>
<td>LDC</td>
<td>Leicester Diabetes Centre</td>
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<tr>
<td>LICT</td>
<td>Light-intensity continuous training</td>
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<tr>
<td>LPA</td>
<td>Light-intensity physical activity</td>
</tr>
<tr>
<td>MAGE</td>
<td>Mean amplitude of glycaemic excursions</td>
</tr>
<tr>
<td>MET</td>
<td>Metabolic equivalent of task</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>MICE</td>
<td>Moderate-intensity continuous exercise</td>
</tr>
<tr>
<td>MICT</td>
<td>Moderate-intensity continuous training</td>
</tr>
<tr>
<td>MPA</td>
<td>Moderate-intensity physical activity</td>
</tr>
<tr>
<td>MVPA</td>
<td>Moderate-vigorous intensity physical activity</td>
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<tr>
<td>NDPP</td>
<td>National Diabetes Prevention Programme</td>
</tr>
<tr>
<td>NDH</td>
<td>Non-diabetic hyperglycaemia</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<tr>
<td>PPI</td>
<td>Patient and public involvement</td>
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<tr>
<td>PPAR-γ</td>
<td>Proliferator-activated receptor-γ</td>
</tr>
<tr>
<td>RPE</td>
<td>Rating of perceived exertion</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SCFA</td>
<td>Short chain fatty acid</td>
</tr>
<tr>
<td>SGLT2</td>
<td>Sodium-glucose transport protein 2</td>
</tr>
<tr>
<td>SIE</td>
<td>Sprint interval exercise</td>
</tr>
<tr>
<td>SIT</td>
<td>Sprint interval training</td>
</tr>
<tr>
<td>T2DM</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>TZD</td>
<td>Thiazolidinedione</td>
</tr>
<tr>
<td>UHL</td>
<td>University Hospitals of Leicester</td>
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<tr>
<td>VO₂</td>
<td>Oxygen uptake</td>
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<tr>
<td>VPA</td>
<td>Vigorous-intensity physical activity</td>
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<tr>
<td>VT</td>
<td>Ventilatory threshold</td>
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Definitions

**β-cell function**
The ability of the pancreatic β-cells to respond to changes in blood nutrient content and varying degrees of insulin sensitivity such as reducing insulin stimulation during exercise.[1]

**Dysglycaemia**
A composite of any combination of non-diabetic hyperglycaemia, impaired glucose tolerance or impaired fasting glucose.

**Exercise**
Exercise is a subset of physical activity that is planned ... structured ... has as a final or an intermediate objective for the improvement or maintenance of physical fitness.[2]

**Glycaemic variability**
Oscillations in daily blood glucose levels including postprandial spikes, hyper- and hypoglycaemic events.

**High-intensity interval exercise**
Repeated short (<5 min) bursts of vigorous or higher intensity exercise interspersed with recovery periods of either lower intensity physical activity or complete rest performed acutely (single bout).

**High-intensity interval training**
High-intensity interval exercise performed more than once per week for a minimum of two weeks.

**Impaired fasting glucose**
Fasting glucose level greater than 6.1 mmol·L⁻¹ and less than 6.9 mmol·L⁻¹.[3]

**Impaired glucose tolerance**
Two hour glucose levels greater than 7.8 mmol·L⁻¹ and less than 11.1 mmol·L⁻¹ following consumption of a 75g glucose load in an oral glucose tolerance test.[3] Also referred to as postprandial hyperglycaemia.

**Insulin Sensitivity**
When a normal level of insulin is able to adequately stimulate glucose uptake.[4]
Physical Activity

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure.[5]

Signs (of disease)

Objective evidence or observations of disease presence.

Symptoms (of disease)

Subjective experiences of a disease i.e. what or how the patient feels

\( \text{VO}_2\text{max} \) (maximal oxygen uptake)

The oxygen uptake attained during maximal exercise intensity that cannot be increased despite further increases in exercise workload, thereby defining cardiorespiratory fitness.[6]

\( \text{VO}_2\text{peak} \) (peak oxygen uptake)

The maximal oxygen uptake attained during a maximal exercise test that does not necessarily reach a plateau. Indicates that the individual may not have reached their maximal capacity.
“Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save and preserve it”

Plato, 350 BC
1. Background

1.1 Type 2 Diabetes

1.1.1 Prevalence & implications

An estimated 422 million people worldwide are thought to suffer from diabetes, 85-90% of whom have type 2 diabetes (T2DM). This number has grown exponentially throughout the last 35 years, mainly due to increasing prevalence in developing countries, but also attributable to the growing and aging populations of the “developed” world. In the UK, 6% of the population suffers from T2DM,[7] with a further 1% thought to be living with the condition undiagnosed.[8] T2DM and its associated complications increases medication prescription, hospital admissions and risk of premature death.[9] There is also a high prevalence of individuals with non-diabetic hyperglycaemia (NDH), estimated to be 7.8% of the population worldwide. NDH is defined as an HbA1c level above normal but not high enough to be classified as T2DM. According to NICE guidelines, this level is 6.0-6.4% (42-46 mmol·mol⁻¹). These individuals are at a higher risk of developing T2DM than those with normoglycaemia, with a 5-10% conversion rate per year.[10] The cost of treating T2DM and its complications costs the NHS an estimated £10 billion annually; 10% of the total budget, with this expected to rise to 17% by 2036. The economic burden of T2DM; sick days and reduced productivity – by individuals at work but working inefficiently (“presenteeism”) – is estimated to be an additional £13 billion per year.[11]

1.1.2 Definition & diagnosis

T2DM is defined as a metabolic disorder characterised by chronic hyperglycaemia.[12] T2DM is diagnosed if fasting plasma glucose levels are greater than 7.0 mmol·L⁻¹ and/or glycated haemoglobin levels are greater than 6.5% (48.0 mmol·L⁻¹).[13] T2DM can also be diagnosed following an oral glucose tolerance test (OGTT) if plasma glucose levels are greater than 11.1 mmol·L⁻¹ two hours after consumption of a 75g glucose load.[3]

1.1.3 Epidemiology

For probably more than a century, T2DM has been associated with obesity.[14] Indeed, obesity, most commonly defined as a body mass index (BMI; weight in kg divided by height in metres squared) ≥30kg·m⁻², has received much attention in the investigation of risk factors for T2DM, and not without good reason: the finding that risk of T2DM is positively associated with BMI is strong and consistent.[15, 16] Other risk factors for T2DM; notably family history, dietary
composition, alcohol consumption, smoking and physical inactivity, have also been established for decades.\[17\]

Interestingly, the “recent” rise in the global prevalence of T2DM was attributed to “Westernisation” (reduced activity levels and hypercaloric diets) as early as 1934,\[18\] and confirmed between 1960-70 during the urbanisation of isolated, rural communities such as the Pima Indians,\[19\] Pacific Islanders\[20, 21\] and several others.\[22\] Since then, prospective observational studies have consistently shown that the risk of developing T2DM is exponentially higher in those who are obese\[23\] and inactive than those who are normal weight and whom participate in regular physical activity.\[24\] For instance, in the male physicians study, men who performed physical activity once per week were 20% (9-44%) less likely to develop T2DM than those not reporting any physical activity, even after adjustment for BMI.\[25\] Similar relationships were observed in women, although the relationship was not as strong when controlling for BMI.\[26\] A cross-cultural study of non-Caucasian individuals also concluded that both BMI and physical inactivity were independently associated with T2DM and impaired glucose tolerance.\[27\]

1.1.4 Pathogenesis

Although hyperglycaemia is the manifestation of T2DM, is toxic to blood vessels and causes damage downstream at a cellular level, T2DM is actually a condition of impaired insulin action; the consequence of which is hyperglycaemia. Eventually, with increasing strain on the pancreas, impaired insulin production also becomes a cause of hyperglycaemia in T2DM. Insulin is the main regulator of blood glucose levels. It is a hormone produced in the pancreas and secreted by pancreatic β-cells. Insulin keeps blood glucose within narrow limits by regulating glucose uptake into muscle and fat cells, as well as influencing hepatic glucose output.\[28\] In healthy individuals, β-cells react to changes in blood nutrient content, stimulating or inhibiting the production of insulin in high or low nutrient concentrations respectively.\[1\] β-cells are also able to adapt to varying states of insulin sensitivity e.g. reducing insulin secretion following physical activity. When glucose tolerance is impaired, as in NDH and T2DM, β-cell function is inadequately low for a specific degree of insulin resistance and either insulin secretion, insulin action or both are impaired and hyperglycaemia ensues.\[29\] Insulin resistance is therefore a recognised precursor to T2DM.\[12\]

In healthy individuals, acute elevation of plasma glucose, usually the result of consumption of a meal, stimulates pancreatic β-cells to release insulin into the blood stream. At the skeletal muscle, which is responsible for approximately 80% of glucose disposal,\[30\] insulin binds with a receptor on the cell membrane (insulin receptor-1; IRS-1) which begins a cascade of signalling
that ultimately leads to the translocation of GLUT-4 (Glucose transporter type 4) to another site on the cell membrane (Figure 1.1). Glucose then enters the cell via the GLUT-4 carrier protein and is either transported to the mitochondria for respiration or synthesised into glycogen.

Physical inactivity and overweight/obesity results in visceral adipose tissue expansion via accumulation of stored triglycerides. Downstream, this leads to increases in both circulating and intracellular inflammatory cytokines and non-esterified free fatty acids that cause disruption to the insulin signalling pathway in a self-perpetuating manner. The consequent reduction in glucose uptake means that plasma glucose levels rise above the normal narrow limits. Over time, chronic NDH becomes toxic and damages, amongst others, the very cells that buffer changes in glucose concentration; the pancreatic β-cells. Given that most obese individuals with insulin resistance and/or dysglycaemia do not develop T2DM, it appears that impairment of β-cell function to a level at which insulin production is insufficient to compensate for reduced insulin sensitivity is what distinguishes those who progress to T2DM from those who do not.[31]
Figure 1.1 Critical nodes of the insulin signalling cascade and the effects of physical activity (L) and obesity (R).

Normally, an increase in plasma glucose stimulates pancreatic β-cells to release insulin. At the cell membrane, insulin binds to a receptor. This is recognised by IRS-1 which leads to the phosphorylation of PI3-K. PI3-K then activates Akt via PDK-1. The activated form of Akt stimulates GLUT-4 translocation to the cell membrane. Obesity disrupts this pathway as excess circulating FFA’s induce oxidative stress, inflammation and cytokine production which cause a phosphorylation of IRS-1 that prevents it from phosphorylating PI3-kinase. The lipid “ceramide” is also increased in obesity and inhibits Akt activation. NADPH oxidase also causes oxidative stress and inhibits PPAR-γ which in turn reduces GLUT-4 expression. Physical activity induces an insulin independent contraction-mediated pathway that stimulates GLUT-4 translocation and activation.

Stimulates: □□□□□ Inhibits: A CoA – acyl coenzyme A; Akt – serine threonine kinase; AMPK – adenosine monophosphate-activated protein kinase; eNOS – endogenous nitric oxide synthase; FFA – free fatty acid; GLUT-4 – glucose transporter type 4; GSK-3 – glycogen synthase kinase-3; IL-6 – interleukin 6; IKK – inhibitor of nuclear factor kappa B kinase; IRS-1 – insulin receptor substrate 1; JNK – c-Jun N-terminal kinase; NADPH – nicotinamide adenine dinucleotide phosphate; NO – nitric oxide; PDK-1 - Phosphoinositide-dependent kinase-1; PI3-K – Phosphoinositide 3-kinase; PKC – protein kinase C; PPAR – Peroxisome proliferator-activated receptor; R_4 – rate of disposal; ROS reactive oxygen species; TNF – tumour necrosis factor
Here, I will provide a brief description of the mechanisms by which physical inactivity and overweight/obesity cause insulin resistance. These signalling cascades are depicted in Figure 1.1.

1.1.4.1 Inflammation

Adipose tissue is metabolically active and insulin sensitive. Excessive levels of nutrients i.e. glucose and fatty acids released into the blood stream from the gastro-intestinal tract can cause adipocyte stress. In addition, rapid adipocyte hypertrophy can result in localised hypoxia as the supporting vasculature may be unable to expand at the same rate, limiting oxygen and nutrient levels.[32] On exposure to these stressors, an inflammatory cascade of pro-inflammatory cytokines including tumour necrosis factor-α, interleukin-6 (IL-6) and C-reactive protein (CRP) is released into the circulation.[33] These cytokines stimulate an intracellular inflammatory process which, via a number of pathways, inhibit IRS-1 activation and translocation of GLUT-4 (right hand side of Figure 1.1).[34] Adiposity induced cytokines also diminish β-cell function as circulating IL-6 also stimulates inflammation in these cells. Additionally, IL-6 inhibits glycogen synthesis which signals for a reduction in glucose uptake. Intramyocellular inflammatory cytokines are also produced in response to reactive oxygen species (ROS) which accumulate because of mitochondrial stress from increased levels of intracellular free fatty acids (FFA).

1.1.4.2 Fatty acid accumulation

Fatty acids are stored primarily as triacylglycerols in adipose tissue. Signals (catecholamines, cortisol, low insulin concentration) for the lipolysis of triacylglycerols release FFA’s into the blood stream.[35] Some of these are delivered to skeletal muscle where a proportion will be oxidised as a readily available source of energy. Surplus (the result of excessive nutrient intake), reduced FFA oxidation (as a result of physical inactivity) and increased expression of lipoprotein lipase,[36] will stimulate the formation of acyl-coenzyme A (ACoA) and ceramide. These proteins, by impairing IRS-1 and serine threonine kinase (Akt), prevent GLUT-4 translocation to the cell membrane (right hand side of Figure 1.1). Accumulation of FFA’s also inhibits skeletal muscle glucose metabolism and stimulates hepatic gluconeogenesis. This promotes lipolysis further leading to even higher levels of FFA’s.[29] Circulating FFA’s exacerbate β-cell inflammation as they inhibit intracellular production of anti-inflammatory proteins. Eventually, as blood glucose levels gradually increase, the β-cell’s buffering ability to clear waste products from glucose metabolism is impaired. This leads to the generation of large amounts of ROS which causes damage to parts of the cell.[29]
1.1.4.3 Other factors

Genetics

While the incidence of T2DM correlates strongly with reductions in physical activity levels and that this recent increase is associated with the “technological revolution”, it is generally accepted that there is also a genetic component in the development of T2DM. For instance, offspring of one parent with T2DM have a 40% risk of also developing the condition, with the risk increasing to 70-90% when both parents have the condition. Interestingly, a study in Sweden found that the highest relative risk of developing T2DM was in individuals with two affected sibling, irrespective of parental diabetes status. Further support for a genetic component of T2DM comes from twin studies which suggest that the concordance rate for monozygotic twins is higher than that for dizygotic twins, with concordance reported from 20-91% and 10-43% respectively. Although these ranges overlap, within studies the concordance is always higher in monozygotic than dizygotic twins.

Identifying the genes involved in the development of T2DM has proved difficult despite advances in genetic mapping. This is likely due to interactions between genes and genes and the environment. Nonetheless, mutations of a few genes appear to be associated with risk of T2DM within a specific ethnic group, with a few potentially common between ethnicities. These genes are predominantly associated with insulin production and receptor signalling, glucose transport and inflammation.

Epigenetics has recently attracted attention as it brings together environmental and genetic factors. Defined as; reversible and modifiable changes in heritable gene expression in the absence of changes in DNA sequence, there is evidence that epigenetic changes are linked to the development of T2DM. Most likely to affect heritability are gestational diet and hyperglycaemia, changes to β-cells and exercise-induced alterations to skeletal muscle gene expression.

Gut bacteria

Although it has been known for decades that gut bacteria play an essential role in the absorption of vitamins, minerals and nutrients, only more recently has the likely effect this has on energy balance, obesity and health been appreciated. This is perhaps surprising given the size, diversity and independent genome of the bacteria that colonise our gut throughout our lives. Our gut flora may begin to develop during gestation where there is a passage of microbes between the mother and the foetus. The most important colonisation of the gastro-intestinal tract occurs
soon after birth, the composition of which depends on genetic factors, delivery type, maternal flora, environment hygiene and infant diet. The proportion of bacteria in the infant gut microbiome is highly variable during the first few years of life. After the age of three, the composition stabilises and remains relatively unchanged throughout adulthood.[47]

There is convincing empirical evidence, albeit mainly in mice, that the composition and diversity of gut bacteria affects energy balance and weight gain. For instance, faecal transplantation from obese and lean mice, animals and humans into germ-free mice resulted in weight gain and weight maintenance respectively, despite equal caloric intake.[48-50] Looking at things from the opposite perspective, there is also evidence that obesity influences gut bacteria. A number of studies have found higher levels of *Firmicutes* than *Bactroidetes* in the gut flora of obese compared to lean mice,[51] a finding replicated in some[48] but not all[52] studies on humans. It is arguable that body mass associated with an obese microbiome is an independent risk factor for T2DM. In addition, it is thought that gut bacteria may also directly affect inflammation and insulin resistance.

As gut bacteria harvest energy from the diet a number of short chain fatty acids (SCFA’s) are produced from indigestible carbohydrates.[53] There are three main SCFA’s involved in human metabolism; acetate, butyrate and propionate. Low levels of butyrate, found to be associated with obesity and T2DM, appear to be associated with insulin resistance and inflammation.[54] Furthermore, reduced gut flora diversity lowers the pH of bile acid which, in turn, increases cholesterol accumulation and inflammation.[55]

As yet, the direction of causation between gut microbiome composition, obesity and T2DM has not been elucidated. However, given that changes in diet macronutrient composition (to include high levels of non-starchy polysaccharides), increases in physical activity,[56, 57] and faecal transplantation, which is becoming more popular, can result in beneficial alterations to gut flora and consequentially reductions in body weight and insulin resistance, this makes for a promising new line of research in the field.

**Environmental factors**

The technological revolution is a double-edged sword; not only facilitating a sedentary and overabundant lifestyle, but at the same time increasing emissions of particulate matter and reducing the amount of surrounding green space; both of which have been shown to be harmful to health.
Lockwood et al.\textsuperscript{[58]} were the first group to report a link between air pollution and diabetes prevalence. Since then, several studies have explored the possibility that air pollution exposure may be a risk factor for T2DM. It is difficult to determine whether individuals at risk of or with T2DM are more susceptible to negative effects of air pollution exposure, or whether people with T2DM are more likely to live in areas with higher levels of pollution. However, results from prospective cohort studies have generally demonstrated a higher incidence of T2DM in individuals whose residence is in a more polluted area.\textsuperscript{[58]} Interestingly, this risk appears to be greatest in those with fewer other risk factors such as being inactive or a smoker.\textsuperscript{[60]}

Experiments conducted on rodents have shown that acute exposure to particulate matter causes a reduction in insulin sensitivity.\textsuperscript{[61, 62]} To date, only one group have carried out a comparable study on humans, with similar results. Brook et al.\textsuperscript{[63]} proposed that exposure to air pollution is likely to exacerbate systemic inflammation by stimulating a stress response, causing oxidative stress and affecting endothelial function. In addition, it is possible that pollutant constituents toxic to the insulin signalling cascade are able to enter into circulation.

While exposure to pollution may not contribute to the risk of T2DM as much as other factors such as diet and lifestyle, there is strong evidence for a negative association (and certainly no benefits).\textsuperscript{[64]} Furthermore, high levels of pollution aggravate a number of chronic health conditions, including T2DM. It may also contribute to the explanation as to why reduced greenspace is associated with higher risk and prevalence of T2DM.\textsuperscript{[65-68]} The relationship between greenspace and diabetes incidence is independent of area deprivation, BMI and physical activity level.

Given that air pollution levels and urbanisation are increasing, it is important that ways in which exposure to, or better still, production of harmful particles are minimised. Keeping access to greenspace a priority in urban planning is one way to achieve this.

1.1.5 Signs, symptoms and complications

Insulin resistance and dysglycaemia can occur more than 10 years before the onset of T2DM.\textsuperscript{[69]} Often the first sign of impaired glucose regulation is postprandial hyperglycaemia.\textsuperscript{[70]} While an individual’s blood glucose may return to normal levels after a period of fasting, this clearing takes more time than in a healthy individual. This is a sign that peripheral (muscle), as opposed to basal (hepatic and renal) insulin sensitivity is sub-optimal.\textsuperscript{[71]} Postprandial hyperglycaemia has been identified as an independent risk factor for cardiovascular disease (CVD) in those with\textsuperscript{[72]} and without overt T2DM.\textsuperscript{[73, 74]}
Despite considerable internal disruption, symptoms during this period of dysglycaemia are often subtle and difficult to distinguish from signs of ageing. These may include; fatigue, polyuria, polydipsia, blurred vision, loss of muscle mass (and possibly body mass), sweating, palpitations, increased wound healing time and susceptibility to infection. In some cases, symptoms may only present after onset of disease meaning that unless an individual is screened regularly, T2DM can remain undiagnosed for 4-7 years. This is problematic because microvascular damage, particularly to the feet, kidneys and eyes can occur in the presence of asymptomatic hyperglycaemia. Sustained unmanaged or poorly controlled blood glucose levels can lead to severe complications such as gangrene and amputation, renal failure and blindness. T2DM is now the leading cause of all of these.

Both T2DM and insulin resistance are independent risk factors for CVD, the leading cause of death in this population. Around 50-75% of individuals with T2DM also suffer from hypertension; the incidence increasing with age, HbA1c and duration of T2DM. A combination of high blood pressure, obesity and chronic inflammation contributes to atherosclerosis; the narrowing of arterial walls. Vascular occlusion increases the risk of stroke, coronary heart disease and cerebrovascular disease; the incidence of which is increased in T2DM.

Other indicators of reduced glycaemic stability e.g. variation in fasting glucose levels have also been linked to CVD in T2DM. A systematic review concluded that, overall, the coefficient of variation (CV) of fasting glucose was a stronger predictor of cardiovascular complications than mean fasting glucose or HbA1c. However, variation in fasting glucose does not necessarily reflect daily glucose excursions. Several researchers have called for attention to be given to glycaemic variability, which has recently been defined as; pathological, within-day glucose fluctuations, as it may be an independent predictor of micro- and macrovascular complications. For instance, Sartore et al. found that 72 hour continuous glucose monitor (CGM) measured glycaemic variability was associated with diabetic retinopathy although this relationship was no longer present when duration of diabetes diagnosis was included in the model. To date, the evidence linking glycaemic variability to diabetes complications in individuals with T2DM is scarce. This is presently due to the novelty of the technology and paucity of available data as opposed to the absence of a relationship. However, a recent prospective study has shown that, in individuals at high-risk of T2DM, glycaemic variability was associated with progression to T2DM, independent of HbA1c and fasting glycaemia. These findings are yet to be replicated, but stimulate an interesting new line of research worthy of further investigation.
1.1.6 Prevention and management

Given that obesity and physical inactivity increase risk of T2DM, it follows that weight loss, induced by a healthy diet and physical activity will help prevent diabetes. Indeed, it is well established that individuals of a healthy weight and who participate in regular exercise are 30-50% less likely to develop diabetes than those who do not. Studies indicate that individuals who engage in four key health behaviours; not smoking, moderate alcohol consumption, healthy diet and regular physical activity throughout their lifetime have between a 75-90% reduced risk of mortality per year than those who do not do any of these. It is striking therefore, that only about 30% of people maintain all four of these behaviours throughout their lifetime.

Physical activity and dietary control form the cornerstones of diabetes management, with many of those who implement these behaviours successfully able to manage their disease medication-free. For most though, lifestyle behaviour change presents as a major challenge, something which may be more difficult for those already with T2DM. Therefore, with declining β-cell function, the majority of individuals with T2DM are prescribed glucose lowering medication. Metformin is the first line drug treatment when HbA1c rises above 6.5% (48 mmol·mol⁻¹). Metformin is a highly effective glucose lowering agent which reduces endogenous glucose production and insulin resistance. Other beneficial actions include a reduction of carbohydrate absorption and low-density lipoprotein cholesterol, and stimulation of FFA oxidation.

Dual therapy is considered if HbA1c levels continue to rise despite the prescription of metformin. Seven drugs are available for use alongside metformin. Sulfonylureas are organic compounds that act directly on pancreatic β-cells to stimulate the production of insulin, thus reducing plasma glucose levels. Sulfonylureas are widely used, but carry with them a risk of hypoglycaemic episodes, often at night. Sulfonylureas are associated with weight gain however, the glucose-lowering effects outweigh the negative impact this has on insulin sensitivity. Thiazolidinediones (TZD) are organic compounds that bind to peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ is involved in the transcription of insulin signalling genes including lipoprotein lipase and GLUT-4 (Figure 1.1). Pioglitazone is a member of the TZD family and a PPAR-γ agonist which ultimately reduces hepatic glucose output and increases muscle glucose uptake by enhancing the effectiveness of endogenous insulin action. It is also associated with weight gain. DPP-IV (dipeptidylpeptidase-IV) inhibitors prevent the DPP-IV enzyme from breaking down incretin hormones which produce insulin and reduce hepatic glucose output. Commonly referred to as gliptins, this class of drugs has a low incidence of hypoglycaemia and does not cause weight gain. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) also work by a similar mechanism by
mimicking the action of endogenous GLP-1. Not only does this hormone stimulate insulin production, it also reduces gastric emptying and food intake. More recently, SGLT2 (sodium-glucose transport protein-2) inhibitors have been approved and recommended for use by individuals who cannot tolerate other drugs or are at high risk for hypoglycaemia.\cite{97} SGLT2 is primarily expressed in the kidney and promotes reabsorption of glucose. By inhibiting SGLT2, glucose is excreted in the urine, preventing it from re-entering the bloodstream. By causing polyglycosuria, this drug often results in weight loss and a reduction in blood pressure however, it also increases susceptibility to urinary tract infections. If HbA1c continues to rise, triple therapy (combinations of these drugs) or insulin-based treatment may be recommended.\cite{98, 99}

While pharmacotherapy is paramount in the management of T2DM, the increasing financial burden of T2DM is necessitating more effective promotion of physical activity and healthy food choices which, once implemented, carry with them no on-going cost above that of routine check-ups. Several landmark randomised controlled trials have demonstrated that individuals of all ethnicities at high risk of T2DM can significantly reduce this risk with lifestyle interventions.\cite{100} In the United States Diabetes Prevention Programme, both lifestyle intervention (physical activity & dietary control) and glucose-lowering medication (metformin) were effective at preventing T2DM in individuals with elevated blood glucose, but lifestyle was 39% (24-51%) more effective than metformin.\cite{101} Similarly, in Finland, compared to control conditions, lifestyle intervention prevented development of T2DM by 58% (48-66%).\cite{102} In the Chinese Da Qing study, 41% (33-49%) of participants who were at high risk of developing T2DM in the exercise intervention group went on to develop the condition compared to 68% (60-75%) in the control group. Interestingly, adding dietary advice did not further prevent T2DM, with 46% (37-55%) of participants in the diet plus exercise group going on to develop T2DM (between groups comparison not significantly different).\cite{103} Importantly, these benefits are likely to persist well after the intervention. For example, a 20 year follow-up of the Da Qing study revealed that those who had been assigned to intervention groups still had a 43% lower incidence of T2DM.\cite{104}

Despite these unequivocal findings from lifestyle intervention studies, probably due to the difficulty in implementing long-term behaviour change, the relative contribution of diet and, specifically, physical activity research in predicting long-term clinical outcomes is limited compared to trials investigating pharmaceutical therapies. Furthermore, most studies investigating the long-term effect of lifestyle intervention are in pre-diabetic individuals making it difficult to compare with pharmacotherapy which is not routinely prescribed prophylactically. To date, there is only one randomised control trial investigating the effects of intensive lifestyle intervention versus standard care (glucose-lowering medication plus advice from health care
professionals) on cardiovascular events in individuals with T2DM. This study, the LookAHEAD trial, was terminated early because, despite greater weight loss and HbA1c reduction in the intervention group, there were no differences in cardiovascular events after nearly 10 years.\textsuperscript{[105]}

Therefore, the group with the most potential to benefit from such behaviour changes are those regarded as at high risk of T2DM specifically, individuals with NDH. In response to the increasing incidence of and burden T2DM is having on public services, the UK government has launched a national diabetes prevention programme (NDPP).\textsuperscript{[106]} Using a step-wise screening process, a risk score is being used to identify individuals at high risk of NDH. These individuals are invited to their general practitioner (GP) surgery for a blood test. Those found to have NDH are invited to attend evidence-based lifestyle education sessions, tailored to suit individual preferences and requirements.

This thesis will focus on the role of physical activity in the prevention and management of T2DM, and how the evidence generated might be incorporated into diabetes prevention strategies and physical activity guidelines.

1.2 Physical Activity

1.2.1 Physical activity and health

As previously alluded to (section 1.1.3), physical inactivity is independently associated with a high risk of developing T2DM. As raised in section 1.1.6, regular participation in physical activity is likely to reduce this risk. In fact, being physically active reduces the risk of numerous other conditions including CVD,\textsuperscript{[107]} renal and liver disease, some cancers\textsuperscript{[108]} and mental health conditions.\textsuperscript{[109]} The first documented association specifically between physical activity and health was made in the 1950’s. In seminal studies conducted by Jerry Morris, it was observed that bus conductors had a lower incidence of CVD than their bus driving peers.\textsuperscript{[110]} This was a landmark observation because conductors and drivers were of comparable age, ethnicity and socio-economic status and were likely to lead similar lifestyles apart from their work, making these relatively well controlled investigations. Following this, cross-sectional studies revealed that participation in regular physical activity and/or higher levels of cardiorespiratory fitness is associated with lower risk of all-cause mortality\textsuperscript{[111-113]} and morbidity, particularly in T2DM.\textsuperscript{[114, 115]} Overall, epidemiological studies indicate that individuals who participate in regular physical activity are 30-50\% less likely to develop T2DM than those who do not.\textsuperscript{[116]} More recently, the relationship between sedentary time and T2DM has been identified as important. Extended
periods of sedentary time are also associated with development of T2DM, independent of total physical activity undertaken.\[^{117, 118}\]

Experimental studies have since demonstrated potent effects of physical activity training on HbA1c,\[^{119}\] blood pressure,\[^{120}\] and hyperlipidaemia\[^{121}\] as well as increases in cardiorespiratory fitness\[^{122}\] and overall life expectancy\[^{123}\] in patients with T2DM. Similarly, breaking sedentary time with light activity breaks or even standing has been shown to have profound effects on glucose and insulin action.\[^{124}\]

The full spectrum of research methodology therefore; from epidemiological observations through to randomised controlled trials, demonstrates the benefits of physical activity on health in general, and specifically T2DM. In contrast to pharmaceutical therapies, in the absence of underlying health conditions, there are no negative implications or side effects of participating in moderate-intensity physical activity (MPA).\[^{100}\]

1.2.1.1  Mechanisms by which physical activity improves T2DM

Here, the pathways involved in glucose regulation that are affected by physical activity will be described.

Physical activity, by definition, stimulates muscle contraction and this appears to signal two insulin-independent pathways that facilitate glucose disposal.\[^{125}\] Cross-bridge formation of muscle fibres releases calcium ions into the muscle cell, and these increase expression of protein kinase C (PKC). Energy expenditure as a result of muscle contraction changes the AMP:ATP (adenosine monophosphate; adenosine triphosphate) ratio. As a result, AMP kinase (AMPK) is upregulated and activates endogenous nitric oxide synthase (eNOS) phosphorylation, increasing intracellular nitric oxide (NO) concentration. Both PKC and NO stimulate GLUT-4 translocation to the cell membrane (Figure 1.1). This pathway is not affected by insulin resistance or its associated stressors making it an effective glucose lowering mechanism in individuals with hyperglycaemia and/or insulin resistance.\[^{126}\]

There is also an acute increase in insulin sensitivity immediately post-activity that lasts up to 48 hours.\[^{127}\] The signalling pathway involved in this phenomenon is unclear, but appears to be linked with muscle glycogen storage. If physical activity decreases muscle glycogen stores, glucose uptake will increase in proportion to the amount used in order to replenish stores.\[^{128}\] It is possible that AMPK is also involved in this insulin-dependent pathway, but precisely what its role is has not been defined.\[^{129, 130}\]
Exercise training or regular participation in physical activity is also associated with enhanced insulin signalling, separate to the improved insulin sensitivity following an acute bout of exercise. For instance, insulin sensitivity is higher in trained athletes than untrained individuals even when measured after a period of rest. This is most likely due to optimisation of the basal insulin signalling pathway (centre of Figure 1.1). Muscle biopsies have revealed greater number and activation of GLUT-4 vesicles, enhanced insulin receptor phosphorylation and tyrosine kinase activity and, as a consequence, increased activation of PI3-K and Akt. Perhaps most importantly though, the improved oxidative capacity of trained skeletal muscle prevents the deleterious accumulation of FFA’s and inflammatory cytokines associated with obesity and inactivity.

At the tissue level, acute exercise increases muscle fibre recruitment which demands greater blood flow than when at rest. As long as an individual is not hypoglycaemic, this will increase glucose, as well as oxygen, delivery to the muscles. Given that exercise will draw on muscle glycogen stores, muscle perfusion also increases in order to enhance glucose uptake and maintain supply to the mitochondria. In fact, in healthy individuals, muscle interstitial glucose concentration is higher during moderate exercise than at rest indicating that increased glucose disposal is important under these conditions. Regular exercise training improves circulation and skeletal muscle blood flow via increased muscle capillary density and reduced vascular resistance, thereby augmenting glucose delivery both at rest as well as during exercise. Interestingly, this pathway is also influenced by insulin in a dose-dependent manner suggesting that insulin resistance is likely to inhibit this mechanism.

1.2.2 Physical activity guidelines

1.2.2.1 The FITT Principle

Physical activity training has four main elements: frequency (the number of times physical activity is performed e.g. per day, per week); intensity (the relative capacity or power, as a percentage of their maximum, at which an individual performs); time (the duration for which physical activity is performed) and type (the mode of activity e.g. aerobic, resistance). Total activity volume reflects the interaction between frequency, intensity and time.

1.2.2.2 Classification of physical activity intensity

There are five distinguishable levels of physical activity intensity, defined in Table 1.1
<table>
<thead>
<tr>
<th>Table 1.1 Classifications of exercise intensity</th>
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<tr>
<td><strong>Relative intensity</strong></td>
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<td>METs</td>
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<td>%HR_{max}</td>
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<td>%VO_{2max}</td>
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MET – metabolic equivalent task; HR_{max} – maximum heart rate; VO_{2max} – maximal oxygen uptake

1.2.2.3 Development of physical activity guidelines

The first physical activity guidelines were published in 1975 and provided recommendations on how to improve cardiorespiratory fitness.\[^{137}\]\ These were based on evidence from intervention studies which consistently demonstrated that per minute, vigorous-intensity physical activity (VPA) was more effective at improving fitness than MPA. These studies however, often did not control for total exercise volume as different intensities were performed for equal amounts of time therefore comparing a greater total volume of the higher-intensity exercise.\[^{138}\]\ The observation that improvements, if not of as great a magnitude as VPA, were also made in the groups performing MPA led to a re-evaluation of what level of physical activity was required to produce important physiologic adaptations that were beneficial to health.

The first physical activity guidelines specifically for the promotion of health were published in the 1990’s.\[^{139}\]\ These recommended that the healthy adult perform 20-60 minutes of aerobic training at 60-90% of maximum heart rate (HR_{max}) or 50-85% maximal oxygen uptake (VO_{2max}) on 3-5 days of the week. In addition, to maintain fat-free mass, 8-12 repetitions of 8-10 resistance exercises should be performed on at least two days of the week. The rationale behind these guidelines was that this was the minimum amount of physical activity required to maintain a level of fitness that would significantly reduce the risk of chronic degenerative disease.

These recommendations have been adapted only slightly in the last 25 years; primarily to make them easier for the public to follow. The prevailing guidelines are that 150 minutes of MPA or 75 minutes of VPA should be performed per week in bouts of at least 10 minutes separated by no more than one day. In addition, resistance or weight-bearing exercises involving large muscle groups should be completed on at least two days per week.\[^{140}\]\ A large body of evidence supports a potent dose-response relationship between physical activity and health\[^{141-143}\] that extends beyond the recommended amount. The guidelines are therefore considered as a minimum and the benefits of engaging in volumes exceeding this amount are acknowledged.
1.2.3 Current situation

1.2.3.1 Adherence

Despite unequivocal evidence demonstrating the essential role of physical activity in maintaining health and the emphasis placed on lifestyle choices in the prevention and management of chronic disease, only a minority of people meet the minimum recommendations. In the Health Survey for England; a survey of a nationally representative sample of 15,000 adults, only 34% reported activity levels which met the guidelines. When objective measures of physical activity were employed (N = 4007), this proportion fell to 5%. These levels of physical inactivity contribute to the World Health Organisation’s (WHO) identification of physical inactivity as the fourth leading modifiable risk factor for premature death behind hypertension, smoking and hyperglycaemia.

1.2.3.2 Barriers to Physical activity

The first step to finding solutions to the issue of participation is to identify the reasons why individuals do not engage in physical activity to begin with. Qualitative methods and questionnaires have identified common themes in perceived barriers towards physical activity in older, overweight/obese or individuals with T2DM. These can be summarised as: lack of time (due to family, household and occupational responsibilities); lack of knowledge; cultural factors (e.g. language, gender roles); access issues (due to transport, facilities and financial resources); psychological barriers (e.g. self-consciousness, entrenched attitudes) and environmental factors (e.g. safety, weather). “Lack of time” is a barrier common to many population subgroups independent of socio-economic status, ethnicity or disease status. This observation has led researchers to investigate ways in which significant health benefits can be achieved with a smaller time commitment.

1.2.3.3 Future Directions

Recognition of the low compliance to national guidelines and the multi-faceted impact of physical inactivity has led to an evaluation of approaches by which participation can be augmented. Patient feedback has suggested that generalised advice is inappropriate in many cases as individual differences mean that chronic conditions are experienced uniquely and that this should be acknowledged by health care professionals. Physical activity guidelines therefore, should encompass a wide range of options including advice on progressing from very low levels of physical activity, how to get the most out of short periods of physical activity, and which modes are likely to improve their condition most effectively.
1.2.3.4 Vigorous-intensity physical activity

As previously alluded to, per minute, higher-intensity physical activity brings about greater benefits than that of a lower intensity. This observation has been shown to be consistent across study design and outcome. For instance, an early review by Wenger & Bell\[^{152}\] demonstrated that increases in cardiorespiratory fitness were optimal at training intensities 90-100% of VO\(_{2}\max\), independent of training duration (mins/session) and frequency (sessions/week). Cohort studies comparing self-reported physical activity intensity with mortality\[^{153}\] and T2DM incidence\[^{154}\] indicate that those who report higher levels of VPA are at lower risk than those reporting less or none at all. These observations have been supported by randomised training studies which have demonstrated that the higher the exercise intensity, the lower the total exercise time required to achieve similar improvements in insulin sensitivity\[^{155}\] and HbA1c.\[^{156}\]

Despite these well-established advantages to VPA, the number of people who engage in activity of this intensity is even lower than that of MVPA; the majority of which is made up of MPA.\[^{157},\,158\] Barriers specific to VPA appear to relate to “affect” (how one feels during activity) and fear of injury or adverse event.\[^{159}\]

1.3 High-intensity interval training

In an attempt to address these barriers, high-intensity interval training (HIIT) has recently attracted interest as a health-related exercise programme. In fact, HIIT, in various forms, has been used effectively to improve fitness for over a century.

1.3.1 History

The idea of incorporating short efforts of VPA interspersed with periods of recovery in order to improve fitness was (knowingly) first conceived by the Finn, Hannes Kolehmainen to train for a 10km race in 1912.\[^{160}\] Following this, various arrangements of HIIT were employed by middle and long distance runners to notable success. These athletes intermittently trained at intensities equal to “race pace”. Nonetheless, interval training did not become mainstream until the 1940’s when Swedish cross-country coach Gostar Holmar consistently led his squad to victory against the Fins for about a decade.\[^{161}\] Their success was attributed to “Fartlek training”, a somewhat arbitrary amalgamation of jogging, running and sprinting within a one hour training session. After the Second World War, sports science became more prominent in the development of athlete training programmes and the unstructured and varying speeds and times that comprised Fartlek training were refined and specified to individuals and their sports. Athletes who used interval training, which now featured consistency and/or structure in the length and intensity of
efforts, set a series of world records in middle distance running during the following 20 years. As a consequence, the technique has been adopted by almost every endurance athlete and coach irrespective of discipline.[162] HIIT was effective because it increased the length of time at which an athlete could sustain their maximum velocity without over-loading their training programme.[163]

The Swedish Scientist Per Oløf Åstrand and colleagues pioneered scientific investigation into interval training, optimising programmes to increase VO$_{2\text{max}}$.[164] Between 1960 and 1975 his group also attempted to detail the mechanism of action of HIIT and the wider physiological responses beyond sports performance. In doing so, they were successfully and safely able to incorporate HIIT into rehabilitation programmes for heart failure patients who typically demonstrate critically low levels of fitness. Interval training has since been incorporated into the American Heart Association guidelines for cardiac rehabilitation[165] and employed with great success.[166-168]

1.3.2 Types of HIIT

By adapting the rigorous daily interval programme designed by Joan Parra and colleagues,[169] Burgomaster et al.[170] are credited with developing the first low-volume interval training protocol for the purpose of increasing endurance capacity. In their first training study, healthy volunteers performed repeated Wingate efforts with four minutes recovery between each interval three times per week for two weeks.[171] The Wingate efforts involved 30 seconds “all-out” pedalling against a resistance equal to 0.075 kg·kg body mass$^{-1}$ and the number of intervals increased from four to seven over the course of the intervention. This type of interval training has commonly been referred to as sprint interval training (SIT). Adaptations have been made to make SIT more achievable for non-athletic populations, for example applying a lower resistance (e.g. 0.05 kg·kg body mass$^{-1}$,[172] or as a proportion of lean rather than total mass[173]) or performing shorter efforts.[174] Generally, any protocol that employs efforts greater than the exercise intensity achieved at 100% VO$_{2\text{max}}$ is referred to as SIT. This protocol is attractive given that it requires up to just three minutes of exercise per session, or nine minutes per week; eight times less than the current guidelines for VPA. The interval training carried out in cardiac rehabilitation settings looks very different and has been dubbed “aerobic interval training” (AIT) which, most commonly, involves four times four minute (hereafter, 4 x 4 minutes) repetitions at 90% HR$_\text{max}$, with three minute active recovery periods at around 70% HR$_\text{max}$ and takes a minimum of 35 minutes. Somewhere in between, protocols requiring less time than traditional physical activity programmes, and involving vigorous-intensity, but sub-maximal exercise have been
designed. This has been addressed primarily by changing the effort:recovery time ratio,[175, 176] and using walking rather than running or cycling protocols.[177]

1.3.3 HIIT for the prevention and management of lifestyle disease

The evolution of HIIT research has culminated in the current exploration of the minimum amount of exercise required to promote health benefits. This has coincided with today’s fast-paced style of living as well as the lifestyle disease epidemic. HIIT has therefore recently gained research and media attention for potentially being an attractive and effective therapeutic health tool for the prevention and management of lifestyle disease.

1.3.4 Effects of HIIT on health

In Burgomaster et al.’s training study an increase in VO_{2peak} was not observed;[171] possibly attributable to the relatively short, two-week duration of the intervention. However, time trial time to fatigue was significantly improved following two weeks of SIT training. Since then, the protocol has been adopted by a number of research groups and larger studies of longer duration have produced significant increases in VO_{2max}[178, 179] and maximal peak power,[179] indicating that improvements in anaerobic performance may also occur.

In addition to VO_{2peak}, the effect of HIIT on other health related outcomes has been investigated, particularly in heart or lung failure patients.[166, 180] More recently, the effect of HIIT on markers of glycaemic control and insulin resistance has received attention. Probably the first study investigating the effects of HIIT on insulin sensitivity was conducted by Devlin et al.[181] Patients with T2DM cycled at 85% VO_{2max} for two minutes with three minute rest periods until volitional exhaustion. Insulin sensitivity was assessed using a euglycaemic hyperinsulinaemic clamp. They found that, compared to the control condition (no exercise) fasting glucose the following morning was lower, and glucose utilisation and hepatic insulin sensitivity increased to levels that were comparable to those observed in non-diabetic individuals.

1.3.4.1 Acute studies

The first explorations of the effects of “low-volume” interval exercise on outcomes related to T2DM were conducted on young, healthy individuals.[182, 183] Interestingly, in these normoglycaemic individuals, whereas continuous exercise significantly increased insulin sensitivity, sprint interval exercise (SIE) did not. On the other hand, in overweight/obese individuals, a practical form of HIIE performed in the morning, reduced continuous glucose monitor (CGM) measured glucose area under the curve (AUC) more than moderate-intensity continuous exercise (MICE). This effect was maintained until the next morning when breakfast
AUC was also significantly lower in the HIIE condition.\[^{184}\] Similarly, Terada et al.\[^{185}\] conducted a study on individuals with T2DM comparing the effect of HIIT and MICE on glycaemic variation when performed in either a fasted or postprandial state. They found that although MICE lowered breakfast AUC to a greater extent than HIIE, HIIE reduced 24 hour AUC, mean amplitude of glycaemic excursion (MAGE) and time spent in hyperglycaemia (defined in this study as >10 mmol·L\(^{-1}\)). None of these interventions affected fasting glucose.

### 1.3.4.2 Training studies

These acute studies are supported by a large number of training studies. With a few exceptions,\[^{173, 186-190}\] SIT interventions have been conducted on young and/or healthy individuals. Of these, those that reported measures of insulin sensitivity or glucose regulation indicate that SIT can improve outcomes in healthy individuals\[^{191, 192}\] and that more than two weeks may be required to observe improvements,\[^{193}\] but the findings are not consistent.\[^{174, 194}\] Sandvei \textit{et al.}\[^{195}\] found no change in homeostatic model assessment (HOMA) measures of insulin resistance when measured more than 48 hours after the last bout of exercise, but did observe an increase in $\beta$-cell function. This suggests that, in healthy individuals, it may be that SIT stimulates adaptations in $\beta$-cells which improves acute insulin sensitivity. Similarly, in overweight, obese or T2DM participants, only one short duration (two week) SIT intervention has resulted in significant improvements in insulin sensitivity,\[^{196}\] although this effect was only present 24 and not 72 hours after the last bout of exercise. Two weeks of SIT also improved insulin sensitivity in individuals with the metabolic syndrome, but to a similar extent as following moderate-intensity continuous training (MICT).\[^{190}\] Other studies reported no change in insulin sensitivity.\[^{173, 187, 189}\]

The idea that SIT may be inappropriate for clinical populations has been raised publicly by a number of health physiologists.\[^{197, 198}\] To some extent this concern has been reflected in the HIIT research, with most studies involving “non-healthy” and/or older populations employing AIT or HIIT rather than SIT protocols. In healthy participants, HIIT does not alter fasting glucose\[^{199-203}\] or insulin levels, but does have a positive impact on insulin sensitivity.\[^{201, 203, 204}\] In individuals with or at risk of T2DM, or with CVD, results have been mixed, with some studies producing improvements in insulin resistance\[^{176, 205-208}\] and glycaemic control,\[^{209, 210}\] whereas others have not found any changes in these outcomes.\[^{177, 211-215}\]
1.4 Summary

In summary, prevention and management of T2DM is a growing problem in the UK, and one that is likely to overwhelm NHS resources in the not too distant future. Physical activity is known to improve outcomes related to T2DM, yet despite efforts to increase participation, physical activity levels are still falling each year. Interventions and initiatives designed to encourage physical activity to at least meet the minimum recommendations have so far not made a consistent impact. Many barriers to physical activity have been identified, including “lack of time” and dislike for vigorous-intensity exercise. High-intensity interval training offers a solution to these issues as it requires less time and may be more enjoyable than continuous, moderate-intensity and probably continuous vigorous-intensity exercise. However, to date, the effects of HIIT on markers of metabolic health are inconsistent and the suitability of HIIT for a population at risk of or with T2DM is under contention. Thus, its potential to be offered as an alternative therapeutic health tool to traditional, moderate-intensity continuous physical activity requires further investigation.

1.5 Aims

The main objective of this PhD was to provide evidence about vigorous-intensity physical activity, in particular HIIT, and its influence on blood glucose regulation and insulin sensitivity. To achieve this, my PhD:

i. Pools the current available evidence regarding the effect of HIIT on outcomes relating to T2DM and quantifies this effect by using systematic review and meta-analysis to analyse training studies.

ii. By means of a cross-sectional analysis of baseline data from a randomised control trial in a population at high risk of dysglycaemia, examines A) whether bouts of MVPA lasting less than 10 minutes are associated with markers of insulin sensitivity, and B) the physical activity intensity at which differences in blood glucose and insulin levels occur, and how increasing physical activity intensity changes the magnitude of these differences.

iii. Explores the effect of an acute bout of a practical model of HIIT on postprandial glycaemic responses and insulin sensitivity in individuals at high risk of T2DM.

In the broader context, this work contributes to the demand for more individualised public health messages which provide more choice for different populations with specific needs. In the
future, evidence generated from this research could be used in a revision of the guidelines for physical activity which may include HIIT.
Chapter overview

This chapter reports a systematic review and meta-analysis of the effects of HIIT on glycaemic control and insulin sensitivity in individuals with or at risk of T2DM. It is an updated version of work that was published in Obesity Reviews (2015; 16(11)). At the time the original review was conducted, only one narrative had evaluated the overall impact of HIIT on blood glucose and insulin resistance.\textsuperscript{[216]} When I performed a systematic search in March 2015, fifty studies met the inclusion criteria, 11 of which included participants at high risk of T2DM. When updating the search for this thesis, a further 14 had been conducted in a population with or at high risk of T2DM. Given the growing interest surrounding HIIT, and its potential application in healthcare settings, in the discussion of the original article I highlighted the need for larger, longer studies in clinical populations. This has begun to be addressed with the available data for this population having more than doubled in the last two years. Therefore, in keeping with the aims of this thesis, here I present the results of studies in which participants are described as at high risk of or with T2DM. High risk was defined as studies with populations described as having the metabolic syndrome, with NDH, or having T2DM.

Twenty-five studies with a variety of HIIT interventions and reporting at least one of the following outcomes; fasting glucose, fasting insulin, HbA1c or insulin resistance/sensitivity were included. Descriptive intervention characteristics were systematically reviewed and outcome data quantitatively synthesised. Meta-regression was also conducted to assess factors that might mediate outcomes. The chapter concludes with the recommendation that future HIIT interventions be conducted in non-laboratory settings with the aim of assessing the feasibility of, and adherence to, HIIT.

Key findings

- Compared to baseline, improvements in insulin resistance, HbA1c, fasting glucose and insulin, cardiorespiratory fitness and body mass occurred following HIIT training as well as when compared to non-exercising control groups.

- There were no differences in the effects of HIIT compared to MICT.
• Meta-regression suggested that the longer the intervention, the greater the improvement in fasting glucose.

• Individuals with the highest levels of insulin resistance and fasting glucose at baseline experienced the most pronounced benefits of HIIT training.

Publications and conference presentations

The original work relating to this chapter was published in the journal Obesity Reviews (Appendix 1):


Poster presentations of the original research were given at:

Fifth NIHR Infrastructure Doctoral Research Training Camp, July 2014 (Ashridge Business School, Berkhamsted, UK)

Royal Society of Medicine Exercise Medicine Conference, June 2015 (Royal Society of Medicine, London, UK)

Author contribution

In order to conduct this research I attended courses on how to perform systematic review and meta-analysis using journal databases and statistical software respectively. I was therefore able to conduct the literature search, extract and analyse the data myself. Gary O’Donovan independently performed data extraction to ensure accuracy. I wrote the first draft of the manuscript and addressed reviewer comments. I then independently revised the search and conducted the updated analysis reported here.

2.1 Introduction

For HIIT to be recommended as a therapeutic health tool, interventions must demonstrate consistent benefits in a variety of health outcomes that are equal or superior to traditional exercise training programmes. A number of meta-analyses have concluded that SIT, HIIT and AIT have a potent effect on cardiorespiratory fitness in a variety of populations.\[^{178, 179, 217, 218}\] This is important because fitness is a strong predictor of all-cause mortality,\[^{113}\] including in individuals
with T2DM. Nonetheless, it is still important to understand fully the benefits HIIT may have on markers of metabolic health such as glucose regulation, insulin sensitivity and weight control. One narrative review concluded that despite a reduction in total work volume compared to continuous training, overall, HIIT has positive effects on metabolic outcomes. A recent meta-analysis compared both HIIT and high-intensity continuous training with MICT and low-intensity continuous training (LICT) in individuals with T2DM. This study concluded that higher-intensity training was more effective at reducing HbA1c, but that there was no difference in the effects of exercise training intensity on fasting glucose, fasting insulin or HOMA-IR. In seven out of the eight studies included, interventions were matched for total volume indicating that the benefits to HbA1c could be achieved with a lower time commitment and training load than performing MICT or LICT. This review only included studies involving individuals with T2DM, and excluded studies that did not report HbA1c, thus providing important evidence for the management of established T2DM. As described in Chapter 1.1.6, diabetes prevention is a global priority. It is useful, therefore, to establish whether HIIT also has the potential to prevent or delay the onset of T2DM. Taking this into account, the aim of this meta-analysis was to assess the magnitude of the impact of HIIT on glucose and insulin regulation, body weight and cardiorespiratory fitness compared to controlled conditions or continuous exercise training in individuals at risk of or with T2DM. A secondary aim was to determine whether observed metabolic changes were mediated by characteristics of the training protocol and/or concurrent changes in participant physiology (e.g. cardiorespiratory fitness, body weight).

2.2 Methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to conduct and report this review.

2.2.1 Search strategy and inclusion criteria

Medline (1946-13/03/2015), Embase (1970-13/03/2015) and SportDiscuss (1953-30/03/2015) were searched for HIIT intervention studies that reported a measure of glycaemic control. Due to access restrictions, the updated search was conducted in Medline, PubMed, Scopus and Web of Science (all 2015-24/04/2017). A widely accepted definition of HIIT is; at least two bouts of vigorous- or higher intensity exercise interspersed with periods of lower intensity exercise or complete rest. “High-intensity interval training” is not a MeSH term therefore words and phrases commonly used to describe HIIT were searched in titles and abstracts using the following search terms: “high-intensity interval”, “aerobic interval” and “sprint interval”. These were then
combined with the following terms using Boolean commands: intermittent, Wingate, supramaximal, exercise, training, programme, glucose, insulin, glycaemic, and HbA1c. Wildcards: *, ? and $ were used so that both English and American spellings would be returned. Appendix 2 gives a detailed description of the search strategy. Titles and abstracts of returned articles were evaluated based on the following inclusion criteria: human participants aged 18 years or over described as at high risk of or with T2DM e.g. metabolic syndrome and/or NDH, participants receiving a HIIT intervention and at least one measure of glycaemic control defined as: HbA1c, fasting glucose, fasting insulin, postprandial or post-challenge glucose response, or any measure of insulin resistance assessed pre- and post-intervention. Participants described only as overweight or obese were not included as these individuals are at low to medium risk of T2DM in the absence of other risk factors[222] with a conversion rate of 1-2% depending on BMI [223, 224]. HIIT had to be prescribed at least three times per week for two weeks. Two weeks was deemed the minimum period needed to show training adaptations; defined as a temporary or extended change in structure or function that results from performing repeated bouts of exercise and that is independent of the immediate or short-term effects produced by a single bout of exercise.[225] Both controlled and uncontrolled studies were included. Articles were excluded if HIIT was prescribed in combination with another intervention e.g. diet restriction; resistance training, if participants were healthy, had diagnosed Type 1 Diabetes, or if medication had been altered throughout the intervention. Abstracts, case reports, observational studies and studies not published in English were also excluded.

2.2.2 Risk of bias and study quality

Risk of bias was evaluated based on the PRISMA recommendations which suggest assessing randomised control trial quality using the Cochrane risk of bias tool.[226] This tool consists of five items that have been shown to have an effect on biasing the results of an intervention. Studies with control groups were checked for random sequence generation, allocation concealment, blinding, participants lost to follow-up, and whether an intention-to-treat analysis had been performed. Risk of bias was assessed as being as high, low or unclear. Uncontrolled trials were not assessed.

2.2.3 Data extraction and synthesis

Reviewers were not blinded to study authors, institutions, or manuscript journals. If the abstract was considered to be relevant to the review, or did not contain enough information regarding the inclusion or exclusion criteria, full-texts were retrieved for further evaluation. References included in identified studies and previous reviews or commentaries were also hand searched.
Where there was uncertainty by the first reviewer regarding appropriate studies, the full text was obtained and a second reviewer (Tom Yates) approached for discussion. If evidence of participant repetition was evident participants were only included once, however if necessary, multiple articles were used to obtain all required data.

If, according to the methodology relevant measurements had been taken but the results not reported, or values had been presented in figures, authors were contacted and asked to provide the missing data. When no reply was received the study/outcome was either omitted from the analysis [227] or values estimated from figures [187, 228, 229]. Where only pre and post-intervention data were presented, change data were imputed based on guidelines from the Cochrane Handbook for Systematic Reviews of Interventions [230].

A data extraction form was created and data regarding participant characteristics and disease status, protocol specifics, MICT interventions, markers of glucose regulation, insulin resistance, \( \text{VO}_{2\text{max}}/\text{VO}_{2\text{peak}} \), body composition and compliance, attrition, and adverse events were entered. A number of studies reported results from both acute (up to 48 hours) and longer term (72 hours) blood samples. If this was the case, the 72 hour reading was included in the analysis. Postprandial or post-challenge glucose levels were extracted but not analysed as there were not enough data to perform meaningful comparisons.

Where the HOMA model was used, insulin sensitivity was expressed as insulin resistance to account for the directional effect of exercise since a beneficial effect would increase sensitivity and decrease resistance. HOMA-IS% values were inverted (100/HOMA-IS%). [231]

2.2.4 Statistical analysis

Stata V.14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA) was used to conduct the meta-analyses. Pairwise comparisons comparing the effect of HIIT on glucose/insulin parameters and \( \text{VO}_{2\text{max}} \) to that of either MICT or control (CON) were carried out on studies that had two or more groups. In keeping with other exercise-related meta-analyses of continuous outcomes [119, 232] and following best practice [230], weighted mean differences were calculated in the pairwise comparisons for fasting glucose and insulin, HOMA-IS, body mass and \( \text{VO}_{2\text{max}} \). Standardised mean differences were used to account for the different dynamic measures of insulin resistance.

When studies had a HIIT group only (\( n = 7, 28\% \)), within group intervention effect sizes were calculated to estimate the change from baseline. All studies with a control group were included in both the between and within group comparisons. Within group comparisons are based on
unstandardised data, so only HOMA-derived insulin resistance measures could be assessed in this analysis.

HIIT interventions were categorised based on common protocol characteristics; Wingate, 10 x 60 seconds, 4 x 4 minutes or other. Data were presented according to HIIT protocol.

A sensitivity analysis for insulin resistance was also performed to assess whether the length of time elapsed before blood was sampled following the last training session affected the outcome. Based on what was reported, time to post-test blood samples was categorised as not reported, <24, 48 to <72 and ≥72 hours.

Random effects models using Cohen’s d were carried out to account for the differences in study protocol and duration. These data are presented as effect size (95% confidence interval; CI). Statistical heterogeneity of the treatment effect among studies was assessed using the chi-squared test. A threshold α value of <0.05 was considered statistically significant and an I² test with values greater than 50% were indicative of high heterogeneity.

2.2.4.1 Publication bias
Publication bias based on reporting of the main outcomes was assessed using a contour-enhanced funnel plot of each trial’s effect size against the standard error. Funnel plot asymmetry was assessed by visual interpretation. If publication bias was apparent, Begg & Egger tests were used as a secondary determinant. Significant publication bias was deemed apparent if p<0.1.

2.2.4.2 Meta-regression
Where significant results were found, meta-regression was performed in an attempt to determine whether baseline levels, exercise volume variables and changes to body weight and VO₂max mediated observed changes.

Interval intensity, weekly high-intensity exercise duration and total training period (weeks) were deemed the most relevant components of HIIT protocols. Where possible, using regression equations derived from early work, interval intensity was converted to a percentage of VO₂max in order to be able to directly compare exercise prescriptions. Wingate intensity was assumed to be 130% VO₂max. High-intensity exercise duration was estimated by multiplying the number of high-intensity intervals x interval length x the number of sessions per week and controlled for intensity and the number of weeks the study was run.
Change in body weight and cardiorespiratory fitness were also entered into the regression given their association with the primary outcomes.[239, 240]

For within group regression, change summary data were used as the dependent variable and were weighted by the standard error. In studies with a control group, the dependent variable was the mean difference calculated from the pairwise comparison, with each study weighted by the standard error of its effect size.

2.3 Results

2.3.1 Study characteristics

Study selection flow is presented in Figure 2.1. The initial searches returned a total of 6269 articles (Medline n = 3569, Embase n = 1933, SportsDiscuss n = 707). The revised searches (since 2015) returned 702 articles (Medline n = 305, PubMed n = 162, Scopus n = 174 and Web of Science n = 61). Of these, 454 were original articles. Titles and abstracts of returned articles were searched for suitability leading to the retrieval of 408 full-texts over both searches. Of these, 378 did not fulfil the inclusion criteria. Five of these had reported muscle, as opposed to plasma, glucose content. The total number of papers included in the analysis was 25, described in Table 2.2. Seven (28%) studies did not have a control group and were therefore only included in the within group analyses. Of the 18 (72%) controlled trials eight (32%) had a MICT group, seven (28%) a non-exercising control (CON) group and three (12%) had both. One study[241] compared HIIT to a resistance training (RT) intervention. The RT group was excluded and the study assessed as a non-controlled trial.
2.3.1.1 Study quality and risk of bias

The 19 controlled trials were assessed for risk of bias (Table 2.1). Random sequence generation was deemed at low risk of bias in 10 (53%) studies and high in two (11%) studies that did not randomise participants. Five studies (26%) reported some degree of allocation concealment, but it was unclear in 11 (58%) studies whether this had been attempted. Due to the nature of the interventions, it is difficult to fully blind investigators however, six (32%) studies were blinded where possible e.g. at baseline and follow-up measurements or the data analyst. It was unclear in two (11%) controlled and three (16%) uncontrolled studies how many participants were lost to follow-up. None used the intention-to-treat principle for statistical analysis.
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<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>19</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Steckling (2016)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Unclear</td>
<td>90</td>
<td>NR</td>
</tr>
<tr>
<td>Stensvold (2010)</td>
<td>Described</td>
<td>Done</td>
<td>Unclear</td>
<td>No</td>
<td>7</td>
<td>NR</td>
<td>80</td>
</tr>
<tr>
<td>Støa (2017)</td>
<td>Not</td>
<td>Not</td>
<td>Unclear</td>
<td>No</td>
<td>23</td>
<td>NR</td>
<td>75</td>
</tr>
<tr>
<td>Terada (2013)</td>
<td>Described</td>
<td>Unclear</td>
<td>Some</td>
<td>No</td>
<td>Unclear</td>
<td>97.2</td>
<td>NR</td>
</tr>
<tr>
<td>Tjonna (2008)</td>
<td>Reported</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>13</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Random sequence generation: Not – non-randomised; reported – states that participants were randomised but not how; described – randomisation methods detailed
Concealment of allocation sequence: Unclear – not reported; Not – sequence not concealed to investigators; Done – sequence concealed to follow-up testers and data-analysts
Blinding: Unclear – not reported; Not – states follow-up non-blinded; Some – some investigators could be blinded
ITT – intention to treat; NR – not reported

NR – not reported
2.3.1.2 *Publication bias*

Visual interpretation of funnel plots suggested limited publication bias and as such no statistical adjustment was made. See Appendix 3 for figures.

2.3.1.3 *Heterogeneity*

Heterogeneity statistics are presented in Table 2.3. $I^2$ values were generally high, with all the within group comparisons indicative of wide heterogeneity (mean score = 89.1%). Controlled trials scored lower, with some showing homogenous statistics (mean CON = 49.2%; MICT = 31.3%).

2.3.2 *Participants*

There was a total of 665 participants included in the analysis, of which 381 (59%) underwent a HIIT intervention. Participants were aged 27-69 years and were described as having poly-cystic ovary syndrome[215] (N = 17 (3%)), non-alcoholic fatty liver disease[213] (N = 23 (3%)), metabolic syndrome (N = 308 (51%)) or T2DM (N = 317 (45%)).

2.3.3 *Exercise intervention characteristics*

Exercise interventions are described briefly in Table 2.2. Study protocols varied widely between both HIIT and MICT interventions. Nine studies employed the 4 x 4 minute AIT protocol and two a Wingate SIT protocol with the remaining 14 using other types of HIIT. The number (range 4-60), duration (range 8-230 seconds) and intensity (range 70-97% VO$_{2\max}$) of high-intensity intervals, as well as duration (range 12 seconds – 3 minutes) and intensity (range from complete rest - 70% HR$_{\text{max}}$) of recovery intervals varied between these HIIT protocols. Exercise session duration (mean 31 minutes, range 15-60 minutes) total training volume (MVPA/session x sessions/week x weeks trained; range 11-7740 minutes) and total length of intervention (range 2-16 weeks) also varied widely between all studies. Continuous training ranged from 30-60 minutes per session at intensities between 50% VO$_{2\max}$/HR$_{\text{max}}$ to 75% HR$_{\text{peak}}$. 
Table 2.2 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Wks</th>
<th>Mode</th>
<th>HIIT Intervals</th>
<th>Time (min)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sprint interval training</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freese (2015)</td>
<td>USA</td>
<td>45</td>
<td>52</td>
<td>Metabolic syndrome</td>
<td>6 Bike</td>
<td>4-8 x 30 s @ 9% FFM (Wingate)</td>
</tr>
<tr>
<td>Shaban (2014)</td>
<td>Canada</td>
<td>9</td>
<td>40</td>
<td>T2DM</td>
<td>2 Bike</td>
<td>4 x 30 s @ 100% eWLmax</td>
</tr>
<tr>
<td>Sjoros (2017)</td>
<td>Finland</td>
<td>21</td>
<td>49</td>
<td>NDH/T2DM</td>
<td>2 Bike</td>
<td>4-6 x 30 s @ 10% FFM (Wingate)</td>
</tr>
<tr>
<td><strong>Aerobic interval training</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almenning (2015)</td>
<td>Norway</td>
<td>17</td>
<td>27</td>
<td>PCOS</td>
<td>10 TM/B</td>
<td>4 x 4 min @ 90% HRmax 2-wk⁻¹</td>
</tr>
<tr>
<td>Mora-Rodriguez (2014)</td>
<td>Spain</td>
<td>48</td>
<td>52</td>
<td>Metabolic syndrome</td>
<td>16 Bike</td>
<td>10 x 60 s @ 95% HRmax 1-wk⁻¹</td>
</tr>
<tr>
<td>Heggelund (2011)</td>
<td>Norway</td>
<td>19</td>
<td>31</td>
<td>Metabolic Syndrome</td>
<td>8 TM</td>
<td>4 x 4 min @ 90% HRmax</td>
</tr>
<tr>
<td>Hollekim-Strand (2014)</td>
<td>Norway</td>
<td>37</td>
<td>56</td>
<td>T2DM</td>
<td>12 TM</td>
<td>4 x 4 min @ 80-85% HRpeak</td>
</tr>
<tr>
<td>Ramos (2016)</td>
<td>Australia</td>
<td>43</td>
<td>57</td>
<td>T2DM/Metabolic syndrome</td>
<td>16 TM/B</td>
<td>4 x 4 min @ 90-95% HRmax</td>
</tr>
<tr>
<td>Steckling (2016)</td>
<td>Brazil</td>
<td>17</td>
<td>54</td>
<td>Metabolic syndrome</td>
<td>12 TM</td>
<td>4 x 4 min @ 90-100% HRmax</td>
</tr>
<tr>
<td>Stensvold (2010)</td>
<td>Norway</td>
<td>21</td>
<td>50</td>
<td>Metabolic syndrome</td>
<td>12 TM</td>
<td>4 x 4 min @ 90% HRpeak</td>
</tr>
<tr>
<td>Støa (2017)</td>
<td>Norway</td>
<td>38</td>
<td>59</td>
<td>T2DM</td>
<td>12 Jog</td>
<td>4 x 4 min @ 82% VO₂max</td>
</tr>
</tbody>
</table>

Note: VO₂max = Maximum oxygen uptake, MICT = Moderate-Intensity Continuous Training.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Duration</th>
<th>Age</th>
<th>Primary Diagnosis</th>
<th>Exercise Type</th>
<th>Intensity</th>
<th>Recovery</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tjonna (2008)</td>
<td>Norway</td>
<td>32-52</td>
<td>16</td>
<td>Metabolic syndrome</td>
<td>TM</td>
<td>4 x 4 min</td>
<td>3 min</td>
<td>16</td>
<td>Non-exercising</td>
</tr>
<tr>
<td>Alvarez (2016)</td>
<td>Chile</td>
<td>23-45</td>
<td>16</td>
<td>T2DM</td>
<td>Jog</td>
<td>8-14 x 30-58 s</td>
<td>120-96 s</td>
<td>24</td>
<td>Non-exercising</td>
</tr>
<tr>
<td>Alvarez (2017)</td>
<td>Chile</td>
<td>35-34</td>
<td>12</td>
<td>Metabolic syndrome</td>
<td>Bike</td>
<td>12 x 60 s</td>
<td>2 min</td>
<td>38</td>
<td>Resistance training*</td>
</tr>
<tr>
<td>Cassidy (2016)</td>
<td>UK</td>
<td>23-60</td>
<td>12</td>
<td>T2DM</td>
<td>Bike</td>
<td>120-230 s</td>
<td>3 min</td>
<td>27</td>
<td>Non-exercising</td>
</tr>
<tr>
<td>Alvarez (2017)</td>
<td>Chile</td>
<td>35-34</td>
<td>12</td>
<td>Bike</td>
<td></td>
<td>2-8 x 2 min</td>
<td>2 min</td>
<td>10-34</td>
<td>30 min @ 50-70% VO₂max</td>
</tr>
<tr>
<td>Cassidy (2016)</td>
<td>UK</td>
<td>37-48</td>
<td>6</td>
<td>TM</td>
<td></td>
<td>10 x 30 s</td>
<td>3 min</td>
<td>19</td>
<td>NCT</td>
</tr>
<tr>
<td>Fex (2014)</td>
<td>Canada</td>
<td>16-60</td>
<td>12</td>
<td>NDH/T2DM</td>
<td>XT</td>
<td>10 x 30 s</td>
<td>3 min</td>
<td>60</td>
<td>60 min @ &gt;55% PEER</td>
</tr>
<tr>
<td>Hallsworth (2015)</td>
<td>UK</td>
<td>23-53</td>
<td>12</td>
<td>NAFLD</td>
<td>Bike</td>
<td>120-230 s</td>
<td>3 min</td>
<td>27</td>
<td>Non-exercising</td>
</tr>
<tr>
<td>Karstoft (2013)</td>
<td>Denmark</td>
<td>32-58</td>
<td>16</td>
<td>T2DM</td>
<td>Walk</td>
<td>10 x 3 min</td>
<td>3 min</td>
<td>60</td>
<td>60 min @ &gt;55% PEER</td>
</tr>
<tr>
<td>Little (2011)</td>
<td>Canada</td>
<td>8-63</td>
<td>2</td>
<td>T2DM</td>
<td>Bike</td>
<td>10 x 60 s</td>
<td>60 s rest</td>
<td>24</td>
<td>NCT</td>
</tr>
<tr>
<td>Madsen (2015)</td>
<td>Denmark</td>
<td>23-56</td>
<td>8</td>
<td>T2DM</td>
<td>Bike</td>
<td>10 x 60 s</td>
<td>60 s @ 90% HRmax</td>
<td>19</td>
<td>Non-T2DM controls*</td>
</tr>
<tr>
<td>Maillard (2016)</td>
<td>France</td>
<td>16-69</td>
<td>16</td>
<td>T2DM</td>
<td>Bike</td>
<td>60 x 8 s</td>
<td>12 s</td>
<td>20</td>
<td>40 min @ 55-60% HRR</td>
</tr>
<tr>
<td>Mitranun (2014)</td>
<td>Thailand</td>
<td>43-61</td>
<td>12</td>
<td>TM</td>
<td></td>
<td>4-6 x 60 s</td>
<td>2 min</td>
<td>30-40</td>
<td>Non-exercising</td>
</tr>
<tr>
<td>Robinson (2015)</td>
<td>Canada</td>
<td>38-52</td>
<td>2</td>
<td>Metabolic syndrome</td>
<td>Bike</td>
<td>4-10 x 60 s</td>
<td>2 min</td>
<td>10-20</td>
<td>20-50 min @ 60-65% HRpeak</td>
</tr>
<tr>
<td>Terada (2013)</td>
<td>France</td>
<td>14-62</td>
<td>12</td>
<td>T2DM</td>
<td>TM/B</td>
<td>7-14 x 60 s</td>
<td>3 min</td>
<td>30-60</td>
<td>30-60 min @ 70-75% HRpeak</td>
</tr>
</tbody>
</table>

eWLmax – estimated maximum workload; FFM – fat free mass; HIIT – high-intensity interval training; HR – heart rate; HRR – heart rate reserve; IR – insulin resistance; MICT – moderate-intensity continuous training; NCT – non-controlled trial; NDH – non-diabetic hyperglycaemia; PCOS – poly-cystic ovary syndrome; PEER – peak energy expenditure rate; RPE – rate of perceived exertion; T2DM – type 2 diabetes; TM – treadmill; TM/B – choice of treadmill or bike; VO₂max – maximum oxygen uptake; Wks – weeks; XT – elliptical cross-trainer; * Not included in analysis
Training modalities

In most cases HIIT was carried out in an exercise laboratory supervised by an investigator or trained exercise physiologist. One (4%) study investigated the practicality of home-based HIIT and two (8%) provided instructions for participants to exercise unsupervised in a gym. An exercise bike was used in 11 (44%) studies, seven (28%) used a treadmill, one (4%) an elliptical cross-trainer and two (8%) a free-living walking environment. Three (12%) studies allowed participants to choose between treadmill and exercise bike throughout the intervention.

Compliance, attrition and adverse events

Adherence to the intervention was reported by 15 (60%) studies and was 94±5% of exercise sessions. Minimum adherence to be included in analysis was specified by 14 (56%) studies and ranged from 70-85% attendance of exercise training sessions. Mean dropout from follow-up measurement was 15±8% in the 20 (80%) studies in which attrition was clear. Adverse events were reported in 13 (52%) studies. There were 3 injuries attributable to the exercise interventions; 2/3 (67%) occurred in the HIIT group. Injuries did not necessarily result in the affected participant having to drop out from the study or discontinue the intervention. No serious adverse events relating to the interventions were reported (see Table 2.1).

2.3.4 Meta-analysis

Data for fasting glucose, fasting insulin, HbA1c, insulin resistance, VO2max and body weight were included in the meta-analysis. Effect sizes for within groups and comparisons with CON and MICT are presented in Table 2.3. Within studies figures are presented in Appendix 4.

2.3.4.1 Insulin resistance

Insulin resistance was estimated in 15 (60%) studies. Of these, 11/15 (73%) had at least one control group. The HOMA model was employed by all studies. There was a significant reduction in HOMA score of -0.38 (-0.62, -0.14) with HIIT compared to baseline (Figure A 6.7). This effect persisted when HIIT was compared to a non-exercising control group (WMD -0.32; -0.54, -0.10), but there was no difference compared to MICT (-0.10; -0.47, 0.27; Figure 2.2a & b).

Sensitivity Analysis

When studies were categorised by the time between final exercise session and post-test blood sample, compared to MICT the improvement in insulin sensitivity was maintained only in the
studies in which it was reported to have been measured at least 72 hours after the last exercise session, although this was only based on two studies (Figure A 6.8b).

![Diagram showing change in insulin resistance after high-intensity interval training (HIIT) compared with control (CON) and moderate-intensity continuous training (MCT)]

**Figure 2.2** Change in insulin resistance after high-intensity interval training (HIIT) compared with a. control (CON) and b. moderate-intensity continuous training (MCT)
Baseline and post-intervention HbA1c was reported by 15 (60%) studies. Of these, 12/15 (80%) had at least one control group. Compared to baseline, there was a -0.34% (-0.56, -0.12%) reduction in HbA1c (Figure A.6.9). The effect compared to CON was stronger, with HbA1c levels -0.59% (-1.00, -0.18%) lower following HIIT. There was no change in HbA1c compared to MICT (Figure 2.3a & b).

**Figure 2.3** Change in HbA1c after high-intensity interval training (HIIT) compared with a. control (CON) and b. moderate-intensity continuous training (MICT)
Fasting glucose was reported in 22 (88%) studies. Of these, 16/22 (64%) were compared to at least one control group. There was a reduction in fasting glucose of -0.27 mmol·L\(^{-1}\) (-0.50, -0.05 mmol·L\(^{-1}\)) with HIIT compared to baseline (Figure A 6.10). This reduction was different compared to the CON (-0.57; -1.08, -0.07 mmol·L\(^{-1}\)) but not MICT (Figure 2.4a & b).

**Figure 2.4** Change in fasting glucose after high-intensity interval training (HIIT) compared with a. control (CON) and b. moderate-intensity continuous training (MICT)
2.3.4.4 Fasting insulin

Fasting insulin was reported in 15 (60%) studies. Of these, 11/15 (73%) were compared to at least one control group. There was a significant reduction in fasting insulin from baseline of -1.96μU·L⁻¹ (-3.22, -0.69μU·L⁻¹; Figure A 6.11). This effect was maintained compared to a non-exercising control group (-2.77μU·L⁻¹; -4.61, -0.93) however, there was no difference compared to MICT (Figure 2.5a & b).

![Image of Table and Graph]

Figure 2.5 Change in fasting insulin after high-intensity interval training (HIIT) compared with a. control (CON) and b. moderate-intensity continuous training (MICT)
2.3.4.5 Cardiorespiratory fitness

Cardiorespiratory fitness, expressed as VO$_{2\text{max}}$, was reported in 17 (68%) studies. Of these, 13/17 (76%) compared change in VO$_{2\text{max}}$ to a control group. Compared to baseline, there was a 0.26L·min$^{-1}$ increase in VO$_{2\text{max}}$ with HIIT (0.15, 0.37; Figure A 6.12). This increase was similar in comparison to CON (0.40; 0.11, 0.68; Figure 2.6a) and attenuated but still significant when compared to MICT (0.20; 0.04, 0.36 Figure 2.6b).

![Figure 2.6 Change in cardio-respiratory fitness after high-intensity interval training (HIIT) compared with a. control (CON) and b. moderate-intensity continuous training (MICT)](image-url)
2.3.4.6  Body Weight

Studies reported body weight (3/25; 12%), body mass index (1/25; 4%) or both (18/25; 44%). Of these, 16/22 (73%; body weight) and 15/20 (75%; body mass index) compared HIIT to at least one control group. Compared to baseline, there was a 1.18kg reduction in weight following HIIT (-1.82, -0.53kg; Figure A 6.13). Compared to CON, the reduction was 1.64kg (-2.01, -1.28kg; Figure 2.7a). In contrast, there was no difference in weight loss following HIIT compared to MICT overall (-0.43; -1.39, 0.52kg; Figure 2.7b). As expected, a similar pattern of changes was observed for BMI (data not shown).

FIGURE 2.7 Change in body weight after high-intensity interval training (HIIT) compared with a. control and b. moderate-intensity continuous training (MICT)
Table 2.3 Effect sizes of comparisons of high-intensity interval training after vs. before the intervention, compared to control and continuous training

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HOMA-IR</th>
<th>HbA1c (%)</th>
<th>Fasting glucose (mmol·L⁻¹)</th>
<th>Fasting insulin (μU·L⁻¹)</th>
<th>VO₂max (L·min⁻¹)</th>
<th>Body mass (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
<td>22</td>
<td>15</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>ES (95% CI)</td>
<td>-0.38 (-0.62, -0.14)</td>
<td>-0.34 (-0.56, -0.12)</td>
<td>-0.27 (-0.50, -0.05)</td>
<td>-1.96 (-3.22, -0.70)</td>
<td>0.65 (0.48, 0.81)</td>
<td>-1.18 (-1.82, -0.53)</td>
</tr>
<tr>
<td>p</td>
<td>0.002</td>
<td>0.002</td>
<td>0.019</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I² (%)</td>
<td>92.2</td>
<td>97.4</td>
<td>92.7</td>
<td>93.3</td>
<td>98.5</td>
<td>92.0</td>
</tr>
<tr>
<td><strong>Compared to control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td>7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>WMD (95% CI)</td>
<td>-0.32 (-0.55, -0.10)</td>
<td>-0.59 (-1.00, -0.18)</td>
<td>-0.57 (-1.08, -0.07)</td>
<td>-2.77 (-4.61, -0.93)</td>
<td>0.49 (0.15, 0.82)</td>
<td>-1.64 (-2.01, -1.28)</td>
</tr>
<tr>
<td>p</td>
<td>0.005</td>
<td>0.004</td>
<td>0.025</td>
<td>0.003</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I² (%)</td>
<td>30.8</td>
<td>79.0</td>
<td>92.2</td>
<td>29.2</td>
<td>92.3</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Compared to MICT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>WMD (95% CI)</td>
<td>-0.10 (-0.47, 0.27)</td>
<td>-0.05 (-0.18, 0.08)</td>
<td>-0.09 (-0.37, 0.20)</td>
<td>-0.75 (-2.67, 1.18)</td>
<td>0.49 (0.17, 0.80)</td>
<td>-0.43 (-1.39, 0.52)</td>
</tr>
<tr>
<td>p</td>
<td>0.588</td>
<td>0.428</td>
<td>0.561</td>
<td>0.446</td>
<td>0.003</td>
<td>0.376</td>
</tr>
<tr>
<td>I² (%)</td>
<td>80.1</td>
<td>0.0</td>
<td>37.3</td>
<td>0.0</td>
<td>92.3</td>
<td>53.9</td>
</tr>
</tbody>
</table>

* Within group effect sizes reflect the difference between the before and after values in the HIIT arm of all, controlled and non-controlled trials

CI – confidence interval; ES – effect size; HOMA-IR – homeostatic model assessment of insulin resistance; I² – Chi squared measure of heterogeneity; MICT – moderate-intensity interval training; N – number of studies included; VO₂max – maximum oxygen uptake; WMD – weighted mean difference
2.3.5 Meta-regression

Table 2.4 shows the β coefficients and 95% confidence intervals for the regression analyses. Interestingly, HIIT characteristics; interval intensity and weekly high-intensity exercise were positively associated with fasting glucose levels in the within group comparison. In contrast, study duration was inversely associated with fasting glucose levels. There were no other associations between HIIT characteristics and markers of insulin sensitivity or glycaemic control.

Improvements in HOMA-IR observed in the within group comparison were inversely associated with baseline scores. Using the regression equation, baseline HOMA-IR score would have to be ≥2.98 to experience a reduction of -0.5 units or more. In addition, improvements in fasting glucose in the within group and non-exercising control comparisons were associated with baseline levels. The regression equation suggested that for a 0.1 mmol·L⁻¹ or greater reduction in fasting glucose, baseline glucose would have to be ≥5.5 mmol·L⁻¹ (within group comparison) or ≥5.3 mmol·L⁻¹ (non-exercising control group comparison).
Table 2.4 Meta-regression coefficients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HOMA-IR</th>
<th>HbA1c</th>
<th>Fasting glucose</th>
<th>Fasting insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-coefficient (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WG</td>
<td>CON</td>
<td>WG</td>
<td>CON</td>
</tr>
<tr>
<td>Interval intensity</td>
<td>0.025 (-0.025, 0.075)</td>
<td>-0.002 (-0.034, 0.031)</td>
<td>0.013 (0.002, 0.024)</td>
<td>0.053 (-0.114, 0.221)</td>
</tr>
<tr>
<td></td>
<td>-0.204 (-0.730, 0.320)†</td>
<td>-0.090 (-0.685, 0.504)†</td>
<td>0.005 (-0.023, 0.032)</td>
<td>0.051 (-0.254, 0.355)</td>
</tr>
<tr>
<td>Time at high-intensity·wk⁻¹</td>
<td>0.040 (-0.005, 0.085)</td>
<td>0.002 (-0.014, 0.019)</td>
<td>0.025 (0.014, 0.035)</td>
<td>0.047 (-0.162, 0.255)</td>
</tr>
<tr>
<td></td>
<td>-0.010 (-0.046, 0.027)†</td>
<td>0.003 (-0.009, 0.015)†</td>
<td>0.013 (-0.008, 0.035)</td>
<td>-0.047 (-0.099, 0.005)</td>
</tr>
<tr>
<td>Weeks</td>
<td>-0.049 (-0.163, 0.066)</td>
<td>-0.018 (-0.139, 0.103)</td>
<td>-0.060 (-0.091, -0.028)</td>
<td>0.011 (-0.570, 0.592)</td>
</tr>
<tr>
<td></td>
<td>-0.011 (-1.413, 1.392)†</td>
<td>-0.145 (-0.305, 0.016)†</td>
<td>-0.137 (-0.215, -0.059)</td>
<td>-0.412 (-1.207, 0.381)</td>
</tr>
<tr>
<td>Baseline level</td>
<td>-0.412 (-0.679, -0.145)</td>
<td>-0.037 (-0.315, 0.241)</td>
<td>-0.248 (-0.416, -0.080)</td>
<td>-0.351 (-0.706, 0.003)</td>
</tr>
<tr>
<td></td>
<td>-0.187 (-0.664, 0.145)</td>
<td>-0.531 (-1.983, 0.921)</td>
<td>-0.432 (-0.668, -0.195)</td>
<td>-0.257 (-0.856, 0.342)</td>
</tr>
<tr>
<td>Change in VO₂max</td>
<td>-0.078 (-0.893, 0.737)</td>
<td>-0.238 (-1.384, 0.907)</td>
<td>-0.258 (-1.000, 0.430)</td>
<td>0.431 (-6.334, 7.196)</td>
</tr>
<tr>
<td></td>
<td>-0.381 (-4.234, 3.472)</td>
<td>0.837 (-45.644, 47.318)</td>
<td>-0.819 (-2.511, 0.874)</td>
<td>10.875 (-26.737, 48.487)</td>
</tr>
<tr>
<td>Change in body mass</td>
<td>-0.051 (-0.502, 0.401)</td>
<td>-0.016 (-0.211, 0.179)</td>
<td>0.137 (-0.115, 0.390)</td>
<td>-0.180 (-1.569, 1.209)</td>
</tr>
<tr>
<td></td>
<td>-0.156 (-0.836, 0.523)</td>
<td>-0.001 (-0.513, 0.512)</td>
<td>0.322 (-0.061, 0.705)</td>
<td>0.580 (-1.893, 3.053)</td>
</tr>
</tbody>
</table>

† Entered into model separately due to limited available data

CI – confidence interval; CON – non-exercising control group comparison; HbA1c – glycated haemoglobin; HOMA-IR – homeostatic model assessment of insulin resistance; WG – within group comparison
2.4 Discussion

2.4.1 Main findings

The results of this meta-analysis suggest that HIIT is as effective at improving measures of insulin resistance and glycaemic control as continuous exercise in individuals at risk of or with T2DM. Specifically, fasting glucose levels were reduced by 0.57 mmol·L⁻¹ and HbA1c by 0.59% compared to non-exercising control groups. There were also favourable effects on fasting insulin (-2.77 μU·L⁻¹), VO₂max (0.40L·min⁻¹) and body weight (-1.6kg) compared to a non-exercising control, which were comparable to those caused by MICT despite a lower overall training volume in the HIIT groups. In addition, cardiorespiratory fitness improved compared to MICT, to an extent comparable with previous meta-analyses of HIIT interventions.\(^{[217, 218]}\)

The primary modifiable elements of HIIT protocols, defined here as interval intensity and weekly time spent at high-intensity, did not consistently alter intervention effectiveness in terms of insulin resistance, fasting glucose, HbA1c or fasting insulin. Unexpectedly, higher-intensity intervals and time spent at high-intensity per week were associated with higher fasting glucose levels. In contrast, the longer the training intervention, the greater the improvement.

The higher HOMA-IR scores and fasting glucose levels were at baseline, the greater the reduction with HIIT, suggesting that HIIT may be most beneficial in those with the most severe dysglycaemia. Although body weight and cardiorespiratory fitness both improved following HIIT, changes in these outcomes did not predict improvements in insulin resistance or glucose regulation.

The findings from this meta-analysis extend the conclusions made by Adams\(^{[216]}\) who inferred that HIIT resulted in similar acute physiological adaptations as continuous training despite a lower energy expenditure. They complement the results from the study by Liubaoerjijin et al.\(^{[220]}\) who showed that the effects of both high-intensity continuous and interval training on fasting glucose, fasting insulin and HOMA-IR were comparable to those observed following MICT. On the other hand, Liubaoerjijin et al. found that HIIT was superior to MICT in reducing HbA1c, something not observed in the current study. This could be attributable to the inclusion of only participants with T2DM and studies lasting at least 12 weeks in the former analysis.

2.4.2 Clinical application

Under supervised, laboratory conditions HIIT is effective in improving insulin sensitivity and potentially therefore improving glycaemic control and diabetes-related outcomes. The 0.59%
reduction in HbA1c observed in this meta-analysis is comparable with declines reported previously following eight weeks of continuous exercise training, after which HbA1c was around 0.6% lower. \textsuperscript{119, 243, 244} This is a smaller, but comparable decrease to that observed with dual therapy glucose lowering medication. \textsuperscript{245} These reductions are likely to be clinically significant as a 0.9% reduction in HbA1c has been associated with a 13-25% reduced risk of diabetic complications including nephropathy and retinopathy. \textsuperscript{246, 247} It is worth noting that pharmacotherapy induced reductions in HbA1c have either been weakly, or not at all associated with reductions in cardiovascular mortality. \textsuperscript{248, 249} The leading cause of death in T2DM \textsuperscript{250} Physical activity, on the other hand, is known to reduce risk of CVD in individuals with T2DM, particularly when cardiorespiratory fitness is improved. \textsuperscript{113, 251, 252} Therefore, HIIT could be a viable option for glycaemic regulation, prevention of diabetic complications and CVD mortality.

Interestingly, meta-regression did not reveal a relationship between baseline HbA1c and change following HIIT. This could mean that HIIT has the potential to improve HbA1c regardless of severity. However, the negative association with fasting glycaemia does not add support for this hypothesis. Furthermore, the regression analysis suggests that to achieve the observed reduction in HOMA-IR of 0.4 units, baseline HOMA needs to be at least 2.7, a value that has been associated with the 50% most insulin resistant individuals within a population \textsuperscript{80, 81} and indicating that HIIT may improve insulin sensitivity only in those who are insulin resistant. It should be noted though that all studies reported that participants were dysglycaemic according to HbA1c (grand mean = 6.6%), but not necessarily according to HOMA-IR (grand mean = 2.6 units) which could explain this discrepancy. Given that HbA1c is a more stable measure of dysglycaemia between populations than HOMA-IR, it is reasonable to infer that HIIT is likely to cause reductions in individuals at risk of as well as with T2DM. Indeed, this appeared to be the case when this meta-analysis was not limited to those with or at high risk of T2DM. \textsuperscript{253} HIIT therefore has the potential to be used as an alternative therapeutic strategy to traditional physical activity interventions for those with or at risk of T2DM.

2.4.3 Potential mechanisms

Improvement in peripheral insulin sensitivity is one of the main mechanisms that explains the enhancement in glycaemia following exercise training and has been widely demonstrated following both acute and chronic exercise training, \textsuperscript{254} and is likely to occur following HIIT.

Improvements in insulin sensitivity have been associated with a reduction in body weight. \textsuperscript{255} We found that HIIT reduced both insulin resistance and body weight, although meta-regression did not reveal an association between these two factors. This is congruous with the findings of
Karstoft et al.\textsuperscript{[256]} who found that changes in body composition following HIIT explained less than 25% of improvements in insulin sensitivity in patients with T2DM. However, we were unable to determine whether body composition or fat distribution were affected by HIIT. A reduction in abdominal adiposity – often achieved with exercise training\textsuperscript{[257]} – may cause an improvement in hepatic insulin sensitivity,\textsuperscript{[258]} and it may be this that resulted in an improvement in HOMA-IR scores, rather than overall weight loss.

Furthermore, given the protective effect of cardiorespiratory fitness on HbA1c,\textsuperscript{[122]} morbidity\textsuperscript{[259]} and mortality\textsuperscript{[219]} in T2DM, it is notable that change in VO\textsubscript{2}max also did not predict changes in insulin resistance or glycaemic control in this study. It therefore appears that some adaptations associated with increased muscle oxidative capacity may be independent of those that promote metabolic health. Nonetheless, by providing evidence that HIIT leads to equivalent reductions in insulin resistance as MICT despite a lower overall workload, our study suggests that either the interval modality, or the greater exercise intensity facilitate benefits observed with continuous moderate-intensity exercise training. These are explained in more detail in the Overall Discussion, section 5.3. Briefly, there are a number of established metabolic pathways that are likely to be enhanced by HIIT, with some support from recent investigations. These include skeletal muscle glucose uptake,\textsuperscript{[260]} GLUT-4 content\textsuperscript{[188, 261]} and muscle glycogen depletion induced insulin sensitivity.\textsuperscript{[128, 174]}

With specific regards to prolonged exercise training, adaptations have been associated with changes in body composition, muscle physiology\textsuperscript{[188, 260-263]} and glucose metabolism\textsuperscript{[264]}. The results from this study suggest that HIIT has the potential to induce similar adaptations as MICT, despite a lower overall training volume.

The mechanisms that may be enhanced following HIIT compared to MICT need further elucidation as there is disagreement as to the optimum volume and intensity of exercise that stimulates the greatest benefits\textsuperscript{[265, 266]} and which of these factors is more important in metabolic health. We found no consistent relationships between exercise intensity or time spent at high-intensity and changes in glucose or insulin parameters, and it is unclear why longer periods spent exercising at the highest intensities were associated with increases in fasting glucose. It should be noted though, that the three studies that employed the highest intensity Wingate protocols were in the shortest 25% of studies in terms of number of weeks of training and therefore may not have been long enough to induce changes in fasting glucose.

Overall, it is difficult to determine which characteristics of HIIT protocols induce the observed improvements in these outcomes. HIIT presents a unique challenge to optimising exercise...
prescription given the range of variables that can be manipulated. Some, but not all, studies suggest that exercise intensity is the primary factor determining the degree of metabolic adaptations though these investigations have not assessed HIIT programmes specifically which, as discussed, introduce more nuanced exercise variables. The handful of training studies which have directly compared different intensity intervals have reported little difference between sub-maximal vigorous-intensity and maximal-intensity intervals. Lunt et al. found improvements in cardio-metabolic outcomes in 45 sedentary, overweight adults that were superior in SIT and AIT to MICT, but not different between HIIT groups. The HIIT groups were not matched for energy expenditure, with the AIT group performing significantly more physical activity than the SIT group. Boyd et al. compared 60 second intervals at either 100% or 70% VO₂peak in 19 overweight and obese men for three weeks. They found that VO₂peak and markers of oxidative capacity improved in both groups with the improvements in the lower-intensity group non-significantly smaller than those in the higher-intensity group. However, the lower-intensity group performed less total work as the intervals were the same length as in the higher-intensity group. There were no changes in insulin sensitivity. Another study compared energy matched HIIT with 60 second intervals at 80% (low), 115% (moderate) or 150% (high) of pre-training peak work rate in healthy young adults. They found that VO₂peak improved in all groups but significantly more in the moderate than low group, with no difference between moderate and high. Taken together with those from the current study, these results indicate that increasing intensity enhances benefits up to a threshold, above which the magnitude of improvements remains the same.

2.4.4 Strengths and Limitations

The strengths of this review include the comprehensive search strategy employed, the use of random effects meta-analysis and the focus on metabolic outcomes and participants at high risk of or with T2DM. The studies included in this analysis mostly (20/25; 80%) lasted at least eight weeks and 11 out of the 15 (73%) studies which measured HOMA-IR reported taking blood samples ≥48 hours after the last bout of exercise in order to avoid confounding with any acute effects on insulin sensitivity.

However, this meta-analysis is not without limitation. Firstly, there was wide heterogeneity between HIIT and MICT interventions making it difficult to generalise conclusions and make direct comparisons between HIIT and MICT. This issue was addressed to the best of our ability by performing meta-regression. Nonetheless, this study highlights the need for more randomised controlled trials to be carried out in the future using standardised continuous
training protocols. In addition, it is possible that the use of HOMA-IR may underestimate the impact of HIIT on insulin sensitivity given that HOMA is more representative of hepatic insulin resistance\cite{231} and exercise is more likely to affect peripheral insulin resistance.\cite{132}. This is demonstrated by the attenuation of the superior effect of HIIT to MICT found in the first version of this meta-analysis, which included dynamic measures of insulin sensitivity not available in the present analysis.\cite{253} It is also difficult to apply the reduction in HOMA-IR score found in this meta-analysis in a wider context and the clinical relevance of a change of 0.3 units may not be sufficient to reduce the risk of CVD in insulin resistant individuals. On the other hand, it may be that insulin sensitivity would continue to improve with on-going training however, there was no evidence that effect sizes were greater in studies of a longer duration and therefore this is speculation.

Despite the safety concerns associated with HIIT, just over half the included studies reported whether there were any adverse events or issues during maximal exercise tests or screening. Three injuries were reported to be a result of the interventions thus making it difficult to determine whether HIIT carries more risk than MICT.

Furthermore, HIIT has been promoted as being a time-efficient exercise modality. This review provides some support that exercise induced health benefits can be achieved with as little as 12 ± 6 minutes of VPA performed three times per week. However, it is worth noting that in total, exercise sessions took 31 ± 10 minutes to complete. It is important to elucidate whether the requirement to set aside 30 minutes three times per week to perform HIIT addresses the perceived barrier to physical activity of “lack of time”. With this in mind, it is also important to consider other barriers, such as enjoyment and perceived exertion during HIIT compared to MICT, something not considered in this meta-analysis. Although HIIT requires participants to exercise at a higher intensity than MICT, albeit for a shorter period of time, the intermittent nature of efforts could be perceived to be less tedious or more rewarding than a longer, continuous effort. According to cognitive behavioural theory, successfully completing bouts of “hard” exercise may result in feelings of achievement and reward thus increasing self-efficacy and motivation to repeat the behaviour.\cite{270} Please refer to Section 5.4.2 for a more in depth discussion of psychological responses to HIIT.

2.4.5 Suggestions for future research

Our results suggest that HIIT per se has the potential to improve clinically important health outcomes, regardless of the precise protocol employed. Therefore, the feasibility of performing HIIT in non-laboratory settings with realistic supervision ratios should be assessed. Only five of
the studies included in this review were conducted in either a “free-living” or “real world” context.\cite{177, 212, 213} If HIIT is to be recommended to the general population it must be practical and accessible. Furthermore, a greater understanding of the potential mechanisms stimulating the more potent effects of HIIT compared to continuous training should be elucidated so they can be maximised through exercise training. For instance, it would be useful to establish whether there is an optimal intensity: duration ratio so that protocols can be manipulated to an individual’s preference.

2.4.5.1 Conclusions

In conclusion, this study shows that HIIT conveys benefits to metabolic health which are equivalent to the effect of traditional continuous training. HIIT may therefore be suitable as an alternative in the promotion of metabolic health and weight loss. However, given the identified limitations, more research is needed to determine both behavioural responses long term clinical benefits.
3 Associations of A) increasing physical activity intensity and B) performing continuous vs. intermittent physical activity with markers of insulin sensitivity

Chapter overview

This chapter reports two cross-sectional analyses of data from the Walking Away from Type 2 Diabetes randomised control trial. The results of the three year follow-up study had not been published when this analysis was started. Analysis A explores the relationship between exercise intensity and markers of insulin sensitivity. In Analysis B, using baseline, 12 and 36 month data combined, I investigate how accumulating MVPA in continuous bouts of ≥10 minutes compared to sporadically (<10 minutes) is associated with markers of insulin sensitivity. Due to the volume of participant data lost to follow-up, for Analysis A, it was decided that baseline analysis was most appropriate. Originally, this study was carried out using predefined categories of physical activity intensity (i.e. light, moderate and vigorous-intensity physical activity) however, given the negligible participation in vigorous-intensity physical activity, the idea to analyse this relationship on a more continuous scale arose. Using 500 count per minute (cpm) intensity bands from 0 to >4500 cpm, I present the relationship between increasing physical activity intensities and markers of insulin sensitivity. The chapter concludes with a discussion of the implications the findings have for physical activity guidelines.

Key findings

Analysis A

- Favourable differences in 2 hour glucose and insulin responses and insulin sensitivity get larger with increasing physical activity intensity.

- The lowest intensity band (0-499 cpm) was positively associated with postprandial responses and negatively associated with insulin sensitivity levels.

- The relationship between physical activity intensity and markers of insulin sensitivity appears to be linear up to 4000 cpm (approximately 4 METs), with no additional benefit observed above this level.
**Analysis B**

- Total and continuously accumulated (≥10 minutes) MVPA were favourably associated with fasting and 2 hour insulin and insulin sensitivity.

- Sporadically accumulated MVPA was negatively associated with 2 hour insulin levels although this did not translate to a relationship with Matsuda-ISI.

- The results were similar when a 2 minute break in continuous bouts was allowed, and when BMI was included in the model.

**Publications and conference presentations**

Analysis B has been published in Medicine and Science in Sports and Exercise (Appendix 5):


**Author contribution**

Although these are secondary data analyses, I significantly contributed to the generation of data used in this chapter by spending a three week placement at Unilever conducting biochemical analysis of the 36 month plasma and serum samples used in Analysis B. This includes running insulin ELISA’s to produce data reported in this chapter. Dr Charlotte Edwardson processed the accelerometer data for both studies but I was responsible for combining and cleaning accelerometer, demographic and biochemical datasets.

**Analysis A**

Dr Alex V Rowlands helped to generate the idea to analyse the data in 500 cpm increments. I performed all the statistical analyses, wrote this report and prepared the manuscript for publication (Appendix 6).

**Analysis B**

Dr Danielle Bodicoat provided statistical support on how to analyse the data and, taking her advice, I was able to carry out the statistical analysis and evaluate the results presented here.
3.1 Introduction

The physical activity guidelines (described in section 1.2.2) are easy to follow and appear to be a rare instance where “one size fits all”; the rationale being that all individuals would significantly reduce their risk of chronic disease if they followed them.[271] In practice, these simple instructions are restrictive and vague, not necessarily disease specific and as such do not appear to encourage participation.[145] The barriers to exercise, described in section 1.2.3.2, suggest that there is a demand for a greater variety of evidence-based recommendations. Furthermore, there has been a recent shift towards personalised medicine, which aims to increase the number of people benefitting from the treatment they receive by targeting therapy based on an individual’s physiology. Unlike pharmaceutical medication, physical activity has profound beneficial effects on the underlying physiology of numerous conditions, making it an effective all-round treatment. However, it is reasonable to propose that specific exercise prescriptions could be designed to target different health outcomes. The challenge facing exercise physiologists is in devising a range of novel exercise regimes that are both effective and appealing. The current interest in HIIT is one example of the move in this direction.

In a similar way that technology is facilitating the use of precision medicine, development of devices such as accelerometers, which track physical activity in free-living conditions is providing reliable, rich data that can be used to more accurately quantify the dose-response relationship between physical activity and health. Historically, physical activity volume, measured using questionnaires, was dichotomised into high versus low levels and prospectively associated with the relative risk (RR) of disease or mortality.[272] Studies almost unanimously reported greater relative risk reductions in the groups performing higher levels of physical activity. As investigations progressed, graduated categories of physical activity volume such as total time, metabolic equivalent task (MET) hours or energy expenditure (measured in kilocalories) per week were calculated to assess the cumulative effect of increasing physical activity levels on health.[141, 142, 273] These reports demonstrate that the RR of disease or mortality is reduced with each increment in physical activity volume, with the most pronounced reductions observed between the lowest levels of physical activity i.e. increasing from none to some physical activity.

The limitations of using self-report to measure physical activity have been extensively critiqued.[274] In summary, the majority of physical activity questionnaires were developed in Western countries and aimed at white, middle-aged, working-middle class men and women,[275] meaning that results are generalisable mainly to Caucasians. In addition, time and cost considerations mean that recall must either be broad over a long period (up to a year), or
detailed and for a short period, 24 hours to one week. Not only are there problems with recall ability, but questionnaires are subject to interpretation of terms and desirability bias.\(^{274}\) It is also difficult to accurately recall low-intensity and low-volumes of sporadic physical activity.\(^{276, 277}\) Empirical evidence has demonstrated that the correlation between self-reported and objectively-measured physical activity is weak, especially when individuals are asked to estimate activity intensity, with light-intensity physical activity (LPA) often reported as MPA.\(^{149, 278}\) Furthermore, the lowest unit these questionnaires demand physical activity to be recalled in is five minute bouts,\(^{279}\) which could be argued to be the minimum period in which physical activity can be self-reported to any degree of accuracy.

The use of accelerometers addresses these issues to a large extent, enabling comprehensive surveillance of free-living physical activity in large population samples. To date, the scope of objectively measured physical activity has mostly been restricted to broad overviews of activity behaviour with the opportunity to describe more nuanced patterns yet to be fully grasped. This chapter presents two analyses of the same data-set, each addressing an aspect of physical activity guidelines and population surveillance.

### 3.1.1 Intensity

The progression of objective measures of activity monitoring technology is facilitating research into physical activity interventions encompassing the entire intensity spectrum; from replacing sedentary time with LPA\(^{117, 118, 280}\) to investigation of the minimum volume of maximal intensity physical activity required to improve health.\(^{281}\) However, classifying intensity using accelerometer data presents its own challenge. To allow comparison with previous research, accelerometer-measured physical activity intensity has been calibrated against energy expenditure and walking speeds then categorised as sedentary, light, moderate or vigorous, with MPA and VPA usually combined and analysed as MVPA.\(^{136}\) However, the number of counts accumulated reflects an absolute, as opposed to a relative intensity that is specific to a particular device. For example, the most commonly used waist-worn accelerometer (Actigraph) cut-points were calibrated on young (mean age 24 years), recreationally active individuals where a treadmill walking speed of 4.8 km·h\(^{-1}\), equivalent to three METs (the lower threshold for MPA)\(^{282}\) recorded ~3000 cpm. It is likely that in a sedentary population, a walking speed of 4.8 km·h\(^{-1}\) is likely to elicit an intensity greater than three METs, but an accelerometer would still record 3000 cpm. Therefore, it is necessary to determine population-dependent cut-points. As demonstrated by the Generation 100 study,\(^{283}\) this can have numerous permutations e.g. depending on sex or fitness level, even in a relatively homogenous population.
Another important consideration is that whilst the “construct validity” of these thresholds have been tested, albeit mostly in young, healthy populations, the “external validity” (e.g. the dose-response relationship between incremental accelerometer measured physical activity intensities and health outcomes) has received less attention.

3.1.2 Bout length

The development of accelerometer epoch record length has brought the recommendation that activity bouts should be at least 10 minutes in duration into question. The evidence supporting this claim is sparse, and it is possible that it reflects the hitherto difficulty in assessing the effect of physical activity bouts shorter than this on health. In 2009, Murphy et al. concluded that there was little difference in health outcomes when physical activity was accumulated in bouts <10 minutes compared to longer, continuous bouts of equal energy expenditure, although the available data was limited to fitness and blood pressure outcomes only. There was not enough information to determine the effect of bout length on outcomes such as adiposity, lipaemia and glycaemia. Nonetheless, this review supports the notion that MVPA could be accumulated in bouts lasting <10 minutes.

Since the use of accelerometers has become widespread, it is becoming possible to determine whether physical activity accumulated in bouts <10 minutes are beneficial to various aspects of health. Several cross-sectional studies have reported that there is no difference in health outcomes when MVPA is performed in bouts lasting ≥10 minutes or less (hereafter; continuous bouts and sporadic bouts, respectively) when controlling for total MVPA. For instance, results from 2019 middle-aged males and females in the Framingham Heart Study showed that both continuous and sporadic MVPA were inversely associated with more favourable blood lipid levels, body composition and overall Framingham risk score. Similarly, in the Canadian Health Measures Survey, accelerometer data from 1119 adults showed that both continuous and sporadic accumulation of MVPA were associated with incidence of the metabolic syndrome, with no difference between them. Several reports from 2003-2006 NHANES data show that regardless of whether it is accumulated continuously or sporadically, MVPA is associated with a lower BMI, incidence of metabolic syndrome and its contributing factors, and seven year mortality risk. In individuals with moderate or high risk of T2DM, both continuous and sporadic MVPA were associated with lower HbA1C. It appears that the recommendation to perform MVPA is based on what has previously been measurable, rather than what is physically plausible. To the best of my knowledge, no studies have reported the association of continuous vs. sporadic MVPA with markers of glucose regulation and insulin sensitivity.

The aims of this chapter therefore, were, in the free-living environment of individuals at high risk of T2DM recruited from primary care in the UK to A) determine the association of time spent in objectively assessed incremental physical activity intensities with markers of insulin sensitivity and B) assess whether MVPA accumulated in bouts of 10 minutes or more differentially predict markers of insulin sensitivity compared to when MVPA is accumulated in bouts of any length.

The hypotheses were that A) that there would be a dose-response relationship between intensity and markers of insulin sensitivity and B) there would be no difference between sporadically and continuously accumulated MVPA and markers of insulin sensitivity.

3.2 Methods

Retrospective analyses of data from the Walking Away from Type 2 Diabetes randomised control trial are reported in this chapter. In brief, 833 participants from 10 primary care practices who were identified as being at high risk of dysglycaemia/undiagnosed T2DM (individuals scoring within the 90th percentile in each practice) were invited to take part and, following baseline assessment, practices were randomly assigned to either a control or intervention arm. Participants from control practices were given a lifestyle advice leaflet based on psychological theories of disease representations.[291] Participants from intervention practices were invited to take part in a pragmatic evidence-based structured education programme designed to promote physical activity and a healthy lifestyle. The programme involves attendance at a three hour group education session. The primary aim of the education session was to promote walking activity by targeting perceptions and knowledge of dysglycaemia and physical activity self-efficacy, as well as facilitating self-regulation such as goal setting, self-monitoring (using pedometers) and relapse prevention.[292] Intervention allocation was not considered in either analysis. All participants provided written informed consent and ethical approval was obtained from a local NHS research ethics committee.

3.2.1 Participants

Individuals identified as being at high risk of or with dysglycaemia; impaired glucose tolerance (2 hour glucose ≥7.8 and <11.1 mmol·L⁻¹) and/or impaired fasting glycaemia (fasting glucose ≥6.1 and <6.9 mmol·L⁻¹) or undiagnosed T2DM were recruited from primary care practices in Leicestershire, UK during 2010. Potential participants were identified using the Leicester Practice Risk Score, which has been shown to have good reliability in predicting prevalent dysglycaemia[157, 293] and includes questions about anthropometry, ethnicity, family history and antihypertensive therapy; each weighted based on epidemiological evidence. Participants were
unaware of their diabetes risk before entering into the study and were excluded if they had known T2DM or were unable to take part in any walking activity. Baseline measurements were performed before treatment allocation by trained staff, who were blinded to study outcomes and followed standard operating procedures.

3.2.2 Objective measurement of physical activity

Participants were instructed to wear a waist-worn accelerometer (Actigraph GT3X, Pensacola, FL, USA) for seven consecutive days, removing for water-based activities and non-waking hours. Data were recorded in 15 second epochs and re-integrated into 60 second epoch files for this analysis. Total wear-time, steps per day and number of valid days were calculated. For a day to be considered valid, at least 600 minutes of wear-time had to be recorded; non-wear time was defined as more than 60 minutes of continuous zero counts. All accelerometer-derived variables were computed by summing the values over all valid days and calculating the mean value per valid day. Data were analysed using a commercially available software package (KineSoft V3.3.76, Kinesoft, New Brunswick, Canada; www.kinesoft.org).

3.2.2.1 Analysis A

Activity intensity was generated in 500 cpm increments up to 4499 cpm. Any counts recorded above 4500 cpm were grouped together due to a loss of power above this intensity. Using a regression equation from a similar population, we estimated the number of METs the midpoint of these increments equated to (Table 3.1). The number of minutes spent within each intensity band per day was calculated by summing the number of minutes recorded and dividing by the number of valid days.

<table>
<thead>
<tr>
<th>Intensity (cpm)</th>
<th>0-499</th>
<th>500-999</th>
<th>1000-1499</th>
<th>1500-1999</th>
<th>2000-2499</th>
<th>2500-2999</th>
<th>3000-3499</th>
<th>3500-3999</th>
<th>4000-4999</th>
<th>≥4500</th>
</tr>
</thead>
<tbody>
<tr>
<td>METs</td>
<td>2.3</td>
<td>2.6</td>
<td>2.9</td>
<td>3.2</td>
<td>3.5</td>
<td>3.7</td>
<td>4.0</td>
<td>4.3</td>
<td>4.6</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Estimation based on equation from Hall et al. METs are calculated from the midpoint of the intensity range using the following equation:

\[ EE = \text{METs} \times \left( \frac{60(3.28 + 0.0009 \text{cpm})}{BW} \right) \]

Where BW is body weight (kg) and EE is energy expenditure (kCal·h⁻¹·kg⁻¹).

Cpm – counts per minute; MET – metabolic equivalent task
3.2.2.2 Analysis B

For this analysis, activity was categorised as follows: sedentary behaviour (<100 cpm); LPA (100 to <1952 cpm); MPA (1952 to <5725 cpm) and VPA (≥5725 cpm).[296] For each intensity, time accumulated in bouts lasting <10 minutes, ≥10 minutes (continuous) or ≥10 minutes (with a maximum of a 2 minute break) was calculated. Total MVPA (sporadic and continuous combined) was also calculated.

3.2.3 Demographic, anthropometric & biochemical

On the participants’ first study visit, information regarding ethnicity, smoking status and antihypertensive medication were collected by a health care professional. Body weight (Tanita TBE 611, Tanita, West Drayton, UK), waist circumference (midway between the lower costal margin and the iliac crest) and height were measured to the nearest 0.1kg and 0.5cm respectively.

A standard OGTT using a 75g glucose load was administered to all participants. Individuals were asked to avoid caffeine and strenuous exercise in the preceding 24 hours and to consume only water from 10pm the evening prior to their visit. Fasting and 2 hour post-challenge plasma glucose samples were measured using the glucose oxidase method (Beckman Auto Analyzer, Beckman, High Wycombe, UK) at the Leicester Royal Infirmary. Plasma samples were frozen at -80°C and analysed for fasting and 2 hour insulin at the end of baseline data collection using enzyme linked immune-assay (80-INSHU-E01.1, Alpco Diagnostics 26G Keewaydin Drive, Salen, NH, USA) within a specialist laboratory (Unilever R&D, Bedfordshire, UK). Analysis was conducted by individuals blinded to the patient’s identity and using stable methodologies, standardised to external quality assurance values.

3.2.4 Measures of insulin sensitivity

The HOMA-IS and Matsuda indices were used to estimate insulin sensitivity:[231, 297]

\[
\text{HOMA-IS} = \frac{1}{\text{HOMA-IR}} = \frac{22.5}{(G_0 \cdot I_0)}
\]

\[
\text{Matsuda ISI} = \frac{10,000}{\sqrt{G_0 \cdot I_0 \cdot G_{120} \cdot I_{120}}}
\]

Equation 3.1 Calculation of homeostatic model assessment (HOMA-IS) and 3.2 Matsuda index of insulin sensitivity (Matsuda ISI)

\(G_0 = \) fasting plasma glucose; \(I_0 = \) fasting plasma insulin; \(G_{120} = \) 2 hour glucose; \(I_{120} = \) 2 hour insulin

These models have been shown to correlate reasonably with gold-standard measures of insulin sensitivity.[298] Matsuda ISI is more likely to reflect factors related to insulin release and
peripheral insulin sensitivity whereas HOMA-IS may be a better measure of hepatic insulin sensitivity.\(^{[132]}\)

3.2.5 Follow-up measures

All measures; physical activity, demographic, anthropometric and biochemical were repeated at 12 and 36 months after the baseline visit.

3.2.6 Statistical analysis

Data were analysed using Stata V.14 (StataCorp. 2015, Stata Statistical Software release 14, College Station, TX, USA).

3.2.6.1 Analysis A

Log-linear regression was used to assess the association of physical activity intensity with fasting and 2 hour glucose and insulin levels, and insulin sensitivity at baseline.\(^{[299]}\) Dependent variables were log transformed as they displayed non-parametric distributions. Time spent in each of the physical activity intensity increments was entered into models separately due to the correlation between groupings. Model one was adjusted for age, sex, ethnicity, smoking status, beta-blocker medication and accelerometer wear time. Adjustment for BMI was also made in model two. Sensitivity analyses assessed whether the associations were modified by diagnosis of impaired glucose regulation, sex or age (<65 or ≥65 years). Data were not adjusted for overall physical activity volume (counts per day) due to collinearity (Table 3.2).

3.2.6.2 Analysis B

Two analyses were carried out, first a regression analysis on baseline data in order to allow comparison with Analysis A and second, a generalised estimating equation (GEE) model so that 12 and 36 month data could also be included. Twenty-four month data was not included since insulin was not analysed at this time-point. A GEE model allows longitudinal analysis of repeated measures outcomes on individuals considered to be a random sample of a population representing a specific group. This method also reduces loss of data over time as results are included if they exist at any time point for each participant. The Gaussian family was used as once the data were log transformed it displayed a normal distribution. An exchangeable correlation matrix was applied since the correlation between covariates could be assumed to be the same over time. For both the regression and the GEE analyses, total MVPA was entered separately in its own model and continuous and sporadic bouts were entered together. Both analyses were controlled for wear time, valid days, LPA, age, sex, ethnicity, smoking status, beta-blocker, other anti-hypertensive and lipid lowering medication. In order to examine the extent
to which adiposity may attenuate these relationships, further adjustment for BMI was made. As a sensitivity analysis, models were re-run with continuous bouts allowing for a two-minute exception.

For both studies, coefficients were back transformed and represent the factor by which the outcome is multiplied by (95% CI) for a given unit of time spent at each intensity. Data in the text is presented as the percentage difference (95% CI) in the association between 10 minutes of physical activity and the outcome. Effect sizes were calculated according to Cohen’s $f$ and the $\eta^2$ is presented as a percentage. Effect size magnitudes were interpreted based on those outlined by Cohen (1988) [300] and Miles, & Shevlin (2001) [301] Adjustment was not made for multiple comparisons, therefore data were viewed with caution and in relation to the overall pattern of results.
<table>
<thead>
<tr>
<th>Intensity (cpm)</th>
<th>0 - 500</th>
<th>500 - 1000</th>
<th>1000 - 1500</th>
<th>1500 - 2000</th>
<th>2000 - 2500</th>
<th>2500 - 3000</th>
<th>3000 - 3500</th>
<th>3500 - 4000</th>
<th>4000 - 4500</th>
<th>≥4500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counts per day</td>
<td>-0.474</td>
<td>0.615</td>
<td>0.736</td>
<td>0.780</td>
<td>0.777</td>
<td>0.707</td>
<td>0.627</td>
<td>0.620</td>
<td>0.578</td>
<td>0.561</td>
</tr>
<tr>
<td>0-500</td>
<td>-0.443</td>
<td>-0.544</td>
<td>-0.528</td>
<td>-0.439</td>
<td>-0.321</td>
<td>-0.221</td>
<td>-0.205</td>
<td>-0.147</td>
<td>-0.135</td>
<td></td>
</tr>
<tr>
<td>500-1000</td>
<td>0.863</td>
<td>0.672</td>
<td>0.469</td>
<td>0.265</td>
<td>0.098</td>
<td>0.028</td>
<td>0.026</td>
<td>0.026</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000-1500</td>
<td>0.900</td>
<td>0.703</td>
<td>0.433</td>
<td>0.216</td>
<td>0.129</td>
<td>0.089</td>
<td>0.089</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1500-2000</td>
<td>0.891</td>
<td>0.626</td>
<td>0.372</td>
<td>0.226</td>
<td>0.130</td>
<td>0.100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000-2500</td>
<td>0.816</td>
<td>0.531</td>
<td>0.324</td>
<td>0.193</td>
<td>0.147</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2500-3000</td>
<td>0.783</td>
<td>0.496</td>
<td>0.271</td>
<td>0.151</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000-3500</td>
<td>0.752</td>
<td>0.421</td>
<td>0.209</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3500-4000</td>
<td>0.771</td>
<td>0.411</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000-4500</td>
<td>0.626</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

cpm—counts per minute
3.3 Results

3.3.1 Data inclusion

To be included, a participant had to have a minimum of four valid days of accelerometer data as well as fasting glucose and insulin data to allow for an assessment of HOMA-IS.

3.3.1.1 Analysis A

At baseline, valid accelerometer data were available for 727 (87%) participants and 569 (66%) participants had fasting blood data. Of these individuals, 508 (61%) participants also had complete 2 hour glucose and 2 hour insulin (Figure 3.1). Those who were excluded from the HOMA-IS analysis (N = 158) tended to be younger (61.7 years for missing vs. 63.8; p<0.001) and were more likely to be female (42% vs. 34%; p=0.021). However, there was no difference in BMI, fasting or 2 hour glucose.

3.3.1.2 Analysis B

This analysis includes participants with the above available data collected at least once (i.e. at baseline and/or 12 months and/or 36 months). There were 19 (2%) participants with missing or invalid accelerometer data and, due to cessation of bleeding or insufficient plasma volumes for the fasting insulin analysis, 71 (9%) with missing fasting blood samples at all three time points. In order to be included in the analysis, both accelerometer and fasting data had to be available at a given time point. This meant that a further 48 (6%) participants were excluded (Figure 3.1).

Baseline characteristics of participants included in Analysis A and B are displayed in Table 3.3.
Figure 3.1 Participants included and excluded from the WA analyses
### Table 3.3 Baseline characteristics of participants included

<table>
<thead>
<tr>
<th></th>
<th>Analysis A</th>
<th>Analysis B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (IQR)/number (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>65 [60-69]</td>
<td>65 [59-69]</td>
</tr>
<tr>
<td><strong>Sex (female)</strong></td>
<td>191 (33.6)</td>
<td>256 (36.8)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White European</td>
<td>514 (90.3)</td>
<td>615 (88.5)</td>
</tr>
<tr>
<td>Other</td>
<td>55 (9.7)</td>
<td>80 (11.4)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>49 (8.6)</td>
<td>63 (9.0)</td>
</tr>
<tr>
<td><strong>BMI (kg·m(^{-2}))</strong></td>
<td>31.4[28.4-35.0]</td>
<td>31.4[28.3-35.1]</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-blockers</td>
<td>101 (17.8)</td>
<td>121 (17.4)</td>
</tr>
<tr>
<td>Other hypertensive drug</td>
<td>236 (41.5)</td>
<td>218 (31.4)</td>
</tr>
<tr>
<td>Lipid lowering drugs</td>
<td>195 (34.3)</td>
<td>185 (26.6)</td>
</tr>
<tr>
<td><strong>Accelerometer variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valid days worn</td>
<td>6 [6-7]</td>
<td>6 [5-6]</td>
</tr>
<tr>
<td>Wear time (mins day(^{-1}))</td>
<td>862 [804.3-909.5]</td>
<td>857.7 [797.5-909.0]</td>
</tr>
<tr>
<td>Steps per day</td>
<td>6148 [4425-8174]</td>
<td>6079 [4317-8302]</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFG</td>
<td>25 (4.4)</td>
<td>34 (4.9)</td>
</tr>
<tr>
<td>IGT</td>
<td>97 (17.1)</td>
<td>117 (16.9)</td>
</tr>
<tr>
<td>IFG + IGT</td>
<td>27 (4.8)</td>
<td>33 (4.8)</td>
</tr>
<tr>
<td>Undiagnosed T2DM</td>
<td>18 (3.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.9 [5.6-6.1](^{\dagger})</td>
<td>5.8 [5.6-6.1]</td>
</tr>
<tr>
<td><strong>Markers of insulin sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol·L(^{-1}))</td>
<td>5.2 [4.9-5.7]</td>
<td>5.2 [4.8-5.6]</td>
</tr>
<tr>
<td>2 hour glucose (mmol·L(^{-1}))</td>
<td>6.0 [4.9-7.9]</td>
<td>5.8 [4.8-7.4]</td>
</tr>
<tr>
<td>Fasting insulin (μU·L(^{-1}))</td>
<td>8.8 [6.0-13.0]</td>
<td>8.8 [5.9-13.0]</td>
</tr>
<tr>
<td>2 hour insulin (μU·L(^{-1}))</td>
<td>46.5 [25.8-82.2](^{\dagger})</td>
<td>45.1 [23.8-77.8](^{\ddagger})</td>
</tr>
<tr>
<td>HOMA-IS</td>
<td>0.48 [0.32-0.73]</td>
<td>0.49 [0.32-0.77]</td>
</tr>
<tr>
<td>Matsuda ISI</td>
<td>86.3 [51.7-159.6](^{\dagger})</td>
<td>91.8 [53.4-164.8](^{\ddagger})</td>
</tr>
</tbody>
</table>

\^ \(N = 548\); \(\dagger N = 490\); \(\ddagger N = 615\); due to missing data

IQR–interquartile range; BMI–body mass index; IFG–impaired fasting glucose; IGT–impaired glucose tolerance; T2DM–type 2 diabetes mellitus; HOMA-IS–homeostatic model assessment of insulin sensitivity; ISI–insulin sensitivity index
3.3.2 Analysis A

3.3.2.1 Physical activity

Of those with both valid accelerometer and fasting glucose and insulin samples, mean accelerometer wear time per day was 859 minutes (14.3 hours). Time spent in each 500 cpm intensity banding is shown in Figure 3.2 and the proportion of included participants who recorded at least one epoch in each band is given in Table 3.4. Accelerometer-derived intensity ranged from 0-6000 cpm. Total physical activity volume (counts per day) tended to be correlated more strongly with time spent between 1000-3000 cpm (Table 3.2), indicating most activity was undertaken at the lower end of the MPA range.

![Figure 3.2 Time spent in each 500cpm intensity band at baseline for those included in Analysis A](image)

<table>
<thead>
<tr>
<th>Intensity (cpm)</th>
<th>0-499</th>
<th>500-999</th>
<th>1000-1499</th>
<th>1500-1999</th>
<th>2000-2499</th>
<th>2500-2999</th>
<th>3000-3499</th>
<th>3500-3999</th>
<th>4000-4999</th>
<th>≥4500</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>97</td>
<td>92</td>
<td>79</td>
<td>63</td>
<td>49</td>
</tr>
</tbody>
</table>

Cpm – counts per minute
3.3.2.2  Biochemical outcomes

The regression coefficients (95% CI) presented here and used to generate Figure 3.3 are displayed in Appendix 9, Table A 3.

Fasting and 2 hour glucose

Physical activity intensity was not associated with fasting glucose levels (Figure 3.3a). Physical activity intensities less than 500 cpm were positively associated with 2 hour glucose levels (0.91%; 0.49, 1.33%). Performing physical activity at intensities between 500-2499 cpm was associated with a linear change in the strength of the association with 2 hour glucose (Figure 3.3c). However, effect sizes for these relationships were small, explaining less than 3% of the variance in the model (Table A 1). After this level, there was no clear increase in the strength of association, and the error around each regression coefficient increased. The relationship was attenuated slightly after controlling for BMI, with associations observed up to 1999 cpm (-3.98%; -7.79, -0.01%; Figure 3.3d).

Fasting and 2 hour insulin

Every 10 minutes spent at intensities lower than 500 cpm were associated with higher fasting insulin levels (1.66%; 0.86, 2.47%). Intensities above 500 cpm were associated with lower fasting insulin for each 500 cpm increment up to 3999 cpm, ranging from -2.67% (-4.46, -0.85%) to -20.47% (-29.84, -7.60%). Above this, the difference in the association remained similar (Figure 3.3e). Adjusting for BMI largely attenuated the results (Figure 3.3f). Again, effect sizes for these associations were small, explaining less than 3% of the variance (Table A 1).

Physical activity intensities below 500 cpm were associated with higher 2 hour insulin levels (2.96%; 1.80, 4.14%), an association also observed after controlling for BMI (2.61%; 1.41, 3.82%) and explaining 4.7% of the variance within the model. With each 500 cpm increment in physical activity intensity between 500-3999 cpm, the difference in 2 hour insulin changed from -5.00% (-7.52, -2.42%) to -20.75% (-33.93, -4.95%; Figure 3.3g) for every 10 minutes of activity. These associations explained 2-3% of the variance within the model and are therefore interpreted as small effects (Table A 1). Associations with intensities above 4000 cpm were still statistically significant but there was no further rise in the strength of the association. The relationship when controlling for BMI was attenuated but still significant and followed a similar pattern (Figure 3.3h).
Insulin sensitivity

Below 500 cpm, physical activity intensity was negatively associated with both HOMA-IS and Matsuda measures of insulin sensitivity (Figure 3.3i & Figure 3.3k). Intensities above 500 cpm were linearly associated with differences in HOMA-IS from 2.64% (0.64, 4.68%) to 26.75% (10.99, 44.74%) with each 500 cpm increment up to 3999 cpm per 10 minutes of activity. Similarly, differences in the association with Matsuda ISI ranged from 5.32% (2.76, 7.94%) to 34.66% (13.85, 59.26%). Associations with intensities above 4000 cpm were statistically significant but of a smaller magnitude than those between 3000-3999 cpm. As expected, effect sizes for Matsuda ISI were larger than those for HOMA-IS (3-5% versus 0-3%), but physical activity intensity still explained only small amount of the variance with each model.

After controlling for BMI, associations with HOMA-IR were largely attenuated (Figure 3.3j). However, the relationship with Matsuda was maintained with differences between 500-999 cpm and 3500-3999 cpm 3.91% (1.38, 6.50%) and 23.02% (4.05, 45.46%) respectively for every 10 minutes of activity (Figure 3.3l).

Sensitivity Analyses

Subgroup analysis revealed that there were no differences in any of the outcomes when the data were stratified by diagnosis of dysglycaemia, except for the relationship between physical activity intensities between 500-999 cpm and fasting glucose (p = 0.037). This analysis indicated that the relationship between physical activity and fasting glucose was stronger in those with dysglycaemia. Fasting glucose levels were 0.7% (0.1, 1.2%) lower per 10 minutes of physical activity than those with normal glucose tolerance; 0.1% (0.0, 0.3%). There were no sex or age by intensity interactions.
**Model 1**

![Graph A](image1.png)  
**a. Fasting glucose levels (N = 569)**

![Graph B](image2.png)  
**b. Fasting glucose levels (N = 569)**

![Graph C](image3.png)  
**c. 2 hour glucose levels (N = 567)**

![Graph D](image4.png)  
**d. 2 hour glucose levels (N = 567)**

![Graph E](image5.png)  
**e. Fasting insulin levels (N = 569)**

![Graph F](image6.png)  
**f. Fasting insulin levels (N = 569)**
Figure 3.3 Association between time spent within each PA intensity and markers of glucose regulation and insulin sensitivity
Percentage change in biochemical outcomes associated with a 10 minute increase in time spent in 500 cpm bands of physical activity intensities ranging from 0-≥4500 cpm. Coefficients are plotted at the mid-point of the intensity band. Model 1 was adjusted for age, sex, ethnicity, smoking status, β-blocker medication and accelerometer wear time. Model 2 was further adjusted for BMI. Dotted lines represent cut-points for light and moderate physical activity.[296]
3.3.3 Analysis B

3.3.3.1 Physical activity

For those included in this analysis, median total MVPA per day was 20.5 minutes [9.4-39.8 minutes]. A median of 1.8 minutes [0.0-9.5 minutes] MVPA was accumulated in bouts of at least 10 minutes per week. This increased to 3.7 minutes [0.0-14.0 minutes] when a two-minute break was allowed in the bout. In comparison, 14.2 minutes [7.0-24.0 minutes] was accumulated in bouts <10 minutes per week.

3.3.3.2 Biochemical outcomes

Baseline coefficients are presented in Appendix 7, Table A 2. GEE coefficients are presented in Appendix 9, Table A 3. The data from model two has been presented as controlling for BMI did not appreciably alter the results.

Fasting and 2 hour glucose

In the baseline regression analysis, neither total, continuous nor sporadically accumulated MVPA predicted fasting nor 2 hour glucose. This did not change when 12 and 36 month data were included.

Fasting and 2 hour insulin

At baseline, total and continuous MVPA were not associated with fasting insulin. However, there was an association when MVPA was accumulated in bouts ≥ 10 minutes (-3.84%; -7.28, -0.39%) and similar when a two minute exception was allowed, although the effect size for this association was very small (0.84%). Sporadically accumulated MVPA was not associated with fasting insulin at baseline. Interestingly, relationships were less strong when 12 and 36 month data were included, with 10 minutes of total MVPA associated with -1.95% (-3.65, -0.22%) lower fasting insulin levels. Similarly, continuously accumulated MVPA was associated with -3.41% (-5.95, -0.80%) lower fasting insulin. Results were similar when a 2 minute break was allowed in the 10 minute accumulation (Figure 3.2).

Baseline MVPA was negatively associated with 2 hour insulin. Ten minutes of total MVPA was associated with -5.51% (-8.78, -2.33%) lower 2 hour insulin, although this reflected only a small effect (2.0%). Both continuous and sporadically accumulated MVPA were also associated with 2 hour insulin levels, although the effect sizes for these relationships were very small (less than 2%). The magnitude of these relationships were similar as for total MVPA, with 2 hour insulin levels -6.29% (-11.43, -1.13%) and -5.58% (-11.60, -0.49%) lower for continuous and sporadic
MVPA, respectively. The results were similar when allowing for a 2 minute break (Appendix 7, Table A 2). As with fasting insulin, the pattern of results remained the same when including 12 and 36 month data (Figure 3.2), but relationships were slightly attenuated. For example, continuous MVPA was associated with 4.71% (-8.75, -0.49%) lower 2 hour insulin levels.

Figure 3.4 Percentage change in markers of insulin sensitivity for every 10 minutes of continuous, continuous with a 2 minute exception, total and sporadic MVPA for baseline, 12 and 36 month data. Error bars are the 95% confidence interval. Continuous and sporadic MVPA were entered into models together and total was added separately. Models were controlled for wear time, valid days, sedentary time, age, sex, BMI, ethnicity, smoking status beta-blocker, other anti-hypertensive and lipid lowering medication.

**Insulin sensitivity**

At baseline, total and continuously accumulated MVPA were associated with HOMA and Matsuda indices of insulin sensitivity. The relationships with continuous MVPA were slightly stronger than for those with total MVPA, however the effect sizes for these associations were all very small, explaining less than 2% of the variance within the model. For instance, total and continuous MVPA were associated with 2.27% (0.01, 4.54%) and 4.25% (0.55, 7.96%) higher HOMA scores, respectively (Table A 1). Consistent with the emerging pattern of results, sporadically accumulated MVPA was not associated with insulin sensitivity scores.

As with the other outcomes, when 12 and 36 month data were included, the overall pattern of the results was similar, but relationships were slightly attenuated (Figure 3.3).
Figure 3.5 Percentage change in insulin sensitivity index for every 10 minutes of continuous, continuous with a 2 minute exception, total and sporadic MVPA for baseline, 12 and 36 month data. Error bars are the 95% confidence interval. Continuous and sporadic MVPA were entered into models together and total was added separately. Models were controlled for wear time, valid days, sedentary time, age, sex, BMI, ethnicity, smoking status beta-blocker, other anti-hypertensive and lipid lowering medication.

HOMA – homeostatic model assessment; MVPA – moderate-vigorous physical activity
3.4 Discussion

3.4.1 Main findings

3.4.1.1 Analysis A

The results of study B revealed linear associations between 500 cpm increments in physical activity intensity and more favourable levels of fasting and 2 hour insulin and 2 hour glucose, along with indices of insulin sensitivity. Differences in insulin sensitivity per 10 minutes of physical activity time increased sharply when moving up in 500 cpm bands from 500-3999 cpm; for example, 10 minutes of physical activity between 500-999 cpm was associated with a 5.32% difference in insulin sensitivity (Matsuda ISI) whereas 10 minutes spent between 3500-3999 cpm (roughly equivalent to 4.3 METs\(^{(295)}\)) was associated with a 34.66% difference in insulin sensitivity. There did not appear to be any additional change in the strength of the association at intensities higher than 4000 cpm. Results for 2 hour glucose and insulin and Matsuda ISI remained largely unchanged after adjustment for BMI, whereas fasting measures were attenuated. Based on the accelerometer cut-points validated by Freedson et al.,\(^{(296)}\) our results suggest that, in individuals at risk of dysglycaemia, both LPA and MPA are sufficient to gain significant associations between physical activity and measures of insulin sensitivity; the strength of which is proportional to physical activity intensity up to 3999 cpm (approximately 4.3 METs) above which no further strength in the association is gained.

3.4.1.2 Analysis B

In this cohort of individuals identified as being at high risk of dysglycaemia or T2DM, study A suggests that accumulation of MVPA predicts only insulin-derived outcomes as there was no relationship between total, continuous or sporadic MVPA with fasting or 2 hour glucose. Ten minutes of both total and continuously accumulated MVPA favourably predicted fasting and 2 hour insulin; the strength of the relationship increasing with the amount of continuous physical activity, although 10 minutes of sporadically accumulated physical activity was also associated with 2 hour insulin. These lower insulin levels were reflected in the measures of insulin sensitivity which were also positively associated with 10 minutes of total and continuous MVPA, the relationships diminishing slightly the more intermittent the bouts, with sporadic MVPA not predicting insulin sensitivity after controlling for BMI.
3.4.2 Explanation and implications

3.4.2.1 Analysis A

It has long been accepted that there is a dose-response relationship between physical activity volume (broadly defined as intensity x duration) and health up to a certain level, with the most expeditious benefits occurring when moving from a sedentary inactive lifestyle.\cite{273} By showing that the strength of association between physical activity and insulin sensitivity increases proportionally to the level of intensity is consistent with this theory.\cite{136} Interestingly we found no additional benefit in this cohort for time spent above 4000 cpm, which equates to approximately 4.6 METs.\cite{295} This contrasts with studies that have shown additional benefits of performing VPA compared to MPA on markers of insulin sensitivity. For example, in the Dallas Heart Study of 2566 older individuals, both MPA and VPA were associated with lower HOMA-IR scores, but the association with VPA was nearly seven times stronger than that with MPA.\cite{158} Similarly, data from 1669 middle-aged NHANES participants suggested that the association of VPA with cardio-metabolic risk factors was more than twice that of MPA.\cite{302} These cross-sectional observations are supported by exercise intervention studies which consistently demonstrate that per minute, VPA results in greater improvements than MPA.\cite{220, 253} At the lower-intensity end, a number of cross-sectional analyses have shown that replacing sedentary time with LPA is associated with enhanced insulin sensitivity in individuals at high risk of T2DM, who tend to spend long periods of time in sedentary behaviours.\cite{303}

The observation that there was no additional difference in performing physical activity at the upper end of the MPA range could be attributed to the inactive nature of our cohort resulting in a lack of power in higher intensity bands due to the progressively smaller amount of time spent in each intensity increment (Table 3.4). Indeed, only 49% of our cohort engaged in any activity above 4500 cpm, and in most cases this was in very small quantities.

Another important finding from our study was that undertaking any activity above the sedentary threshold (0-499 cpm) was associated with some degree of greater insulin sensitivity, whereas increased time spent sedentary was associated with worse insulin sensitivity. This finding is consistent with the growing body of evidence showing that greater time spent sedentary is independently associated with the development of T2DM and other morbidity and mortality outcomes,\cite{117} whereas greater time spent in light-intensity physical activity is associated with a reduced risk of mortality, particularly in older adults. Controlled interventions have also demonstrated that breaking sitting time with short bouts of standing and LPA produces benefits in glucose regulation and insulin sensitivity, particularly in higher risk adults.\cite{304, 305} Results from
training intervention studies have been more equivocal with some demonstrating that low-intensity exercise training leads to reductions in HOMA insulin resistance,\textsuperscript{[306]} whereas others have shown no such relationships.\textsuperscript{[307, 308]} It is worth noting though that using the equation from Hall \textit{et al.},\textsuperscript{[295]} 500 cpm is roughly equivalent to 2.4 METs, which is only a small way off the three MET threshold for MPA indicating that even the first intensity increment may, in fact, be MPA in this cohort. It remains to be determined though, the extent to which replacing sedentary time with LPA and MPA impacts prevention and management of T2DM.

When comparing the intensity at which benefits occurred in the current study to accelerometer cut-points from calibration studies, it appears that for an older population at high risk of T2DM, benefits occur at intensities substantially below the threshold traditionally used to define MVPA. The cut-points developed by Freedson \textit{et al.},\textsuperscript{[296]} are widely used and have been well validated.\textsuperscript{[309, 310]} They equate to 1.5, three and six METs for LPA, MPA and VPA respectively. Cut-points for sedentary behaviour were defined later in an analysis of NHANES data\textsuperscript{[311]} and are set at <100 cpm for sedentary behaviour, 100-1951 cpm for LPA, 1952-5724 cpm for MPA and ≥5725 cpm for VPA. Virtually none of the participants from our cohort, who were on average 40 years older than those who were used to calibrate these cut points, performed physical activity at more than 5725 cpm (in the VPA category) and differences in insulin sensitivity per 10 minutes of activity within the MPA range (1952-5724 cpm) varied from 12.37-26.74% and 21.98-34.66% for HOMA and Matsuda respectively. This indicates that large differences in health outcomes could be expected from participation in the moderate range, the upper end of which may, in relative terms, be vigorous in this population. In line with this, accelerometer cut-points specifically for older individuals, which may reflect more accurately associations between physical activity intensity and health in this population, have been investigated. Copeland & Esliger\textsuperscript{[312]} established cut-points based on the VO\textsubscript{2} achieved by 38 elderly individuals during treadmill walking. They suggested that, for individuals over 60 years, ActiGraph cut-points be <50, 50-1041 and >1041 cpm for sedentary time, LPA and MVPA, respectively. They were unable to determine a threshold for VPA as not all participants could maintain the required walking speed for more than six minutes. Our results suggest that the lower intensity bands proposed by the Generation 100 study,\textsuperscript{[283]} which are dependent on sex and cardiorespiratory fitness, could be used to more precisely assess physical activity levels and their associations with health in older people.

Regardless of their definition, cut-points for light, moderate and vigorous physical activity all encompass a wide range of relative and absolute intensity levels. The traditional method of reducing data into time spent in these established categories removes the ability to more
accurately define the dose-response relationship with markers of health. To the best of our knowledge, only one other study assesses objectively measured physical activity on a continuous scale rather than using predefined cut-points. To the best of our knowledge, only one other study assesses objectively measured physical activity on a continuous scale rather than using predefined cut-points.[313] I have extended the findings of this recent study by quantifying associations between participation in physical activity and health, as well as bringing together recent findings that reducing sedentary time and increasing LPA is also beneficial. Processing accelerometer data in 500 cpm intensity increments covers the whole range of intensities, enabling identification of the minimum absolute intensity at which benefits occur in this population, as well as a quantifiable dose-response relationship; all information that will facilitate the development of more achievable interventions with greater improvements.

3.4.2.2 Analysis B

The finding that MVPA predicted insulin but not glucose outcomes is consistent with other studies. For instance, in the ADDITION-Pro study of 1481 individuals at risk of T2DM, MVPA did not predict fasting or post-challenge glucose. The relationship between MVPA and insulin measures were stronger, with favourable associations for 2 hour insulin and peripheral insulin sensitivity after controlling for confounding variables including waist circumference.[157] Similarly, there was no association between objectively measured MVPA and fasting glucose or HOMA-IS measured one year after physical activity assessment in 192 individuals with a family history of T2DM, but there was a negative association with fasting insulin.[314] Healy et al.[315] reported independent associations between both MVPA and sedentary time and 2 hour but not fasting glucose levels in 173 healthy, middle-aged adults; plasma insulin was not measured. Overall, it appears that MVPA is a stronger predictor of insulin sensitivity than glucose regulation, with some evidence to suggest that sedentary time is independently associated with plasma glucose levels, although this was not assessed in the current study.

While total MVPA was favourably associated with insulin sensitivity, scores were slightly (~1%) higher when only continuously accumulated MVPA was counted. Since sporadically accumulated MVPA was not associated with insulin sensitivity, the results from this study indicate that, in accordance with the prevailing physical activity guidelines, to improve insulin sensitivity it may indeed be necessary to perform MVPA in bouts lasting at least 10 minutes. This diverges from the recent conclusions that there is no difference between continuously and sporadically accumulated MVPA and the risk of cardio-metabolic disease, including T2DM.[285, 290]

The findings from the current study are also inconsistent with results from intervention studies. A handful of acute interventions have assessed the effect of short (2-5 minutes) compared to long (≥30 minutes) bouts of MVPA on postprandial glucose and insulin levels. In 70 young,
healthy participants, breaking nine hours sitting time with 18 x 160 second brisk walks lowered glucose and insulin AUC significantly more than performing a single 30 minute walk of equal energy expenditure in the morning.\[316\] In another study, 11 overweight adults with impaired fasting glucose, performing 12 bouts of five minutes at 60-65% VO\(_{2}\text{peak}\) reduced the 12 hour glucose AUC by 15% compared to one 60 minute effort. Both continuous and intermittent MVPA reduced the insulin AUC, with no difference between conditions.\[317\] On the other hand, Miyashita et al.\[318\] found the opposite in 15 post-menopausal women, with a single 30 minute bout of brisk walking reducing the glucose AUC compared to prolonged sitting, and 20 x 90 second brisk walking breaks having no effect. Interestingly, neither physical activity regime affected the insulin AUC compared to control. In addition, results from an unpublished study of 10 overweight individuals\[319\] suggested that glucose outcomes as measured by CGM were improved by 30 minutes walking at 60-70% \(HR_{\text{peak}}\), 21 x two minutes walking bouts at moderate-intensity and eight x two minutes brisk walking at 100% VO\(_{2}\text{max}\) compared to a prolonged sitting condition. Continuous exercise was superior to moderate-intensity intermittent exercise which was superior to high-intensity intermittent exercise however, conditions were not energy matched. Taken together, these studies indicate that there are equivocal effects of performing continuous versus intermittent bouts of MVPA, with neither emerging as the more effective intervention specifically for individuals at high risk of T2DM. Further investigation into the impact of energy-matched continuous and accumulated MVPA on glucose and insulin responses is required. These investigations should include a comparison with light-intensity activity breaks as it could be that the benefits of sporadic MVPA are due to reductions in prolonged sedentary time, rather than accumulation of MVPA per se. Indeed, sedentary time has been found to be an independent risk factor for markers of T2DM.\[117, 118\] Furthermore, studies that have compared light-intensity with moderate-intensity activity breaks have found little difference in the improvements in glucose and insulin responses.\[320, 321\]

Establishing whether every minute counts, so to speak, has numerous implications given the recent directions novel physical activity programmes have taken. From reducing periods spent sedentary, to "exercise snacking"\[322\] and performing very low volume HIIT,\[172, 174\] in response to the perceived barrier of "lack of time", focus has shifted away from long, continuous bouts of exercise. One of the reasons VPA has received fresh attention is, as Study B indicates and is reflected in the physical activity guidelines, that greater health benefits can be achieved per minute, thus reducing the total amount of time one needs to spend active. Just how much this time can be reduced to in a single bout is useful to establish because it could facilitate incorporation of physical activity breaks into school or working days, addressing both issues of
extended sedentary time and participation in MVPA. The information gathered could also help to explain improvements observed following HIIT which, by design, involves non-continuous bouts of VPA in some cases totalling less than 10 minutes of activity per session.

3.4.3 Mechanisms

There are several well-established mechanisms explaining the link between MVPA and improved metabolic health and insulin sensitivity. Skeletal muscle is the primary tissue responsible for glucose disposal[^323] and affects insulin signalling in response to both acute and chronic bouts of physical activity. The precise mechanisms underlying the efficacy of continuous versus sporadic physical activity are unclear. The associations between low levels of total MVPA; in this case approximately 20 minutes per day, mostly at the lower end of the intensity range could be explained better by their mediation of the effects of sedentary time than potential adaptations to physical activity training. It has recently been confirmed that accumulation of sedentary time itself has deleterious effects on insulin action[^124]. Therefore, very small amounts of VPA, or even regular bouts of LPA may be enough to offset these negative consequences.

In terms of intensity, assuming the physical activity levels observed here reflect regular behaviour patterns, we speculate that the higher the intensity of activity engaged in, the more intense the skeletal muscle adaptations that increase insulin sensitivity and drive lower circulating insulin levels[^31]. Any activity >2.5 METs may be sufficient to stimulate the contraction-mediated glucose uptake pathway and induce alterations to the insulin signalling pathway[^324]. However, given the nature of the analysis, cause and effect cannot be inferred.

3.4.4 Strengths and limitations

A major strength of this study is the objective measurement of physical activity in a free-living environment which is likely to be a more accurate representation of day-to-day behaviour than would be demonstrated by a self-report tool. The deployment of a widely used device (Actigraph GT3X) means the results are directly comparable to other data sets. In addition, the study population were at high-risk of T2DM and were recruited from primary care. Typically, this is a group that is hard to reach in lifestyle research despite representing the type of population referred to diabetes prevention programmes. The broad selection of diabetes-related biochemical outcomes that were measured using robust laboratory techniques gives a comprehensive picture of the association of physical activity pattern on markers of insulin sensitivity.
The main limitation of these analyses is the collinearity between intensity increments and activity bouts meaning that it was not possible to distinguish the independent effects of each activity variable. Furthermore, inspection of the effect sizes indicated that these relationships explained only a very small amount of the variance within the model, making it difficult to draw firm conclusions from the results. However, it should be noted that this is likely due to a lack of power rather than the potential of physical activity to promote benefits in insulin sensitivity, although due to the cross-sectional nature of the analysis, we are unable to draw causal inferences. Although more accurate than self-report, accelerometers may underestimate overall physical activity because they are unable to accurately quantify non-step based or weight bearing activities. Moreover, due to individual differences in fitness levels, which were not measured in the original study, performing activity at the same number of counts per minute may reflect different relative intensities within our population.\[^{283}\] It should also be noted that although some statistically significant differences in markers of insulin sensitivity and glucose regulation were observed, the clinical relevance and how this translates to the prevention and management of T2DM remains unclear.

3.4.5 Conclusions

In summary, these studies suggest that both physical activity volume and intensity predict insulin sensitivity. As expected, more favourable levels were associated with longer bouts and higher intensities. Associations with intensity were of a greater magnitude than those with volume. For example, 10 minutes of continuously accumulated MVPA was associated with 4.5% lower Matsuda scores whereas 10 minutes at 2000-2499 cpm (the lower end of the MVPA range) was associated with 16.4% lower scores. However, these factors were not compared directly in this study.

There was little evidence that total, continuous or sporadic MVPA was associated with glucose regulation. Where there were differences in associations with insulin-derived outcomes, continuous MVPA was the stronger predictor of fasting insulin and insulin sensitivity. For a given duration, the higher the exercise intensity, the greater the potential improvement, although this dose-response relationship may not persist beyond a level representative of a moderately paced walk. Together, the results suggest that benefits in insulin sensitivity are likely to occur with participation of any pattern in physical activity, although other factors such as reducing sedentary time or increasing cardiorespiratory fitness may also be important. Future research should continue to investigate the precise dose of physical activity that elicits specific benefits in a particular population. The results reinforce the notion that intensity is relative, and indicate
that this should be reflected in accelerometer cut-points when assessing physical activity levels of older, obese and sedentary individuals. Furthermore, while the recommendation that MVPA be completed in bouts ≥10 minutes is supported, further investigation should be made into whether this is the case for the entire MVPA range; it may emerge that VPA and MPA at the upper end of the intensity threshold may be beneficial in bouts lasting <10 minutes.
Chapter overview

In this chapter, the GO for IT trial will be described. The high-intensity interval exercise (HIIE) protocol employed in this study was selected based on the results of the meta-analysis described in Chapter 2 as well as feedback from patient and public involvement (PPI) meetings (4.2.1.1). While the meta-analysis did not reveal the “optimal” HIIE intervention, it did provide information on balancing the intensity-duration trade-off without curtailing potential improvements in glucose regulation. A protocol involving 10 times 60 second intervals at 90% VO$_{2peak}$ emerged as an acceptable compromise.

The GO for IT study was a randomised, three treatment crossover study investigating the effects of a practical model of an acute bout of HIIE on the postprandial glucose and insulin responses of individuals at high risk of T2DM compared to moderate-intensity continuous exercise (MICE; 30 minutes at 65% VO$_{2peak}$) and a non-exercise control day. The main study was designed to compare differences in white European and south Asian individuals however, due to difficulties recruiting, the results presented here are for the 17 participants who had completed the study at the time of writing.

Key findings

- There was no effect of exercise on glucose AUC compared to control conditions.
- Insulin AUC was significantly lower in HIIE compared to MICE and control.
- HIIE reduced the insulin (incremental area under the curve) iAUC : glucose iAUC ratio to a greater extent than MICE, indicating increased insulin sensitivity in this condition.
- Exercise improved glycaemic variability by reducing the breakfast postprandial spike and glucose fluctuations detected by continuous glucose monitoring.
Author contribution

Having conducted a thorough literature review, I contributed to the development of the research question and study concept. I conducted patient and public involvement meetings to inform the study design and procedures. With input from other researchers within the department to maintain consistency with previous experiments, I wrote the study protocol and supporting information. I was responsible for gaining sponsor (University of Leicester), NHS (Health Research Authority) and Research Ethics Committee approval as well as being the recruitment point of contact for the duration of the study. Using templates from previous studies I developed all the study documents including participant information sheets, standard operating procedures and case report forms. I obtained service support costs to fund recruitment through primary care and managed the recruitment administration. I attended consent, GCP and immediate life support training, and carried out all non-clinical study procedures for all participants, processed and analysed blood samples and performed the data analysis.

It is important to note that some of the procedures carried out as part of the current study were included to allow for secondary analyses by other researchers within the Leicester Biomedical Research Centre and are therefore superfluous to the current investigation, but formed a notable volume of the workload.

4.1 Introduction

The unique nature of HIIE; short periods of vigorous or greater intensity exercise interspersed with periods of active recovery or complete rest, may encourage participation in VPA by reducing the negative affect experienced by sedentary individuals while performing continuous high-intensity exercise. It may also address the barrier to performing physical activity of “lack of time” as health benefits may be achieved following just a few minutes of structured exercise per week. For health professionals, this is a highly desirable goal given the positive relationship between exercise intensity and health outcomes and current low participation levels in overall physical activity. However, as mentioned in Chapter 1, section 1.3.4, the potential benefits of HIIT in the prevention and management of T2DM are yet to be well defined. For HIIT to be recommended as a therapeutic health tool, its safety, efficacy and feasibility in a range of populations must be established. As detailed in Chapter 2, the body of research surrounding HIIT is growing, but gaps in our knowledge and inconsistencies in findings remain. For instance, there are only a handful of longer-term (>8 weeks) HIIT intervention studies conducted on older individuals with or at high risk of T2DM. Similarly, the acute effects of a
single bout of HIIE and long-term training adaptations have not been distinguished. For instance, when insulin resistance is measured >72 hours after the last exercise session of HIIT, the improvement in insulin sensitivity is attenuated,[253] indicating that the potential for HIIT to stimulate chronic changes in insulin signalling and glucose transport is questionable. With regard to acute physiological changes, the established relationship between physical activity and insulin sensitivity, the acceptance that postprandial hyperglycaemia is a major factor in the development of diabetic complications,[329] and the emerging hypothesis that daily glycaemic variability may contribute to diabetes complications,[330] has meant that attention has turned quickly to the potential for HIIE to maintain glycaemic stability.

**Continuous Glucose Monitoring**

Continuous glucose monitoring is a relatively recent technology that enables real-time monitoring and trend prediction of blood glucose levels, thus facilitating tight regulation and prevention of hypo- or hyperglycaemic events. Constant monitoring without the need for repeated finger-prick tests was first made possible by Schichiri et al. in 1982 using telemetry, although their device was relatively invasive requiring venepuncture with a cannula-like device.[331] During the 1990’s, less invasive technologies designed to be more tolerable for users were developed, with the first devices approved by the US FDA (United States Food and Drug Association) in 2005.[332] These either employ a minimally invasive technique of inserting a metallic filament into the interstitial fluid of the subcutaneous tissue, or applying electromagnetic radiation to the skin.[333] Some CGM devices can only be analysed retrospectively, making it possible to blind the wearer to their glycaemic variations and as such providing a useful research tool. Use of CGM by patients with T1DM has resulted in lower HbA1c levels without increasing time spent in hypoglycaemia[334] and quality of life[335] as long as the device is used constantly. Emerging evidence also shows that using CGM also improves HbA1c and glycaemic variability in individuals with T2DM.[336] One of the main challenges when presented with a large, rich dataset using CGM is how to analyse it. There are many ways of indexing glycaemic variability, each with almost endless permutations when appropriate start and end time-points are considered. Preferred methods of assessment have been described[337, 338] and reviewed,[330] generally taking into account the magnitude of daily fluctuations in glucose levels and time spent in hypo or hyperglycaemia, although other outcomes have been reported.[339, 340] Parameters such as postprandial spikes and time spent within 10% of fasting values are more commonly found in short-duration studies of non-diabetic individuals such as the current investigation.
To date, a handful of studies have used CGM to assess the impact of HIIE on glycaemic regulation in free-living[341] and controlled conditions.[184, 342] Gillen et al.[341] found that a single session of HIIE (10 x 60 seconds at 90% of the peak workload achieved at VO₂max; WLpeak) reduced mean 24 hour glucose, time spent in hyperglycaemia and postprandial AUC for the three meals following exercise in seven patients with T2DM. Parker et al.[343] reported similar findings in 23 overweight or obese subjects who performed 8 x 60 second intervals at 100% WLpeak. In contrast, Little et al.[344] found no difference in glycaemic variability on the day of exercise in 10 overweight/obese participants until the evening meal when dinner AUC was lower than in control conditions. Discrepancies in these studies could be attributable to the populations included and the small sample sizes.

**Ethnicity and T2DM**

It is becoming clear that there are differences in diabetes incidence between individuals of different ethnicities. For instance, in the UK, south Asians represent ~7.5% of the total population, but 14% of the diabetic population[345] Evidence indicates that, at equal levels of traditional risk factors e.g. BMI, cardiorespiratory fitness, lipidaemia etc., south Asians are at higher risk of cardiovascular disease than are their white European counterparts.[346, 347] This could be attributed to lower physical activity levels throughout the life course,[348, 349] but may also be due to differences in physiological responses to exercise.[350] One of the aims of the GO for IT study, therefore, was to determine whether there are differences in the glucose and insulin responses of white Europeans and south Asians at high risk of T2DM. Unfortunately, as alluded to above, this was not possible at the time of writing, and therefore ethnicity is considered only briefly in the remainder of this report.

The aim of this study, therefore, was to extend these previous findings by comparing the effect of a commonly used, practical model of HIIE and MICE on the postprandial glucose and insulin responses of individuals at high risk of T2DM to control conditions. A further aim was to investigate the dynamic glucose fluctuations during and after the intervention as measured by CGM. It was hypothesised that both HIIE and MICE would significantly reduce iAUC compared to control, but that there would be no difference between the exercise conditions. A second hypothesis was that both HIIE and MICE would reduce glycaemic variability during the treatment visit, an effect that would continue for at least 24 hours.
4.2 Methods

4.2.1 Design

A single centre, randomised three-treatment three-period crossover trial was designed. The study was registered on the ISRCTN registry on 20/05/2015 with ID 12337078 prior to acquisition of all approvals and recruitment (http://www.isrctn.com/ISRCTN12337078). Sponsor approval was awarded by the University of Leicester (ID 0521), NHS Research and Development approval (now Health Research Authority) by University Hospitals of Leicester (UHL) NHS trust (ID 167328) and ethical approval was received from Nottingham Research Ethics Committee (ID 15/EM/0259). Relevant supporting documents can be found in Appendix 10 & 11.

4.2.1.1 Patient and public involvement

In line with requirements for NIHR funded research, PPI meetings were set up to inform the design of this study. In the first meeting (N = 6), popular examples of sprint, high-intensity and aerobic interval exercise were presented to the group with the pros and cons explained. The group suggested that the 10 x 60 seconds interval protocol would be most attractive, however they recommended that treadmill exercise rather than cycling would be more appropriate given the greater familiarisation with walking compared to cycling within the target population.

In the second meeting (N = 9), drafts of the study materials were examined with comments on use of language e.g. using the talk test to describe intensity, and abbreviations incorporated where possible.

A copy of the most recent protocol (V3) can be found in Appendix 12.

4.2.2 Participants

4.2.2.1 Inclusion criteria

This study recruited individuals aged 50-74 years at “high risk” of developing T2DM, defined as HbA1c ≥5.7 and <6.5% at their most recent blood test within the previous five years. Those of south Asian or white European decent whose HbA1c was confirmed at familiarisation to be within this range, whose BMI was ≥25 kg·m⁻² (SA) or ≥27 kg·m⁻² (WE), and self-reported no more than three 20 minute bouts of vigorous exercise per week were invited to take part in the study. Individuals unable to communicate in English, who were taking glucose-lowering or steroid medication, were not weight stable (more than 5kg fluctuation during the preceding six months), had abnormal resting or exercise electrocardiogram (ECG) or any other contraindications to taking part in vigorous exercise were excluded from the study.
4.2.2.2 Recruitment

With support from the NIHR Clinical Research Network (CRN), participants were recruited through primary care services in Leicestershire, UK. Practice managers at “research ready” GP surgeries were sent an invitation to participate (Appendix 13) on my behalf by members of the East Midlands CRN. Contact details of representatives from interested practices were then passed on to me and I provided the appropriate number of study packs. These contained the participant information sheet (Appendix 14), pre-screening form and reply slip and were posted to potentially eligible individuals by surgery staff to maintain patient confidentiality. Individuals who had previously taken part in studies at the Leicester Diabetes Centre (LDC), had consented to be contacted in the future and met the inclusion criteria were also invited and sent a study pack. The information in the pack instructed interested individuals to contact me directly using the details provided. This gave permission for me to contact them to discuss taking part. Recruitment was rolling, with participants enrolled onto the study until the required number of participants had completed all experimental conditions.

4.2.3 Screening and familiarisation (Visit 1)

A schematic of the study design is presented in Figure 4.1. Following telephone screening, individuals were invited to visit the centre for further screening and study familiarisation. Participants were asked to avoid vigorous activity for 72 hours and alcohol for 48 hours immediately prior to this visit. The procedures in the familiarisation visit were conducted such that the least invasive were carried out first. This was to minimize the inconvenience to the participant if, during the visit, it became apparent that they were not eligible for the study. When this was the case, the familiarisation visit was terminated and participants were debriefed and sent home without completing the remaining procedures.

4.2.3.1 Anthropometry and medical assessment

Visit one lasted up to three hours. The participant information sheet and study procedures were explained fully before consent was taken by myself, having been trained to do so. Participants were then asked to fill out a physical activity and eating questionnaire. Height (Leicester height scale), waist circumference (midpoint between the lower costal margin and iliac crest), weight and body fat (Tanita TBE 611, Tanita corporation, West Drayton, UK) were measured by me to the nearest 0.1cm, 0.1kg and 0.1% respectively.

A comprehensive (30-45 minute) medical history was carried out by a specialist cardiac nurse. This included questions regarding medical diagnoses, current symptoms, recent illness, medication use and lifestyle habits such as alcohol consumption and physical activity levels. Blood pressure was measured in a seated position using a manual sphygmomanometer,
repeated once if stable or a second time if the first two measurements differed by more than ±5 mmHg. Resting ECG was assessed using a Cardiofax GEM ECG machine (Nihon Kohden Corp., Tokyo, Japan). Pending satisfactory results, blood was drawn through a needle from an accessible vein and sent on the same day to the pathology laboratory located at UHL for analysis of HbA1c, full blood count, lipid profile and liver function markers.

4.2.3.2 Maximal exercise test

Participants were given the opportunity to familiarise themselves with the treadmill (Woodway PPS 70 Plus, Woodway USA Inc., Waukesha, WI, USA) and choose a speed they would describe as a brisk walk; faster than their normal pace, but one they believed they could maintain. The exercise test protocol was explained to participants who were instructed to continue for as long as they could, investing their maximum effort. Participants were advised that it was normal for their breathing to become heavy and for them to feel warm, but they should ask us to stop the test if they felt any pain or other discomfort. Exercise ECG, heart rate, VO₂ and respiratory exchange ratio (RER) were monitored throughout the test by the specialist cardiac nurse (ECG & blood pressure) and myself (all other measures). A modified Balke protocol was chosen to determine VO₂peak. This protocol reduces the risk for leg turnover speed to become a limiting factor. After a three minute warm up, participants walked at their chosen speed (mean = 5.1 km·h⁻¹) for one minute at 0% gradient. The treadmill gradient was then increased by 1% every minute until one of the following criteria had been met; adverse symptoms or abnormal ECG (incomplete test), volitional exhaustion or HR reaching 100%, or 85% if taking beta-blockers, of age predicted maximum (220-age) and RER >1.15. At this point, participants were instructed to keep walking, but the gradient and speed were reduced for a three minute cool-down. Blood pressure, ECG and HR were monitored until HR returned to within 10 bpm and blood pressure was within an acceptable range of the resting value as judged by the cardiac nurse.

4.2.3.3 HIIE Familiarisation

Following a minimum of 15 minutes of rest, participants were asked to perform a HIIE familiarisation session. Results from the exercise test were used to calculate the gradient at which the participant was performing at 90% of their VO₂peak. A two minute warm up was followed by three 60 second intervals interspersed with 60 second recovery periods and a two minute cool down.
4.2.3.4 Physical activity monitoring

In order to determine baseline physical activity levels objectively, participants were provided with a wrist-worn accelerometer (GeneActiv, Activinsights, Kimbolton, UK) to wear for seven days on their non-dominant hand and asked to continue with their daily activities as usual. These devices are waterproof therefore, it was recommended that the accelerometer was worn at all times and only removed for practical reasons or if it was becoming uncomfortable. To aid distinction between non-wear time, sedentary time and sleep time, participants were asked to
record in a diary any times they removed the device as well as the time they woke up, got out of bed, got into bed and fell asleep.

4.2.3.5 Randomisation

Participants who successfully completed consent, screening and initial assessment procedures were invited to take part in the treatment condition trial days. Each individual’s trial sequence was randomly allocated by a statistician independent of the recruitment process using permuted blocks of sequences defined by a Latin Square and stratified by ethnicity and sex.

4.2.3.6 Preparation for treatment visits

Participants deemed eligible following familiarisation were invited back to the Leicester Diabetes Centre for three treatment visits separated by a minimum of one week to allow for the acute effects of physical activity on insulin sensitivity to subside (Figure 4.1).[127] Participants were given the following instructions in order to prepare for their treatment visits; to avoid vigorous activity for 72 hours and alcohol for 48 hours prior to each experimental condition, to record all food and drink consumed for two days before the first experimental condition in a food diary and to replicate this diet before the remaining two experimental conditions using their dietary record to guide them. This was so that meals on the day preceding treatment visits were standardised across conditions as far as possible. Additionally, participants were asked to arrive at the laboratory having fasted since 10pm the previous evening before the experimental conditions. Where participants had limited access to motorised transport, taxis were ordered to reduce ambulatory and uncontrolled activity involved in the commute to and from the study centre for each visit. Reproducibility data has shown that insulin responses to meal ingestion are good under these conditions.[357]

4.2.4 Treatment regimens (Visits 2-4)

Figure 4.2 is a schematic representation of the treatment condition procedures. On participant’s arrival at the laboratory, the study procedures were reiterated and consent confirmed orally. Participants were then fitted with a CGM, a cannula, a postural locomotion monitor and given a replacement accelerometer.

![Figure 4.2 GO for IT treatment day schematic](image)

| - blood sample, blood pressure and questionnaires; light shading – standardised meal; dark shading – exercise. | 108 |
Continuous Glucose Monitoring

Within approximately 30 minutes of arrival at the laboratory, a CGM sensor (Enlite, Medtronic, Northridge CA, USA) was inserted either into the abdominal area 50-100mm from the umbilicus or in an area of firm skin in the lumbosacral region as per the manufacturers instructions. A specially designed device (Enlite Serter, Medtronic, Northridge CA, USA) deploys a small (~5mm) needle under the skin to insert the sensor which measures interstitial glucose concentration via detection of glucose oxidase catalysed glucose oxidation.\textsuperscript{[332]} The reader, which stores data every five minutes, is then clipped to the sensor and secured using an adhesive dressing (Hyperfix, BSN Medical GmbH, Hamburg, Germany). Validation studies have demonstrated acceptable accuracy of these devices within 24 hours of insertion \textsuperscript{[358, 359]} including during exercise.\textsuperscript{[360]} Furthermore, similar protocols have been utilised in other published studies.\textsuperscript{[124, 361, 362]} Participants were instructed to wear the CGM for the next seven days when it was either replaced (visits 2 & 3) or removed by the participant and returned to the study coordinator on completion of the trial (visit 4). The CGM must be calibrated with finger-prick blood glucose values at least four times per day therefore participants were instructed on how to accurately take a capillary reading and provided with a kit (TRUEyou mini, Nipro Diagnostics Inc., Zaventem, Belgium), instruction manual and diary to take home with them.

ActivPAL

Postural allocation and walking was quantified using an activPAL professional physical activity monitor (PAL Technologies, Glasgow, Scotland) which was worn throughout each experimental condition only. The activPAL is a single-unit monitor based on a uniaxial accelerometer that was attached directly to the skin using an adhesive dressing midline on the anterior aspect of the thigh. The activPAL device classifies activity in terms of the time spent sitting or lying, standing, stepping, cadence and the number of sit-to-stand transitions.

GeneActiv

In order to coincide with the CGM and so that physical activity engaged in throughout the study could be controlled, participants were again asked to wear a wrist-worn accelerometer (GeneActiv) for one week during and after the treatment visit, starting at time point -1 hour. After the final visit, participants were provided with a free-post padded envelope in which to return the device.
Phlebotomy

A cannula (Braun, Penine Healthcare, Derby, UK) was inserted into an accessible vein in their arm by an individual trained to do so and secured using an adhesive dressing. At each time point, ~27ml of blood was drawn into six monovettes prepared as described in Table 4.1.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Volume (ml)</th>
<th>Temperature</th>
<th>Analyte(s)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoride bottle</td>
<td>2.7</td>
<td>Room</td>
<td>Glucose</td>
<td>Glucose oxidase</td>
</tr>
<tr>
<td>EDTA</td>
<td>9</td>
<td>Room</td>
<td>Insulin, IL-6, Leptin, Follistatin, Fetuin-A, FGF21</td>
<td>ELISA</td>
</tr>
<tr>
<td>Serum gel</td>
<td>2.7</td>
<td>Room</td>
<td>Haematocrit, Triglycerides, CRP</td>
<td>Enzymatic</td>
</tr>
<tr>
<td>Fluoride bottle</td>
<td>2.7</td>
<td>Room</td>
<td>Free fatty acids, Acylated ghrelin, Unacylated ghrelin</td>
<td>Colorimetric assay</td>
</tr>
<tr>
<td>EDTA + PHMB/NaOH solution</td>
<td>2.7</td>
<td>0-5°C</td>
<td>PYY3-36, GLP-1</td>
<td>ELISA</td>
</tr>
<tr>
<td>EDTA + approtinin + DPP-IV</td>
<td>2.7</td>
<td>0-5°C</td>
<td>Acylated ghrelin, Unacylated ghrelin</td>
<td>ELISA</td>
</tr>
</tbody>
</table>

EDTA – ethylenediaminetetraacetic acid; PHMB – polyhexamethylene biguanide; DPP-IV – dipeptidyl peptidase-4; IL-6 – interleukin-6; FGF-21 – fibroblast growth factor-21; CRP – C reactive protein; PYY – peptide tyrosine tyro sine; GLP-1 – glucagon-like peptide-1; ELISA – enzyme linked immunosorbent assay

Monovettes were sourced from Sarstedt AG & Co., Nürmbrecht, Germany

Once the participant was set up and comfortable, the first blood pressure reading and blood sample were taken. Participants were also asked to fill out three simple questionnaires regarding alertness, arousal and appetite. These measures were taken at -1, 0, 0.5, 1 and 2 hours after breakfast and at 0.5, 1, 2 and 3 hours after lunch (Figure 4.2).

Mood and positive affect

Russell’s affect circumplex model of psychological feelings of mood and affect[^363] was used to guide the assessment of affective states and whether these constructs are altered by intervention condition. This is a dimensional approach to the study of affect where emotion is defined in terms of two dimensions; valence (pleasant–unpleasant) and arousal (high–low), and
assessed using two single-item gauges (Appendix 15). The Felt Arousal scale[^364] is a six-point scale from zero; low arousal and six; high arousal. The Feeling Scale[^365] asks participants to rate their feelings on an 11-point scale (very good = +5 and very bad = -5) and was used to assess affective valence.

**Alertness**

Physical activity is thought to affect daytime sleepiness therefore, a modified version of the Karolinska Sleepiness Scale[^366] was used to plot participants’ alertness states throughout the experimental conditions.

**Meals**

After measurements had been taken at time point 0 and 3 hours a standardised meal was provided. The meal contained energy (8 kCal·kg⁻¹) from carbohydrate (51-52%), fat (35%) and protein (14-15%) to reflect a typical British daily macronutrient intake and ensure ecological validity. Participants were instructed to consume all food provided within 15 minutes. Measurements were continued at 0.5, 1, 2 and 3 hours after the first bite was taken.

**4.2.4.1 Treatment conditions**

**Control**

Participants remained seated throughout the test period undertaking typical sedentary behaviours such as watching television, using an electronic device, reading and writing. Walking and standing were restricted as light ambulatory activity may improve glycaemic variability.[^304] When required, participants were transported to the restrooms using a wheelchair.

**Continuous Exercise**

The MICE condition mirrored the control condition (CON) except that in addition, between time points 1 and 2 hours, participants performed MICE. Participants warmed up for three minutes at 3.5km·h⁻¹ with zero gradient before walking for 30 minutes at 65% of the VO₂peak achieved during the maximal exercise test. This was followed by a two minute cool down at 3.5 km·h⁻¹.

This exercise prescription was chosen to match the energy expenditure associated with the HIIE[^184, 367] and to reflect the intensity, time and type guidelines for moderate-intensity continuous exercise.[^140] Heart rate was monitored throughout and recorded every three minutes during exercise (a total of 12 times). At the same time points, having been familiarised with the Borg Rating of Perceived Exertion (RPE) scale[^368] participants were asked to rate their effort.
High-intensity interval exercise

The HIIE condition was identical to the MICE condition, but the exercise involved 10 x 60 seconds of brisk walking at the speed and gradient associated with 90% of the individual’s VO$_{2peak}$\textsuperscript{[209]}. Intervals were interspersed with 60 second active recovery periods at 3.5 km·h$^{-1}$ and 1% gradient. Total exercise time was 25 minutes including the same warm-up and cool-down as in MICE. Heart rate and RPE were recorded every two minutes i.e. at the end of each interval and a total of 12 times to correspond with values recorded during MICE.

Verbal encouragement and reassurance was provided throughout both exercise bouts.

4.2.4.2 Biochemical measurement

Whole blood samples to be analysed for regular clinical outcomes (glucose, triglycerides, CRP and haematocrit) were sent on the same day to the UHL pathology laboratory at the Leicester Royal Infirmary. Plasma FFA samples were ordered from a specialist laboratory at the University of Nottingham. Approximately 15ml of whole blood was immediately centrifuged at 3000 rpm for 15 minutes and processed according to the standard operating procedure (Appendix 16). Prepared plasma samples for all other analyses were then frozen in a -20°C freezer before being transferred to a -80°C freezer until analysis at the end of data collection.

Plasma glucose concentration was determined using a glucose oxidase method on the Beckman Auto Analyser (Beckman, High Wycombe, UK). Plasma insulin concentration was determined using the MSD Human Insulin Assay Kit (Meso Scale Discovery, Gaithersburg, MD, USA). The assay detects insulin using a single-incubation sandwich antibody immunoassay. Briefly, 25μL of anti-insulin labelled with an electrochemiluminescent compound and 25μL of sample was added in duplicate to a 96 well plate pre-coated with a substrate-specific monoclonal antibody. The assay was incubated for 2 hours to allow the insulin-antibody sandwich to bind. Any unbound substances were subsequently washed away with PBS-tween solution before adding a read buffer to provide the appropriate chemical environment. Plates were immediately read on an MSD Sector (Meso Scale Discovery, Gaithersburg, MD, USA) which measures the intensity of emitted light to afford a quantitative measure of the insulin concentration in the sample.

4.2.4.3 Statistics

Sample size

Assuming a standardised difference of 1\textsuperscript{[22, 369]} and a within-person correlation of 0.3,\textsuperscript{[117]} it was estimated that 12 participants altogether would be required for a complete three-treatment, three-period crossover design in order to detect a 10% change in the glucose iAUC with 90% power and allowing for two primary comparisons against control conditions by setting alpha to
0.025 (CON vs. MICE and CON vs. HIIE). To allow for a subgroup analysis between south Asians and white Europeans, the recruitment target was 24 participants (12 WE and 12 SA). While it is hypothesised that larger differences will be observed in SA participants, there is little evidence to support this in terms of glucose iAUC specifically. Therefore, given that the inter-individual variability in this population is unknown and that a larger predicted difference would reduce the required sample size, it was decided it would not be appropriate to reduce the recruitment target in this population. Assuming a drop-out rate of 20%, it was predicted that 30 individuals would need to pass the screening visit.

Analysis

The primary outcome was incremental area under the glucose curve. Incremental AUC was originally used to determine the glycaemic index of foods compared to a 50g glucose load using an OGTT. More recently, it has been used as an index of whole glucose excursions, a marker of postprandial hyperglycaemia. Secondary outcomes include incremental area under the insulin curve, CGM parameters and physiological responses to exercise.

Per-protocol analysis was used to assess all variables (glucose, insulin, CGM, physical activity). For a participant’s results to be included in the iAUC analysis, a minimum of 50% of data had be available from each of the treatment visits (≥5 viable blood samples, including the 0 hour sample). Where participants had missing data, values were imputed using multiple regression. This involved fitting a model by which each predictor variable (age, BMI, ethnicity and fasting values) had its own coefficient and the outcome variable (glucose, insulin) was predicted from a combination of all the variables multiplied by their respective coefficients, plus a residual term. Imputation has been argued to be more appropriate than removing observations with missing data and using regression results in a smaller error than single imputation or last value carried forward.

Descriptive statistics (mean values and frequencies) were calculated for all measured variables. These data are presented as mean (SD) or median [IQR] if not normally distributed.

Glucose and insulin responses

Using the trapezoid method for calculating AUC is commonly used for determining post-challenge responses and has been shown to correlate well with polynomial interpolation. Furthermore, when assessing the effects of an acute intervention it is argued that subtracting the area below the fasting level (calculation of iAUC) results in a more accurate determination of glycaemic rise following a meal as one would not expect fasting glycaemia to change between measurements. However, this technique is problematic if individuals experience
postprandial hypoglycaemia. Therefore, for venous sample analysis, time-averaged (per hour) glucose and insulin concentrations were calculated using the trapezium rule from 0-6 hours. The mean of the fasting values taken at -1 and 0 hours was subtracted from the overall postprandial response. Results are presented as concentration hours (mmol·L⁻¹·h; 95% CI). Postprandial spike was calculated as the difference between the highest glucose concentration following each meal minus the fasting value. As a sensitivity analysis, results were also stratified by sex as differences in glycaemic control between males and females has previously been reported. The trapezium rule was also used to calculate the CGM AUC. Due to the continuous nature of the data, total AUC is presented in mmol·L⁻¹·min. This is consistent with other investigations and has been recommended as a summary statistic. Given that CGM’s were fitted on the morning of the treatment visit and took at least 90 minutes to start recording, CGM AUC was calculated for 1-6 hours (treatment response), 6 hours – midnight (evening response) and 24 hours after the 1 hour time point. Data were not analysed beyond this time point since diet could not be controlled post-intervention. Glycaemic variability was estimated by calculating the coefficient of variance (CV) between the mean and SD of glucose concentration.

The validity of a meal tolerance test to provide an estimate of insulin sensitivity and β-cell insulin response was eloquently justified by Mari et al., who demonstrated that there is a strong correlation between the ratio between insulin and glucose AUC and glucose clearance measured during a euglycamic hyperinsulinaemic clamp. The insulin iAUC : glucose iAUC ratio has been reported in studies investigating the acute effects of physical activity on glucose tolerance. Therefore, insulin iAUC was divided by glucose iAUC to provide an integrated assessment of insulin sensitivity.

Physical activity and posture

Free-living physical activity data were processed using GGIR (an R-package specifically designed to process multi-day raw accelerometer data) by an investigator not involved in the study. The magnitude of wrist acceleration was recorded every five seconds and processed into summary measures of total, five and 10 minute bouts of MVPA and VPA. Cut points for MPA and VPA were 100mg and 400mg respectively. Non-wear time was defined as ≥60 minutes continuous zero counts and at least 600 minutes of wear time had to have been recorded for a day to be considered valid. A minimum of four valid days were required in order to be included in the analysis. To coincide with the CGM data, 24 hours of accelerometer data collected on the treatment day was used in the analysis.
ActivPAL data were recorded in 15 second epochs and were downloaded after participants had left following each treatment visit. The activPAL proprietary software (activPAL Professional V7.2.32, Glasgow, UK) was used to access the recorded data and exported to Microsoft Excel. The total number of minutes spent sedentary, standing and stepping was summed for each participant and a mean calculated for each treatment condition.

All participants were analysed together in order to establish the effect of HIIE in a sample representative of the general population. In accordance with the aims of the original study, which were to determine whether there is a difference between ethnicities in response to exercise, white European participants were analysed separately as this group were recruited to target. There was not enough power to assess the effects in south Asian participants.

Outcomes were assessed for normality using the Shapiro-Wilk test. Where the assumption of normality was violated, the outcome was log transformed. All outcomes were assessed using a 1-way repeated measures ANOVA with treatment as the between-subjects factor. Models were controlled for treatment sequence. Where relevant (treatment postural allocation, CGM outcomes), total time spent at the treatment visit was added as a covariate. The median [IQR] and p-value for each outcome are presented in tables. The percentage difference between medians and F-values are presented in the text. Any significant interactions were followed up with pairwise comparisons of predictive margins. The t- and alpha values are reported in the text.

4.3 Results

4.3.1 Recruitment

Participant flow through the study is presented in Figure 4.3. Nine surgeries posted a total of 645 invitations. A further 114 individuals were invited from LDC databases. In total, 71 (9.4%) people responded positively. Following telephone screening, 36 individuals were invited to attend Visit 1. Common reasons for being excluded over the phone included; estimated BMI <23kg·m⁻² WE or <21kg·m⁻² SA, self-reported physical activity levels ≥3 x 20 minute bouts of vigorous exercise or taking glucose lowering medication. Of the 28 participants who attended the screening visit, 23 completed all study procedures (excluding physical activity monitoring). Blood test results for HbA1c returned the following day revealed that 20 participants were eligible to take part in the study. These participants were allocated a randomised trial sequence. Reasons for not fully enrolling on the study were; work commitments (N = 1), inability to complete the maximal exercise test (N = 2), HbA1c outside inclusion range (N = 3) and BMI too low (N = 2). Following randomisation, three participants withdrew from the study; one due to
work commitments and two due to health issues unrelated to the study, meaning that 17 participants completed all three treatment conditions.

**Figure 4.3** Participant flow through the GO for IT study

### 4.3.2 Participants

Table 4.2 displays characteristics of the 17 participants who completed all three treatment conditions. Participants were obese with HbA1c in the non-diabetic hyperglycaemia range and engaged in $19.1 \pm 17.2$ minutes of MVPA accumulated in bouts of at least five minutes per day. No participants engaged in purposeful VPA (>75 minutes per week). Median $HR_{peak}$ achieved in the maximal exercise test was equal to 101.4% of the age predicted maximum. Only four
participants failed to achieve ≥95% of their age predicted HR$_{\text{max}}$. Three of these individuals were taking beta-blocker medication.
### Table 4.2 Characteristics of participants who completed all 3 treatment trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 17)</td>
<td>(N=10)</td>
<td>(N=7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 [66-69]</td>
<td>68 [66-68]</td>
<td>68.0 [66-73]</td>
</tr>
<tr>
<td>White European</td>
<td>13 (76.5)</td>
<td>6 (60)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.6 [159.2-169.1]</td>
<td>168.6 [166.6-173.0]</td>
<td>158.3 [155.6-162.0]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.6 [76.9-93.8]</td>
<td>87.0 [79.1, 93.8]</td>
<td>79.9 [70.8-95.7]</td>
</tr>
<tr>
<td>BMI (kg·m²)</td>
<td>29.3 [28.4-32.1]</td>
<td>29.7 [28.4, 31.4]</td>
<td>28.7 [28.4-36.5]</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>101.6 [98.0-107.0]</td>
<td>102.3 [99.5-107.0]</td>
<td>100 [98-109.2]</td>
</tr>
<tr>
<td>VO₂peak</td>
<td>26 [22-28]</td>
<td>28 [26, 31]</td>
<td>22 [21-26]</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.9 [5.8-6.0]</td>
<td>6.0 [5.8, 6.1]</td>
<td>5.9 [5.7-5.9]</td>
</tr>
<tr>
<td>Fasting glucose (mmol·L⁻¹)</td>
<td>5.2 [5.1-5.6]</td>
<td>5.4 [5.2, 5.8]</td>
<td>5.4 [4.9-5.4]</td>
</tr>
<tr>
<td>Fasting insulin (µU·mL⁻¹)</td>
<td>11.9 [9.9-20.2]</td>
<td>12.8 [10.6-20.2]</td>
<td>10.6 [8.8-22.6]</td>
</tr>
<tr>
<td>VPA (mins·day⁻¹)</td>
<td>1.5 [0.5-1.9]</td>
<td>1.5 [0.9-1.8]</td>
<td>1.3 [0.1-2.2]</td>
</tr>
</tbody>
</table>

† N = 14; ‡ N = 7 due to device malfunction

BMI – body mass index; VO₂peak – maximal oxygen uptake achieved during exercise test; HbA1c – glycated haemoglobin; MVPA – moderate-vigorous physical activity accumulated in 5 minute bouts; VPA – vigorous intensity physical activity

4.3.3 Physical activity

#### 4.3.3.1 Postural allocation during treatment visits

These data were not normally distributed and were therefore log transformed for analysis. Time spent seated, standing and stepping in each treatment condition is presented in Table 4.3. There was no difference in standing time between the study arms (F = 0.49). There was a significant difference in sitting time between treatments (F = 24.17) with less time spent sitting in HIIE (t = -5.12; p<0.001) and MICE (t = -6.57; p<0.001) than CON, with no difference between HIIE and MICE (t = -1.66, p = 0.110). In addition, significantly more time was spent stepping in the intervention trials (F = 366.42) with more time spent stepping in MICE than HIIE (t = 2.76, p = 0.011) suggesting that MICE took significantly more time than HIIE.

#### 4.3.3.2 Habitual physical activity

These data were not normally distributed and were therefore log transformed for analysis. There was no difference in time spent in MVPA in the 24 hours from the start of the treatment visit (time point 1 hour; F = 0.41). Participating in each treatment also did not affect habitual physical activity. There were no differences in MPA (F = 1.41) or VPA (F = 0.65) in the week after taking part in each trial.

4.3.4 Mood and affect

These data were normally distributed and therefore not transformed.
Overall, participants described themselves as having low arousal (relaxed, calm or bored), feeling "good" and "alert" during the treatment visits. There was no effect of treatment on arousal ($F = 0.06$), feeling ($F = 0.08$) or sleepiness ($F = 0.15$). There was also no difference between feeling ($F = 2.50; p = 0.098$), arousal ($F = 0.63; p = 0.537$) or sleepiness ($F = 2.17; p = 0.131$) scores recorded at the time point immediately after exercise (1 hour).

4.3.5 Responses to exercise

These data were normally distributed and were therefore not transformed.

4.3.5.1 Heart Rate

Mean HR reached during exercise bouts equated to 78.9 ± 6.9% and 77.9% ± 9.1% of $HR_{peak}$ in the HIIE and MICE conditions respectively (Table 4.3). Mean HR elicited by HIIE and MICE were not different (-0.9 bpm; $F = 0.00$).

4.3.5.2 RPE

Mean RPE judged by participants is displayed in Table 4.3. There was no difference in RPE between exercise conditions (-0.7; $F = 2.60$).
**Table 4.3** Physical activity, exercise and psychological parameters during treatment visits

<table>
<thead>
<tr>
<th>Condition</th>
<th>CON</th>
<th>HIIE</th>
<th>MICE</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ActivPAL (mins)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>431.4 [420.2-440.1]</td>
<td>396.2 [390.2-415.1]</td>
<td>391.9 [382.1-424.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stepping</td>
<td>0.6 [0.2-0.9]</td>
<td>25.4 [25.1-26.5]</td>
<td>37.3 [36.7-37.9]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>GeneActiv (mins)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVPA</td>
<td>29.8 [9.9-46.3]</td>
<td>25.3 [16.6-33.8]</td>
<td>18.0 [7.1-48.6]</td>
<td>0.667</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treadmill speed (km·h⁻¹)</td>
<td>-</td>
<td>5.3 [5.3-5.3]</td>
<td>5.3 [5.0-5.3]</td>
<td>-</td>
</tr>
<tr>
<td>Treadmill gradient (%)</td>
<td>-</td>
<td>10.0 [8.0-13.0]</td>
<td>2.5 [1.0-4.5]</td>
<td>-</td>
</tr>
<tr>
<td>HR (bpm)†</td>
<td>-</td>
<td>120 [110.9-126.3]</td>
<td>120.6 [106.8-123.5]</td>
<td>0.987</td>
</tr>
<tr>
<td>Proportion HRmax (%)†</td>
<td>-</td>
<td>78.2 [75.0-84.7]</td>
<td>78.2 [69.7-84.1]</td>
<td>0.940</td>
</tr>
<tr>
<td>RPE</td>
<td>-</td>
<td>12.4 [11.5-13.8]</td>
<td>12.3 [11.4-13.2]</td>
<td>0.128</td>
</tr>
<tr>
<td><strong>Psychological measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousal</td>
<td>1.4 [0.1-2]</td>
<td>1.8 [0.0-2.2]</td>
<td>1.5 [0.6-2.6]</td>
<td>0.939</td>
</tr>
<tr>
<td>Feeling</td>
<td>3.0 [2.0-3.4]</td>
<td>2.6 [2.0-3.2]</td>
<td>2.8 [2.3-3.6]</td>
<td>0.923</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>3.1 [2.8-4.2]</td>
<td>2.8 [3.3-3.4]</td>
<td>3.0 [2.9-3.4]</td>
<td>0.863</td>
</tr>
</tbody>
</table>

Data are presented as median [IQR]

† N = 16 due to device failures

NB. ActivPAL was worn on treatment visits only. GeneActiv data is for the first 24 hours of wear time from time point 1 hour of the treatment visit. Activity includes bouts lasting ≥1 minute.

CON – control; HIIE – high-intensity interval exercise; MICE – continuous exercise; MPA – moderate-intensity physical activity accumulated in bouts ≥5min; VPA – vigorous-intensity physical activity; HR – heart rate; RPE – rating of perceived exertion
4.3.6 Glucose

4.3.6.1 Plasma glucose

Incremental AUC and 2 hour glucose for breakfast and lunch were not normally distributed and were therefore log transformed. Postprandial responses did not violate the assumption of normality so the original data were used in the analysis.

Mean plasma glucose levels recorded at each time point are displayed in Figure 4.4a. Figure 4.4b shows the difference in glucose AUC in MICE and HIIE compared to CON for each participant. There were large differences in individual glucose responses. Nine (53%) participants had a larger glucose AUC in one or both of the exercise conditions. Neither HIIE nor MICE reduced glucose iAUC compared to CON (F = 0.13; Table 4.4). There was a significant effect of treatment on breakfast 2 hour glucose levels (F = 5.45; Table 4.4). Follow-up tests revealed that 2 hour glucose in MICE was 26% lower than CON (t = -3.28; p = 0.003), but no different in HIIE compared to CON (t = -1.93; p = 0.063), with no difference between exercise conditions (t = -1.36; p = 0.185). This effect did not persist into lunchtime (F = 0.49). There was a main effect of treatment on breakfast postprandial spike (F = 3.31; Table 4.4). The reduction in glucose elicited by HIIE was not significantly different to control (t = -1.97; p = 0.058) whereas there was a 26% reduction in MICE (t = -2.42; p = 0.022) compared to CON. There was no difference in breakfast postprandial spike between exercise conditions (t = -0.45; p = 0.656). There was no effect of treatment on the postprandial response to lunch (F = 2.13).
Figure 4.4 a. Mean plasma concentration of glucose during each GO for IT treatment visit. Points represent means, error bars represent standard deviation and b. Difference in glucose iAUC compared to control following a bout of high-intensity interval (HIIE) or continuous moderate intensity exercise (MICE) for each participant. A positive difference reflects a larger iAUC in the exercise condition.

4.3.6.2 Continuous glucose monitoring

All outcomes except for evening CV and AUC were log transformed since they were found to violate the assumption of normality.

Glucose levels recorded by the CGM in each condition is presented in Figure 4.5a. There were no differences between conditions in mean glucose during the treatment period (F = 1.58), the following evening (F = 0.29) or the 24 hour period following exercise (F = 0.10; Table 4.4). Consistent with the results from the venous sampling, there was no difference in glucose AUC between conditions during (F = 2.37), immediately after (F = 1.59) or 24 hours after (F = 0.10) the treatment visit. There was a significant effect of treatment on CV during the visit (F = 3.78) with the CV in HIIE 27% lower than CON (t = -2.71; p = 0.013; Figure 4.5b). There was no
difference between MICE and CON ($t = -1.35, p = 0.192$). This effect did not persist into the evening ($F = 0.49$) or for the 24 hours post exercise ($F = 1.10$).

![Graph](image)

**Figure 4.5 a.** Mean glucose levels measured by CGM from 1 hour postprandial until midnight on each treatment day. Dotted bar indicates when exercise took place. And **b.** Mean coefficient of variation (CV) of glucose levels in control (CON), high-intensity interval (HIIE) and moderate-intensity continuous exercise (MICE) conditions. Error bars represent the standard deviation. 1-way ANOVA with follow-up t-tests identified a significant difference between CON & HIIE.
### Table 4.4 Biochemical outcomes during and after treatment visits

<table>
<thead>
<tr>
<th>Condition</th>
<th>CON</th>
<th>HIIE</th>
<th>MICE</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iAUC (mmol·L⁻¹·h)</td>
<td>11.0 [7.7-12.1]</td>
<td>8.1 [7.6-12.4]</td>
<td>8.6 [7.2-11.0]</td>
<td>0.878</td>
</tr>
<tr>
<td>PPSbreakfast (mmol·L⁻¹)*</td>
<td>4.2 [3.5-4.9]</td>
<td>3.5 [3.0-4.0]</td>
<td>3.1 [2.3-4.0]</td>
<td>0.050</td>
</tr>
<tr>
<td>2h glucosebreakfast (mmol·L⁻¹)</td>
<td>8.3 [7.1-8.7]</td>
<td>7.3 [6.7-7.8]</td>
<td>7.0 [6.3-7.7]</td>
<td>0.009</td>
</tr>
<tr>
<td>PPSlunch (mmol·L⁻¹)*</td>
<td>1.5 [0.8-2.2]</td>
<td>2.1 [0.9-2.4]</td>
<td>2.4 [0.5-2.9]</td>
<td>0.135</td>
</tr>
<tr>
<td>2h glucoeslunch (mmol·L⁻¹)</td>
<td>6.7 [5.9-7]</td>
<td>6.6 [5.8-7.2]</td>
<td>6.5 [5.5-7.1]</td>
<td>0.620</td>
</tr>
<tr>
<td><strong>Continuous glucose monitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean_trt (mmol·L⁻¹)</td>
<td>7.0 [6.3-7.7]†</td>
<td>6.4 [5.7-7.5]‡</td>
<td>6.5 [5.7-7.9]§</td>
<td>0.227</td>
</tr>
<tr>
<td>CV_trt (%)</td>
<td>15.2 [14.1-19.2]†</td>
<td>11.1 [9.4-13.7]§</td>
<td>10.9 [8.4-14.9]§</td>
<td>0.039</td>
</tr>
<tr>
<td>AUC_trt</td>
<td>441.1 [405.5-486.3]†</td>
<td>397.8 [363.5-463.4]§</td>
<td>405.1 [382.0-456.3]§</td>
<td>0.117</td>
</tr>
<tr>
<td>Mean_eve (mmol·L⁻¹)§</td>
<td>6.4 [5.6-7.0]</td>
<td>6.4 [5.7-6.6]</td>
<td>6.11 [5.5-7.9]</td>
<td>0.748</td>
</tr>
<tr>
<td>CV_eve (%)§</td>
<td>17.6 [11.0-19.9]§</td>
<td>15.3 [10.5-17.8]</td>
<td>12.5 [10.2-17.0]</td>
<td>0.617</td>
</tr>
<tr>
<td>AUC_eve§</td>
<td>601.1 [509-716.1]</td>
<td>658.4 [589.8-729.8]</td>
<td>633.3 [590.9-759.4]</td>
<td>0.225</td>
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<tr>
<td>Mean_24h (mmol·L⁻¹)</td>
<td>6.3 [5.8-6.8]†</td>
<td>6.1 [5.7-6.4]§</td>
<td>6.1 [5.8-6.7]§</td>
<td>0.905</td>
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<tr>
<td>CV_24h (%)</td>
<td>19.4 [17.3-24.6]†</td>
<td>18.3 [15.5-23.2]§</td>
<td>15.9 [12.4-26.8]§</td>
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<tr>
<td>AUC_24h</td>
<td>1819.2 [1684.0-1959.4]</td>
<td>1758.2 [1644.1-1861.8]§</td>
<td>1771.9 [1667.9-2615.4]§</td>
<td>0.909</td>
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<tr>
<td><strong>Insulin</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iAUC (μU·mL⁻¹·h)</td>
<td>498.0 [352.4-830.8]</td>
<td>385.0 [303.1-564.0]</td>
<td>443.9 [394.2-571.1]</td>
<td>&lt;0.001</td>
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<tr>
<td>2h insulinbreakfast (μU·mL⁻¹)</td>
<td>120.0 [76.8-182.9]</td>
<td>72.7 [50.2-90.7]</td>
<td>94.9 [76.6-148.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2h insulinlunch (μU·mL⁻¹)</td>
<td>130.4 [94.1-155.7]</td>
<td>79.2 [60.4-140.0]</td>
<td>107.1 [73.1-147.1]</td>
<td>0.003</td>
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<td><strong>β-cell sensitivity index</strong></td>
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<tr>
<td>Ratio IiAUC:GiAUC</td>
<td>57.1 [39.4-82.3]</td>
<td>39.7 [30.0-63.4]</td>
<td>55.3 [36.8-87.6]</td>
<td>0.036</td>
</tr>
</tbody>
</table>

Data are presented as median [IQR]
† N = 16; § N = 15; † N = 14; due to device failures; * outcome not log transformed
24h – readings recorded from 1 hour until the corresponding time the next day; IAUC – incremental area under the curve; CON – control; CV – coefficient of variation; eve – readings recorded from 1 hour to midnight on treatment day; G – glucose; HIIE – high-intensity interval exercise; I – insulin; MICE – continuous exercise; PPS – postprandial spike; trt – readings recorded from 1-6 hours on the treatment visit
4.3.7 Insulin

All insulin outcomes were log transformed as they were found not to be normally distributed.

Mean plasma insulin concentrations are displayed in Figure 4.6. There was a significant difference in insulin AUC between conditions \( (F = 13.93; \text{Table 4.4}) \). HIIE \( (t = -5.27; p < 0.001) \) and MICE \( (t = -2.80; p = 0.009) \) significantly reduced insulin iAUC by 23% and 11% compared to CON, respectively (Table 4.4). There was also a difference between exercise conditions with the iAUC in HIIE 13% lower than that in MICE \( (t = 2.47; p = 0.019) \).

![Figure 4.6 Mean plasma insulin concentration during each treatment visit.](image-1)

Figure 4.6 Mean plasma insulin concentration during each treatment visit. Points represent means, error bars represent standard deviation.

Plasma insulin concentrations were significantly different 2 hours following breakfast \( (F = 13.52) \) and lunch \( (F = 7.24) \) between conditions (Figure 4.7). Follow-up analysis revealed that breakfast 2 hour insulin was 39% \( (t = -5.19; p < 0.001) \) and 21% \( (t = -2.33; p = 0.026) \) lower in the HIIE and MICE conditions compared to CON, respectively. HIIE also reduced 2 hour insulin 23% more than MICE \( (t = 2.85; p = 0.008) \). Similarly, lunch 2 hour insulin was 39% lower in HIIE \( (t = -3.78; p = 0.001) \) and 28% lower in MICE \( (t = -2.27, p = 0.030) \) compared to CON, but there was no difference between HIIE and MICE \( (t = 1.51; p = 0.142) \).
4.3.8 Insulin sensitivity

There was a significant interaction between treatment and the IiAUC : GiAUC ratio (F = 3.71). Follow-up tests revealed that the ratio was 30% lower in HIIE than CON (t = -2.72, p = 0.011), but there was no effect of MICE compared to CON (t = 1.31, p = 0.199). A lower ratio indicates higher sensitivity as less insulin is present for a given amount of glucose.

4.3.9 Sub-group analyses

4.3.9.1 Plasma glucose

Data distributions were similar in white Europeans as in the whole cohort, therefore the data were transformed as for the whole sample.

When white Europeans were analysed in isolation, results were consistent with those of the whole cohort, but were attenuated slightly. There was no longer a difference in breakfast postprandial spike (F = 0.89; p = 0.422). There was however, still a difference in 2 hour glucose after breakfast (F = 3.99; p = 0.032). Follow-up tests revealed that breakfast 2 hour glucose was significantly lower in MICE compared to CON (t = -2.80, p = 0.010), whereas there was no effect of HIIE (t = -1.10; p = 0.281).

4.3.9.2 Continuous glucose monitoring

There was no longer a reduction in treatment CV in the HIIE condition when WE’s were analysed separately. Apart from this, consistent with the findings from the sample as a whole, there were no differences between conditions in any of the CGM outcomes.
4.3.9.3  **Insulin**

There was a significant treatment effect on insulin AUC ($F = 7.59; p = 0.003$). Follow-up analysis showed that the AUC was lower in the HIIE ($t = -3.80; p = 0.001$) but not the MICE ($t = -1.16, p = 0.257$) condition compared to CON. The reduction in HIIE was significantly lower than compared to MICE ($t = 2.64, p = 0.014$). Plasma insulin 2 hours after breakfast was significantly different between conditions ($F = 6.78, p = 0.005$). HIIE significantly reduced 2 hour insulin ($t = -3.58, p = 0.001$) compared to CON, whereas MICE did not ($t = -1.07, p = 0.297$). The reduction in HIIE was significantly different to the response in MICE ($t = 2.52, p = 0.019$). The between treatment differences in lunch 2 hour insulin were also present in WE’s ($F = 3.56; p = 0.044$). Follow-up tests revealed that only HIIE reduced 2 hour insulin compared to CON ($t = -2.67, p = 0.013$).
4.4 Discussion

4.4.1 Main findings

This study aimed to determine whether an acute bout of HIIE or MICE would reduce plasma glucose and insulin iAUC in comparison to control conditions. The results showed that there was no difference in plasma glucose iAUC between conditions and therefore the null hypothesis was accepted. However, there was a reduction in insulin iAUC in the HIIE and MICE conditions respectively, with the AUC in HIIE also lower than that in MICE. A reduction in insulin AUC in the HIIE was implicative of an increase in insulin sensitivity as determined by a reduction in the insulin iAUC : glucose iAUC ratio. There was also evidence of reduced glycaemic excursions in the MICE condition with breakfast postprandial spike and 2 hour plasma glucose significantly lower than in CON. The findings from the CGM data were somewhat consistent with those of the plasma results, also suggesting that there were no effects of exercise on glucose AUC that extended into the evening or morning following the treatment visits. There was, however, a reduction in the CV of glucose levels during the HIIE, but not the MICE treatment period, which, in contrast to the plasma glucose results, indicate that glycaemic variability was lower in HIIE.

4.4.2 Comparison to previous research

To the best of my knowledge, this is the first study to compare the effects of a single bout of HIIE and MICE on glucose and insulin responses compared to control conditions in a population with NDH. Similar studies are summarised in Table 4.5. The findings that neither exercise protocol affected glucose iAUC or mean glucose level on the day of exercise are comparable to the results from a study by Little et al. In this study, 10 overweight or obese individuals took part in two three day trials. After a CGM was fitted and participants were provided with standardised meals, the first day acted as a control day. Returning to the laboratory two hours after breakfast the following day, 10 participants undertook either a HIIE or MICE session before being allowed home and instructed to consume the food provided. Analysis of 48 hours of CGM data revealed no difference in mean 24 hour blood glucose, MAGE, the standard deviation of glucose concentrations or responses to lunch between conditions. Interestingly though, benefits of HIIE in this study appeared to occur 12-24 hours following exercise, with reductions in the glucose responses to dinner and breakfast the following day compared to control, improvements not observed following MICE. In contrast, the reductions in glucose fluctuations observed in the current study occurred almost immediately after (or during) exercise, with a reduction in breakfast postprandial spike and significantly lower plasma glucose levels measured 2 hours after breakfast. A similar study by Parker et al. on 23 overweight/obese individuals,
found that both HIIE and MICE reduced 24 hour glucose AUC, mean blood glucose, peak glucose, time spent above 7 mmol·L⁻¹ and breakfast and dinner AUC compared to control.

There are a number of possible reasons for the discrepancies between these three studies. First, the sample size in the study by Parker et al. was larger and therefore would have had more power to detect changes. However, the sample size calculated for the GO for IT study was based on a conservative estimate from the results from Little et al. Therefore, the lack of effect on glucose AUC should not be due to a lack of power. There were small differences in the exercise protocols between each investigation, for instance, in the GO for IT study participants exercised on a treadmill rather than a bike. However, protocol variables are not consistent between each study and their respective result.

The effects of an acute bout of HIIE on insulin responses have been less rigorously tested. In the study by Parker et al. for instance, insulin measurements were not taken on the control day and only compared between exercise conditions. In this case, MICE resulted in significantly lower plasma insulin than HIIE immediately and 1.5 hours post exercise, whereas in the GO for IT study, HIIE reduced 2 hour insulin more than MICE, and both were lower than control. Studies which have employed sprint interval exercise (SIE) protocols have not found improvements in insulin AUC in healthy or overweight individuals, suggesting that SIE may affect insulin signalling differently to HIIE. Interestingly in the MICE condition, Brestoff et al. found that 3 x 15 minutes at 75% VO₂peak with 2 minutes rest in between reduced insulin AUC, but Meltcalfe et al., using a similar protocol, did not.

Some comparison can be made to studies which have investigated the effect of MICE on postprandial glucose and insulin responses. In 12 pregnant women with gestational diabetes, 30 minutes of low-intensity and 30 minutes of moderate-intensity exercise performed on separate days both reduced glucose AUC compared to seated rest however, insulinaemia was not affected. These findings, possibly attributable to the differences in the physiology of the populations studied, are the reverse of what was observed in the GO for IT study. On the other hand, similar to the findings from the GO for IT study, in nine males with T2DM, 45 minutes of cycling at 50% VO₂max interrupted the postprandial increase in glucose and insulin which consequently reduced the glucose and insulin breakfast AUC. These improvements did not extend to the responses to lunch. The greater magnitude of improvements in the study by Larsen et al. could be explained by the slightly greater volume of exercise undertaken and/or the population included who, having been diagnosed T2DM, may have been more insulin resistant.
4.4.3 Explanation of results

Overall, it appears that some benefits in postprandial glucose and insulin responses can be achieved following acute bouts of exercise, with the effects of HIIE on insulin action greater than those observed with MICE, whereas the reverse may be true for glucose responses. The finding from the GO for IT study; that a model of HIIE which elicited a maximum heart rate of <80% of an individual’s peak improved markers of insulin sensitivity more than MICE is of particular interest. It is possible that the intermittently higher workload demanded in HIIE stimulated muscle contraction and therefore an increase in insulin sensitivity to a greater extent than MICE, despite eliciting a similar mean heart-rate and overall energy expenditure.

However, as summarised in the previous section (4.4.2) and Table 4.5, at what time point (e.g. immediately, following the next meal, nocturnally) in which parameter (e.g. glucose vs. insulin, AUC vs. magnitude of glycaemic excursions) and in which populations (diagnosed T2DM or IGT) HIIE and MICE produce benefits is unclear. It is acknowledged that an individuals’ physiological response to exercise will vary and therefore changes will not be observed in every outcome.\(^{379}\)

While participants acted as their own controls, two participants in particular had very small glycaemic responses in the control condition (Figure 4.4). One participant appeared to experience postprandial hypoglycaemia in the control condition, thus dramatically reducing the AUC. Another had previously been diagnosed with T2DM and although their HbA1c was currently within the NDH range and he was therefore eligible to take part, inspection of his individual results revealed large excursions in plasma glucose. One explanation could be that there are differences in fasting vs. postprandial exercise. A recent systematic review and meta-analysis\(^ {380}\) concluded that exercise performed in the fed state overall resulted in blood glucose levels that were 0.8 mmol·L\(^{-1}\) higher than when exercise was performed in the fasted state. Similarly, insulin levels were 15.0 \(\mu\text{U·L}^{-1}\) higher in the fed than the fasted state. This goes some way to explain why improvements in glucose iAUC were not observed in the GO for IT study, although the finding that insulin iAUC was reduced when exercise was performed postprandial is not consistent with the conclusions of the meta-analysis. It should be noted though, that the meta-analysis did not compare exercise to resting control conditions.

A study similar to the GO for IT investigation carried out by Terada et al.\(^{185}\) compared the effect of HIIE and MICE on CGM measured glucose responses in the fasted and fed (one hour postprandial) states of 10 individuals with T2DM. They found that, when combining the results of the exercise conditions, MAGE, post-lunch iAUC and total (breakfast and lunch combined) iAUC was significantly lower when exercise was performed in a fasted than a postprandial state. They also found that MICE in the fasted state resulted in lower post-breakfast glucose iAUC than
There were no differences between the two types of exercise when it was performed after breakfast. Compared to a non-exercising control day, both HIIE and MICE performed fasted lowered MAGE and total iAUC and HIIE lowered 24 hour, time spent in hyperglycaemia and next day fasting glucose. The only difference in the postprandial exercise condition compared to control was a reduction in total glucose iAUC following MICE, a finding somewhat supported by the reduction in breakfast 2 hour glucose in GO for IT. Although there was no reduction in glucose iAUC with MICE in the GO for IT study; possibly due to the 50% shorter exercise intervention, the study by Terada et al. indicates that greater benefits may be observed when exercise is performed fasted rather than postprandial. In contrast, earlier studies have shown the opposite, meaning that, to date, the general position has been that postprandial exercise is most beneficial. For example, in the study by Larsen et al. (Table 4.5), the exercise was performed 45 minutes postprandial and did result in benefits to glucose and insulin responses. Similarly, Colberg et al. reported that 20 minutes of MICE performed immediately after an evening meal attenuated the postprandial rise in plasma glucose compared to control in 12 individuals with T2DM, whereas this was not the case when exercise was performed immediately prior to meal consumption. However, there was no difference in glucose AUC between exercise conditions. Therefore, the findings regarding fasted vs. postprandial exercise appear to be more equivocal than first thought. One reason for the absence of acute reductions in glucose responses following postprandial exercise is the effect of moderate-vigorous intensity exercise on the ratio between exogenous and endogenous glucose appearance and muscle glucose uptake. In the fasted or post absorptive state, plasma glucose remains constant during moderate exercise of less than 60 minutes duration due to proportional stimulation of liver glycogenolysis in response to glucose uptake. In a fed state, it is possible that endogenous glucose production from the liver combined with glucose provided by a meal exceeds glucose uptake by the muscle during and after exercise, thus resulting in no net reduction in plasma glucose. This phenomenon has been observed in randomised crossover trials. For example, in a group of healthy young men, Gonzalez et al. found that compared to fasted exercise, the postprandial glucose spike following the next meal was higher when exercise was performed 2 hours after breakfast. Additionally, following breakfast, the postprandial spike was also higher in the exercise condition than the sitting condition. These findings indicate that prior meal consumption i.e. breakfast, attenuates glucose uptake following the next meal, and that MICE does not fully compensate for this attenuation. Furthermore, in an untrained population, such as the participants in the GO for IT study, it is also possible that muscle glucose uptake is impaired by reduced membrane permeability and/or GLUT-4 activity, further exacerbating this phenomenon.
It is perhaps surprising, given that there is an increase in insulin sensitivity during and immediately after a bout of exercise,[385] that greater and longer lasting improvements in glycaemic control were not observed. Indeed, although the insulin iAUC : glucose iAUC ratio was only significantly lower in the HIIE condition, it appears that in both exercise conditions there was some degree of increased insulin sensitivity as a similar (HIIE) and lower (MICE) glucose response occurred in the presence of lower insulin concentrations after breakfast and lunch. One reason for this could be that the deleterious effects of the ~five hours participants spent sitting post-exercise outweighed the benefits conferred to glycaemic regulation of performing activity. There is ample evidence that extended periods spent sedentary is an independent predictor of T2DM,[117] and that breaking sitting time with short (2-10 minute) bouts of standing or walking improves glycaemic regulation. For example, substantial reductions in postprandial glucose and insulin levels were reported following intermittent bouts of light walking totalling a workload similar to that of a 30 minute bout of MICE.[124] Furthermore, Peddie et al.[316] found that both glucose and insulin iAUC were reduced during nine hours of sitting interspersed with walking breaks, but not after a 30 minute bout of exercise at 60% VO₂max performed in the morning followed by ~seven hours of sitting. Similarly, Holmstrup et al.[317] found that performing one hour of exercise at 60-65% VO₂max reduced 12 hour insulin AUC but not 12 hour glucose AUC in young obese individuals with fasting glucose >5.5 mmol·L⁻¹. In fact, glucose AUC was higher in the exercise condition than in control. On the other hand, in 20 individuals with T2DM, performing one bout of 45 minutes of cycling significantly reduced 11 hour glucose and insulin AUC compared to taking three 15 minute three MET walks immediately after eating, although the difference in glucose AUC was non-significant between activity conditions (p = 0.06).[386]

The differences in the findings between these studies may be explained by variations in exercise intensity, duration and timing, as well as population physiology, but this lack of homogeneity makes direct comparison difficult.
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Test measures</th>
<th>Selected findings</th>
<th>Findings compared to GO for IT</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects of HIIE vs. MICE &amp; CON</strong></td>
<td></td>
<td></td>
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<tr>
<td>Little</td>
<td>N = 10 OW/Ob</td>
<td>Day 1 – control Day 2 – 10 x 60s @ 90% WLpeak or Day 2 – 30 min @ 35% WLpeak performed 2h after breakfast</td>
<td>CGM on day of exercise and next day</td>
<td>No differences in mean 24h BG, MAGE, SD of BG or lunch G AUC ↓ dinner and next day breakfast G AUC in HIIE &amp; MICE vs. CON ↓ PPS and AUC for breakfast the next day in HIIE vs. MICE &amp; CON ↓ 24h BG, 24h AUC, peak BG &amp; time BG ≥7 mmol·L⁻¹ in HIIE &amp; MICE vs. CON ↓ breakfast &amp; dinner but not lunch AUC in HIIE &amp; MICE vs. CON ↓ insulin immediately &amp; 1.5h post-exercise in MICE vs. CON</td>
<td>Y</td>
<td>No difference in lunch G iAUC</td>
</tr>
<tr>
<td>Parker</td>
<td>N = 23 Ob/OW</td>
<td>Day 1 – control Day 2 – 8 x 60s @ 100% WLmax or Day 2 – 38 min @ 50% WLmax performed 1h after breakfast</td>
<td>CGM and blood samples on day of exercise</td>
<td></td>
<td>N</td>
<td>No difference in morning G AUC</td>
</tr>
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<td></td>
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<tr>
<td>Brestoff</td>
<td>N = 13 Healthy, young</td>
<td>SIE – 5 x 30s @ 125% VO₂peak MICE – 3 x 15 min @ 75% VO₂peak both with 5 min recovery CON – No exercise</td>
<td>2h OGTT day after exercise</td>
<td>No difference in G AUC ↓ insulin AUC in MICE vs. CON &amp; SIE</td>
<td>Y</td>
<td>No differences in G iAUC</td>
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<td>Metcalfe</td>
<td>N = 14 Healthy, young</td>
<td>SIE – 2 x 20s Wingate efforts MICE – MICE – 3 x 15 min @ 75% VO₂peak, 5 min rest recovery CON – No exercise All performed in the evening</td>
<td>2h OGTT morning after exercise</td>
<td>No difference in G AUC No difference in insulin AUC</td>
<td>Y</td>
<td>No differences in G AUC</td>
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<table>
<thead>
<tr>
<th>Study</th>
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<th>Intervention</th>
<th>Test measures</th>
<th>Selected findings</th>
<th>Findings compared to GO for IT</th>
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<td>Similar?</td>
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<td>Avery</td>
<td>N = 12</td>
<td>LICE – 30min @ 35% VO2max</td>
<td>Blood samples during &amp; 2h after exercise</td>
<td>▼ G AUC in LICE &amp; MICE vs. CON</td>
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<td>MICE – 30min @ 55% VO2max</td>
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<td>No difference in insulin AUC</td>
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</tr>
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<td>diabetes</td>
<td>CON – No exercise</td>
<td></td>
<td></td>
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</tr>
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<tr>
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<td></td>
<td>MICE – 30min @ 55% VO2max</td>
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<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CON – No exercise</td>
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<td>N</td>
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<td>Larsen</td>
<td>N = 9</td>
<td>MICE – 45 min @ 50% VO2max</td>
<td>Breakfast and lunch meal tests</td>
<td>▼ breakfast G AUC in MICE vs. CON</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>T2DM</td>
<td>performed 45 min postprandial</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CON – No exercise</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td><strong>Effects of fasted vs. postprandial exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terada</td>
<td>N = 10</td>
<td>HIIE – 15 x 60s @ 100% VO2max</td>
<td>CGM monitoring of breakfast and lunch meal test</td>
<td>▼ MAGE, lunch G iAUC, total iAUC in both fasted HIIE &amp; MICE vs. fed</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td>T2DM</td>
<td>MICE – 60 min @ 55% VO2max</td>
<td></td>
<td>▼ breakfast G iAUC in MICE fasted vs. HIIE fasted</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CON – No exercise</td>
<td></td>
<td>No differences between fed MICE &amp; HIIE vs. CON</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Performed either before or 1h after breakfast</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lunch meal</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Colberg</td>
<td>N = 12</td>
<td>MICEpa – 20 min @ 40% HRR performed immediately before dinner</td>
<td>Meal test during and after exercise</td>
<td>▼ total iAUC in fed MICE vs. CON</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td>T2DM</td>
<td>MICEfed – 20 min @ 40% HRR performed immediately after dinner</td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CON – No exercise</td>
<td></td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>Test measures</td>
<td>Selected findings</td>
<td>Findings compared to GO for IT</td>
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<td>-------------</td>
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<tr>
<td>Peddie</td>
<td>N = 70</td>
<td>MICE – 30 min @ 60% VO&lt;sub&gt;2max&lt;/sub&gt; performed before breakfast Li breaks – 18 x 100s @ 45% VO&lt;sub&gt;2max&lt;/sub&gt; CON – No exercise</td>
<td>Breakfast, lunch and dinner test meals</td>
<td>▼ G AUC in Li breaks vs. MICE &amp; CON</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td>Young, healthy</td>
<td></td>
<td></td>
<td>No difference between MICE &amp; CON</td>
<td>Y No difference between MICE &amp; CON</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▼ I AUC in Li breaks vs. MICE &amp; CON</td>
<td>Not tested</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference in insulin AUC between MICE &amp; CON</td>
<td>N ▼ insulin iAUC in MICE vs. CON</td>
</tr>
<tr>
<td>Holmstrup</td>
<td>N = 11 Ob/IFG</td>
<td>MICE – 60 min @ 60-65% VO&lt;sub&gt;2peak&lt;/sub&gt; MI breaks – 12 x 5 min @ 60-65% VO&lt;sub&gt;2peak&lt;/sub&gt; CON – no exercise</td>
<td>6 x small meal tests</td>
<td>▲ 12h G AUC in MICE vs. MI breaks and CON</td>
<td>Y No difference between MICE &amp; CON</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▲ 12h insulin AUC in CON vs. MICE &amp; MI breaks</td>
<td>Y ▼ insulin iAUC in MICE vs. CON</td>
</tr>
<tr>
<td>Van Dijk</td>
<td>N = 20 T2DM</td>
<td>MICE – 45 min @ ~6 METs performed 30 min after breakfast Li breaks – 3 x 15 min @ ~3 METs CON – no exercise</td>
<td>Breakfast, lunch and dinner meal tests</td>
<td>▼ 11h G AUC in MICE &amp; Li breaks vs. CON</td>
<td>N No differences in CGM measures between conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGM monitoring</td>
<td>▼ breakfast, lunch and dinner G AUC in MICE vs. CON</td>
<td>Y ▼ breakfast 2h glucose in MICE vs. CON</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▼ breakfast AUC in MICE vs. Li breaks</td>
<td>Not tested</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▼ 11h insulin AUC in MICE vs. Li breaks vs. CON</td>
<td>Y ▼ insulin AUC in MICE vs. CON</td>
</tr>
</tbody>
</table>

(i) AUC – area under the curve; BG – blood glucose; CON – control; G – glucose; HIIE – high-intensity interval exercise; HRR – heart rate reserve; IFG – impaired fasting glucose; IGT – impaired glucose tolerance; LI – light-intensity; LICE – low-intensity interval exercise; MAGE – mean amplitude of glycaemic excursions; MI – moderate-intensity; MICE – moderate-intensity interval exercise; N – no; Ob – obese; OW – overweight; PA – post absorptive; PPS – postprandial spike; SD – standard deviation; SIE – sprint interval exercise; T2DM – type 2 diabetes mellitus; VO<sub>2</sub> – oxygen uptake; WL – work load; Y – yes
4.4.4 Implications

Despite the acceptance of the null hypothesis for the primary outcome, that evidence of reduced postprandial glucose and glycaemic variability following exercise is of importance. A comprehensive review of epidemiological evidence linking postprandial hyperglycaemia to CVD in T2DM by Bonora & Muggeo\textsuperscript{[72]} sparked interest into the question of why impaired glucose tolerance appeared to predict diabetes complications to a greater extent than fasting glucose or HbA1c. It is difficult to assess the independent effects of reducing postprandial hyperglycaemia as often improvements are concurrent with reductions in fasting glycaemia. However, studies assessing the effects of acarbose, an oral anti-diabetic agent that inhibits glucose absorption and specifically reduces postprandial glucose response may be able to shed some light on this issue.

In a 3.3 year follow-up study, 1368 participants were randomised to receive either acarbose or placebo. Acarbose treatment was associated with a 49% relative risk reduction for experiencing a cardiovascular event. Unfortunately, OGTT’s were not conducted at follow-up and therefore the effect of acarbose on postprandial glycaemia cannot be determined. In addition, this study did not report incidence of T2DM at follow-up, and therefore the potential for acarbose to prevent T2DM by this mechanism remains unknown.\textsuperscript{[387]} In contrast to this, results from the NAVIGATOR trial,\textsuperscript{[388]} a 6.4 year follow-up study on individuals with impaired glucose tolerance treated with either nateglinide or valsartarn, both, or neither, suggest that there is no relationship between baseline 2 hour glucose and cardiovascular mortality. Again, however, this study did not perform follow-up OGTT’s. It would be pertinent for studies investigating the impact of physical activity on progression to T2DM to assess whether prevention of T2DM is associated with improvements in postprandial hyperglycaemia.

There is also compelling evidence that in individuals with T2DM, oscillating glucose levels cause more acute stress than sustained and postprandial hyperglycaemia. For example, Monnier et al.\textsuperscript{[389]} used CGM to estimate postprandial AUC and MAGE in patients with T2DM and healthy age-matched controls. They found a positive association between glycaemic variability and urinary excretion rates of free 8-iso prostaglandin 2α (8-iso PGF-2α), a marker of oxidative stress. Furthermore, there was no correlation between 8-iso 2α and fasting glucose, HbA1c or 24 hour mean glucose. An elegant study by Ceriello et al.\textsuperscript{[390]} provided support for these findings and demonstrated that the results observed by Monnier et al. were independent of diabetes diagnosis. In this study, glucose was infused using a clamp technique to either maintain a high constant rate of 10 mmol·L\textsuperscript{-1} or 15 mmol·L\textsuperscript{-1} or to alternate between 15 mmol·L\textsuperscript{-1} and 5 mmol·L\textsuperscript{-1} over a 48 hour period. Oxidative stress and endothelial dysfunction estimated by circulating nitrotyrosine, urinary excretion of 8-iso PGF-2α and flow mediated dilatation, respectively, were
increased to a greater extent in both healthy and newly diagnosed T2DM patients whose glucose levels were made to fluctuate than when glucose levels were high but stable. Early explanations for this phenomenon relate to the evidence that postprandial hyperglycaemia causes excessive production of superoxide in the mitochondrial transport chain. The superoxide then reacts with nitric oxide to produce substances toxic to the endothelium resulting in vascular damage which is a major contributor to diabetic complications.[389]

4.4.5 Wider context

By demonstrating that HIIE and MICE confer similar benefits to glucose regulation and that HIIE may increase insulin sensitivity more than MICE, further support for the recommendation of HIIE as an alternative to MICE has been provided. Importantly, HIIE was well tolerated with the mean RPE rating indicating that participants found the exercise “somewhat hard”, which was no different to the rating in the MICE trial and, in addition, HIIE took 10 minutes less than MICE. To date, only a handful of studies have investigated the training effect of performing 10 x 60 second HIIE on measures of glycaemic control and insulin sensitivity. Hood et al.[188] reported that following two weeks of performing HIIT, seven sedentary individuals improved their insulin sensitivity. It is reasonable to conclude that this was a training adaptation as blood was sampled at least 72 hours after the last exercise session. In another study, the same training programme followed by eight individuals with T2DM resulted in improved 24 hour mean and postprandial glucose responses.[209] On the other hand, no improvement in HOMA-derived insulin sensitivity was observed in nine obese individuals after three weeks of 10 x 60 second HIIT,[268] although the use of HOMA as a measure of insulin sensitivity may have masked some effects training might have had on dynamic indices of peripheral glucose control. Therefore, it appears that a low-volume, practical model of HIIT has the potential to induce both acute and lasting adaptations that improve insulin sensitivity, although how this will translate to the prevention and management of T2DM remains to be confirmed with longer-term training studies. Overall however, the work completed in Chapter 2 suggests that HIIT is as, if not more, beneficial than MICE in reducing insulin resistance and HbA1c.[253]

4.4.6 Strengths and limitations

There are several strengths to this study. First, the participants who were recruited through primary care represent a large, but hard-to-reach group who are typical of the type of population likely to be enrolled on to diabetes prevention programmes. Second, employing treadmill walking rather than cycling increases the external validity of the results as this population is more likely to choose walking as their preferred mode of exercise (see section 4.2.1.1 Patient and
public involvement). Third, physical activity was objectively monitored throughout participants enrolment in the study and was not different between conditions. Therefore, habitual physical activity is unlikely to have influenced the results. Fourth, this study provides more support for HIIE as a safe option for individuals at risk of T2DM and other chronic diseases as there were no serious adverse events relating to the exercise. It should be noted though, that one participant without diagnosed angina experienced symptoms during the maximal exercise test which was immediately aborted and the individual referred to their GP. Since this participant had not recently performed high-intensity exercise, it is reasonable to suggest that circulatory restrictions were already manifest but had not previously caused symptoms. In addition, given that she was self-limited by the pain, it is unlikely that performing high-intensity exercise would have caused any immediate danger. During the recovery period after another test, atrial fibrillation was detected by the ECG. The participant was asymptomatic and after a short period (less than 10 minutes) their HR returned to a normal rhythm and speed. Having been referred to the hospital for an exercise stress test, the results were not repeated and the participant was cleared to take part in the rest of the study. Therefore, although HIIE itself was well tolerated, one out of 25 (4%) participants who undertook a maximal exercise test was screened out indicating that maximal exercise may aggravate underlying issues in a large number of people.

There were also other limitations of this study. There was no difference between the HR elicited by each exercise protocol, and the mean HR recorded in both conditions was on the borderline between moderate and vigorous-intensity. This indicates that the exercise protocols did not stimulate the intended intensities. This is unexpected given that the workloads set were based on previous reports where taking the workload reached at 60-65% and 90-95% VO2max elicited the same relative intensity of HRmax in the MICE and HIIE protocols, respectively. This study used cycling as the mode of exercise for HIIE and MICE, whereas in the GO for IT study, following feedback from PPI groups, treadmill walking was used. It appears that cycling and walking elicit different physiological responses when relative intensities are taken in isolation from a maximal exercise test. It is interesting that increasing the treadmill gradient to the level associated with 90% VO2peak for one minute did not induce an increase in HR greater than that experienced after three minutes at ~60% VO2peak. Secondly, although the sample size was based on a conservative estimate of the expected within-person correlation, large variability in inter-individual responses were observed (Figure 4.4). Furthermore, while participants were asked to follow pre-treatment instructions, not everyone was able to adhere to the restrictions prior to each visit, for example due to work or family commitments. It is therefore possible that some of the variability could be attributed to a lack of control between conditions. This observation is important as it has
implications for translation of the findings into free-living conditions. It was also not possible to make comparisons between ethnicities due to difficulties recruiting to the study. Not only does this reduce the novelty of the study, it also has important implications for the practical application of HIIE as willingness to volunteer in the study may reflect attitudes to engage in HIIE. It is unlikely however, that the recruitment method; posting information sheets, is how HIIE would be implemented in clinical care.

There were also some issues with the CGM devices which, in some cases, became detached from the patient, were removed due to discomfort or did not produce data due to patient non-compliance with finger-prick testing. This means that full datasets for these results were unattainable. Furthermore, although the device manual states that recording will begin one hour after insertion, in most cases it was at least 90 minutes before data were available meaning that readings from the 0 hour time point were not available for every patient. Because of the commitment already demanded of the participants, the decision was taken not to invite participants to the laboratory the day before their treatment visit to have the CGM device fitted. Based on the limited effects of exercise on plasma glucose and our inability to control post-intervention diet, CGM data collected more than 24 hours after the treatment visit was not analysed. This suggests that the effects of physical activity on glucose regulation may not be as influential as those of diet, which has important implications for recommendations in practice. On the other hand, it could be argued that given the modest dose of exercise prescribed, the insulin sensitising, and concurrent effects on glucose levels may not have been altered beyond this point.[Mikines 1988 Am J Physiol 254(3)]

4.4.7 Future directions

The acute and training effects of HIIE in individuals at high risk of chronic disease are beginning to be understood in more detail, with promising results. Here, it has been shown that under laboratory conditions, an acute bout of either HIIE or MICE improves some aspects of glycaemic variability and postprandial insulin responses. Several pertinent questions have been raised by the findings of this study. For instance, what are the mechanisms underlying the observed responses? The rates of glucose and insulin appearance and disposal affected by meal consumption and exercise should be determined so that the dynamics can be fully understood. This would ensure that recommendations could be optimised to produce the greatest benefits. It would also be interesting to compare the effects of a single bout of HIIE or MICE with and without those of breaking sedentary time so that it could be determined whether each has independent, additive effects or whether extended periods of sedentary behaviour negate the
beneficial effects of a bout of MVPA. This has important implications for individuals considering enrolment into exercise training programmes. Most importantly, whether lasting benefits would be observed if this type of HIIE was performed regularly should be examined in interventions lasting a minimum of 12 weeks and longer-term 12 month studies. The feasibility of this will be discussed in more detail in the next chapter.
4.4.8 Conclusion

In conclusion, this study has shown that in individuals at high risk of T2DM, both MICE and HIIE reduce glycaemic variability to a similar extent, if not by different mechanisms. A reduction in postprandial insulin response suggests that this is likely to be a result of increased insulin sensitivity, which is enhanced by HIIE more than MICE, although postprandial glucose was lower in this condition. This is important because evidence is growing that improving insulin sensitivity and maintaining glycaemic stability is likely to prevent onset of T2DM, and complications in overt T2DM. HIIE was a safe and well tolerated mode of exercise and therefore further evidence has been provided that HIIE can be recommended as an alternative therapeutic health tool in the prevention and management of T2DM.
Chapter overview

This chapter completes the thesis by giving an overview of the study findings and discussing the implications of the collective results. It examines possible mechanisms by which high-intensity exercise uniquely improves health, before placing the findings in the context of the current debate surrounding HIIT. Based on the well-documented barriers to physical activity, and VPA in particular, the chapter discusses how HIIT might be applied in a clinical setting and, with this in mind, highlights areas for future research. The chapter closes with considerations as to how the findings might influence revisions of physical activity guidelines.

5.1 Thesis summary

The primary aim of this thesis was to assess the efficacy of VPA, specifically HIIE, on the prevention and management of T2DM. Three investigations were carried out in pursuit of this goal; a meta-analysis of the training effects of HIIT on outcomes relating to T2DM, a cross-sectional study assessing the relationship between physical activity bout length and intensity on markers of insulin sensitivity, and an acute experimental study comparing the effects of HIIE and MICE on postprandial insulin sensitivity. This research indicates that, in individuals at high risk of T2DM; HIIT is at least as effective as MICT at improving insulin sensitivity and glycaemic regulation, that increasing physical activity intensity above the sedentary threshold is linearly associated with favourable diabetes related outcomes, and that a single bout of HIIE can improve insulin sensitivity. The combined results of these investigations have contributed to the understanding of the dose-response relationship between activity intensity and glycaemic control, provided empirical support that HIIT has comparable effects to MICT, and highlighted the importance of tailored exercise therapy by proposing that physical activity below the moderate threshold is beneficial for health in people at risk of dysglycaemia. Therefore, it should be possible to tailor physical activity programmes to an individual’s needs based on their baseline level of fitness and/or health. Importantly, this thesis contributes to the growing body of evidence that HIIT can be recommended as an alternative form of physical activity for the prevention and management of T2DM.
5.1.1 Study 1: The effects of HIIT on insulin sensitivity and glycaemic control: a meta-analysis

While the effects of MICT on insulin sensitivity and glycaemic control have been thoroughly investigated, the effects of HIIT are less clear. The first objective of this thesis therefore, was to pool the available literature and determine the overall influence of HIIT on these outcomes. Despite a wide variety of HIIT protocols and participant characteristics, and a paucity of long-term training studies, the initial results were promising. HIIT resulted in equal improvements to MICT in fasting glucose, HbA1c and weight loss. There was also some evidence that HIIT is superior to MICT in improving insulin resistance and VO\textsubscript{2peak}.\cite{253} Using more recently published studies including only participants with metabolic syndrome or T2DM, improvements compared to non-exercising controls were larger, although there was no longer a superior effect of HIIT on insulin resistance or VO\textsubscript{2peak}. It was unclear which aspects of HIIT; intensity level or total time spent at high-intensity produced the biggest effects. The conclusion, therefore, was that HIIT per se has the potential to improve insulin sensitivity and glycaemic control but that further research is required to determine the optimal protocol for maximising outcomes.

5.1.2 Study 2: Associations between A) physical activity bout length and B) physical activity intensity on insulin sensitivity and glycaemic control

These cross-sectional analyses aimed to determine A) whether the recommendation to accumulate MVPA in bouts lasting at least 10 minutes was supported when physical activity was measured objectively, and B) the relationship between accelerometer-measured physical activity intensity and markers of insulin sensitivity in individuals at high risk of T2DM. Study A found few differences between MVPA accumulated in bouts <10 minutes and ≥10 minutes, although in the case of fasting insulin and HOMA-IS, more favourable levels were associated with bouts ≥10 minutes than with sporadically accumulated MVPA. Study B found, up to a threshold, favourable linear associations between 500 cpm increments (approximately 0.3 METs) in physical activity intensity and 2 hour glucose, insulin and Matsuda-ISI, which were independent of BMI. The study suggests that for outcomes relating to T2DM A) there is some empirical support for the recommendation that physical activity be accumulated in bouts ≥10 minutes and B) that favourable associations in markers of insulin sensitivity are observed at intensities well below those that accelerometer cut points suggest are required for health benefits, although the magnitude of these benefits increases in proportion to the intensity up to approximately 4.3 METs.
Study 3: The effect of an acute bout of HIIE on postprandial glucose and insulin responses: the GO for IT study

This proof-of-concept study compared the effects of HIIE and MICE to sitting conditions on post-challenge glucose and insulin levels in individuals at high risk of T2DM. Based on findings from Study 1 and suggestions from PPI meetings, a protocol employing vigorous but submaximal intensities that also required a lower total time commitment than MICE was used (10 x 60 seconds at 90% VO$_{2peak}$ with 60 seconds active recovery). The results showed that both HIIE & MICE reduced the insulin iAUC compared to control, and that this reduction was significantly greater with HIIE. There was also evidence of reduced glycaemic excursions with both HIIE and MICE as implied by a smaller variation in interstitial glucose levels measured by a CGM and a lower postprandial spike in response to breakfast, respectively. The conclusions were that both HIIE and MICE improve insulin action, but that HIIE may improve insulin sensitivity to a greater extent than MICE.

Thesis contribution

Together, the findings from this thesis show that acute and long-term high-intensity interval exercise enhances insulin sensitivity and associated markers in individuals at high risk of T2DM to a similar degree as moderate-intensity continuous exercise, despite requiring a reduced training time. The results from Study 2 (Chapter 3) suggest that up to a point, the higher the intensity at which physical activity is undertaken, the greater the potential improvement. Importantly, Study 2 indicates that this may be true at relative intensities depending on an individual’s ability, and notwithstanding of the absolute intensity at which physical activity is carried out.

The findings add to the growing body of literature investigating the application of HIIT in clinical populations, specifically those with or at risk of T2DM. For HIIT to be recommended as a therapeutic health tool, first and foremost, its efficacy must be consistently demonstrated. By showing that HIIT improves insulin resistance, HbA1c, cardiorespiratory fitness and body weight to a similar extent as MICT (Chapter 2), and that HIIE acutely improves insulin action and glycaemic variability (Chapter 4), Studies 1 and 3 provide evidence for the first requirement, with the findings from Study 3 providing some insight as to how these improvements might occur (i.e. enhanced insulin sensitivity during exercise). Furthermore, by providing detailed, quantitative information about a relatively novel form of exercise, as well as evidence to suggest that lower
absolute intensities than are currently recommended may be sufficient to gain health benefits (Chapter 3), this thesis contributes to the recent call for target specificity in medical research.

5.3 Mechanisms

HIIT has elicited impressive improvements in a wide variety of outcomes that are comparable to those achieved with MICT. This is true even when the HIIT workload is lower than that of MICT, as well as the minimum physical activity recommendations. There are therefore two unique ways in which HIIT might affect physiology in a different manner to MICT. First, that time spent at high intensities unsustainable for extended periods induces distinct effects to lower-intensity exercise irrespective of duration, and second, that the oscillating nature of muscle fibre recruitment during HIIE elicits differential responses to MICE.

5.3.1.1 Sprint interval exercise & training

Several studies have compared SIE with MICE and SIT with MICT and investigated the respective muscle fibre adaptations. While some discrepancies exist in terms of the precise proteins augmented, most studies have reported equivalent acute and training responses to proteins involved in mitochondrial biogenesis, insulin independent and dependent pathways. PGC1-α; the “master” regulator of muscle oxidative capacity, and citrate synthase have been repeatedly shown to increase following SIT.[392-394] Interestingly, adaptations that have historically been associated with very high intensity exercise such as glycogen depletion and type IIa fibre recruitment[268] have been observed following both SIE and MICE,[395] which, in line with the findings from study 2B (section 3.3.3), indicate that adaptations can occur at intensities lower than previously thought.

5.3.1.2 High-intensity interval exercise & training

Less investigation has been made into the mechanisms of action of sub-maximal low-volume HIIT. One study which compared an acute bout of HIIE (3 x 3 minutes at 90% VO2peak with 3 minutes recovery at 50% VO2peak) with MICE (50 minutes at 70% VO2peak) also found that protein expression immediately and three hours post exercise were similar between exercise conditions.[396]

With regards to improvements in glycaemic control and insulin sensitivity, both Hood et al.[188] and Little et al.[209] found increases in markers of muscle oxidative capacity and GLUT-4 content following just two weeks of HIIT (10 x 60 seconds at 90% HRmax), although neither of these studies had a control group so it is impossible to determine how these adaptations would have compared to MICT. Karstoft et al.[256] did find superior effects of 16 weeks of submaximal HIIT
(10 x 3 minutes at 70% VO2peak) compared to MICT (60 minutes at 55% VO2peak) in individuals with T2DM. Using a hyperglycaemic clamp, this study found that HIIT increased AS160 (a protein involved in insulin signalling) phosphorylation during hyperglycaemia. They speculated that this may have increased GLUT-4 translocation or activation as insulin sensitivity improved in the absence of increased GLUT-4 content. There was also some indication of improved muscle glycogen turnover in the HIIT group. Interestingly, there were no changes in citrate synthase level or activity. Therefore, it is possible that some adaptations are intensity-dependent. In this study,[256] where the high-intensity intervals were of a comparable relative and certainly, absolute, intensity to some MICT interventions, they were not sufficient to stimulate some of the adaptations observed previously. Nonetheless, regardless of the underlying pathways involved, it appears that MICT, SIT and HIIT are effective at improving insulin sensitivity.

Fewer studies still have explored the effects interval exercise per se has on muscle and metabolic adaptations. Based on a computational model of skeletal muscle adaptation,[397] Coombes et al.[398] proposed that the differential fluctuations in protein phosphorylation observed after intensity and energy matched HIIE and MICE could be explained by the disturbance and subsequent re-balancing of the ATP:ADP ratio. Exercise can increase muscle ATP demand by up to 100-fold, yet ATP concentration remains relatively stable. To maintain homeostasis in this way, rapid activation of ATP synthesis pathways must occur before a steady state is reached. The repeated rest-exercise alternation distinctive of HIIE may stimulate oxidative signalling cascades and subsequently, adaptations, to a greater extent than MICE. This could explain the similar magnitude of effects of HIIE despite a lower workload to MICE. Further research though, is required to support this theory.

5.3.2 Intensity versus duration

Unsurprisingly, HIIT raises the intensity vs duration debate, with the traditional position being that as long as total exercise volume is kept constant, the two factors are interchangeable. However, with HIIT, there is another nuance to this equilibrium; the intensity and duration of the intervals themselves. The numerous permutations of work:rest durations and intensities and a lack of standardisation has meant that to date, it has been difficult to compare the efficacy of different protocols.

5.3.2.1 Sprint interval exercise & training

A handful of studies, mostly on young, healthy participants, have attempted to do this. Helgerud et al.[200] compared three SIT protocols: one traditional; 30 second efforts with four minutes rest and two with 10 second intervals; one with four and the other with two minutes rest. They found
that it was the duration of the rest period that was important, with both four minute rest protocols eliciting greater improvements in VO\textsubscript{2peak} and exercise performance than the two minute rest protocol. They proposed that the rest periods should be long enough that the power generated in the first 5-10 seconds of the sprints does not diminish with each effort. They therefore suggested that as long as rest periods were kept at four minutes, 10 second Wingate efforts should be sufficient to generate improvements. This could explain why studies that have attempted to reduce total training commitments have had limited success. For example, Skleryk \textit{et al.} \cite{189} shortened the recovery periods to 80 seconds and found no improvements in fitness or metabolic outcomes, which could attributable to these abridged recovery periods. On the other hand, the 35 healthy participants in the study by Metcalfe \textit{et al.} \cite{399} performed two 20 second intervals with a 3 minute 20 second rest and observed improvements in VO\textsubscript{2max} but not insulin sensitivity or OGTT measures.

5.3.2.2 High-intensity interval exercise & training

As implied above (Section 5.3.1.1 and 5.3.1.2), it is likely that SIT and HIIT stimulate distinct physiological responses. When comparing sub-maximal intensity intervals, it appears that, as long as efforts are at the higher end of the vigorous spectrum, there are few differences between energy-matched protocols involving long (two to four minute) and short (15 to 60 seconds) intervals,\cite{200, 400} with some evidence for longer intervals causing greater benefits in metabolic outcomes.\cite{400} Boyd \textit{et al.} \cite{268} found that 10 x 60 second intervals at 70% and 100% peak workload both increased VO\textsubscript{2peak} and muscle oxidative enzymes, but that the improvements in VO\textsubscript{2peak} were of a greater magnitude following the higher-intensity intervals, though this could have been due to the higher overall volume of exercise undertaken in this group. Neither protocol changed fasting glucose, insulin nor HOMA-IR levels however, these young, overweight males had relatively low baseline insulin resistance.

In summary, to date, it is difficult to directly compare the effects of modulating interval length and duration. It appears that VO\textsubscript{2peak} improves with HIIT regardless of the protocol used, but longer intervals may be more effective for metabolic outcomes, a theory supported by the findings from Study One (Chapter 2), where the greatest improvements occurred in studies using HIIT or AIT as opposed to SIT protocols.

5.4 Science can justify IT, will the public?

The practicality of HIIT for non-athletic populations has been hotly debated.\cite{197, 198, 401} HIIT has been criticised as being too hard, unsafe, unenjoyable and requiring specialist equipment,
supervision and encouragement in order to be completed properly. SIT has almost unanimously been disregarded as a viable option for clinical care, even by HIIT proponents, as it requires “all-out” efforts eliciting maximal physiological responses, potentially unattainable and/or harmful to those at risk of myocardial infarction, stroke or other acute injury. However, as tested and discussed, SIT is not the only option, and may not even be the best. Nonetheless, the “best medicine is the one that’s actually taken”. So will people take a HIIT?

5.4.1 Is IT time-efficient?

The resurgence in HIIT research has been fuelled by the claim that it addresses the most common barrier to exercise: a lack of time. The SIT protocol, touted in the scientific and mainstream media as requiring just “nine minutes of exercise a week”, including a five minute warm-up and cool-down, actually takes 37 minutes to complete (Figure 5.1). The 4 x 4 minute protocol, recommended in cardiac rehabilitation and used extensively throughout the HIIT community, has consistently produced clinically relevant improvements in cardiorespiratory fitness, HbA1c and body composition. This protocol involves four minute intervals, usually performed at 90-95% HRmax with three minute recovery periods at 70% HRmax. It is perhaps unsurprising that this protocol elicits impressive benefits given that, if performed three times per week, an individual completes 82% of the recommended amount of MVPA. Including a five minute warm-up and cool-down the protocol time is extended to ≥36 minutes per session (Figure 5.1).
If lack of time truly is the barrier to physical activity, it is important to elucidate whether it is the requirement to accumulate 150 minutes of MPA per week, or the ability to set aside ≥30 minutes at a time to exercise. If it is the former, then HIIT can provide a solution to this barrier given that most protocols are effective carried out three times per week, totalling 90-120 minutes of dedicated exercise time. If, however, it is the latter, then as of yet there are few protocols that have consistently produced benefits in less than 30 minutes per session. For example, Metcalfe et al. have been studying very low volume sprint interval training, assessing the effects of two 20 second Wingate efforts for a total workout duration of 10 minutes.\textsuperscript{172, 174} While VO\textsubscript{2peak}
increased after six weeks of training, there were no improvements in insulin sensitivity. Protocols lasting just over 20 minutes e.g. 10 x 60 seconds (Figure 5.1)\textsuperscript{[404]} and 60 x 8 seconds\textsuperscript{[191, 405]} have also been unable to produce consistent adaptations in glycaemic control despite improvements in VO\textsubscript{2peak}, even when participants are insulin resistant at baseline. However, it is possible that further adaptations may occur over a longer training period as these studies have been of relatively short duration (<6 weeks). Furthermore, reductions in glucose excursions, such as observed in the GO for IT study (Chapter 4.3.6.2) may translate to long term T2DM risk reduction even in the absence of physiological restructuring.\textsuperscript{[406]}

Francois \textit{et al.}\textsuperscript{[322]} investigated the concept of “exercise snacking”; performing six one minute efforts three times per day, on acute glycaemic control. They found significant reductions in postprandial glucose responses compared to an energy-matched single bout of continuous exercise. Overall, the time commitment of this protocol appears small however, the “exercise snacks” took 17 minutes each and as such 51 minutes were dedicated to exercise on the intervention day.

While HIIT is “time-efficient”; producing impressive benefits compared to MICT per minute of VPA, it could be argued that, per session, it is not strictly “time-saving”. On the other hand, given the variety of possible formats HIIT can take, there may be a HIIT workout out there for everyone, depending on their restrictions.

5.4.2 Do people like IT?

Positive feeling during exercise increases adherence to a physical activity programme.\textsuperscript{[407]} Physical activity intensities that exceed the ventilatory threshold (VT) have been associated with negative affect.\textsuperscript{[136]} Therefore, HIIT detractors argue that people will not enjoy and thus not perform HIIT regularly. HIIT proponents argue that this is only true for continuous high-intensity exercise and that the recovery periods make HIIT manageable, more rewarding and less tedious than MICT. An increasing number of studies are testing this hypothesis, reviewed by Decker & Ekkakis.\textsuperscript{[408]} In their excellent paper, the authors criticise studies reporting positive feelings towards HIIE of having been conducted in young, healthy, recreationally active individuals who are not representative of the population HIIT is currently being aimed at. On the other hand, they also criticise studies that have reported negative feelings for having employed low-volume MICE protocols (20 minutes),\textsuperscript{[409, 410]} or impossibly difficult HIIE protocols.\textsuperscript{[411]} They therefore sought to investigate the affective valence, enjoyment and RPE of energy-matched HIIE (4 x 3 minutes at an intensity equal to 115% VT with two minute active recovery periods) and MICE (25 minutes at 90% VT). They found that at the end of each interval, feeling scores were lower than
at corresponding time-points during MICE. Moreover, while feeling decreased throughout both exercise sessions, the decline was steeper in HIIE and ended negatively, whereas it was still positive following MICE. In line with this, RPE was higher throughout and enjoyment was lower after HIIE than MICE. Although this study can be criticised for employing energy-matched exercise protocols when HIIE is often less volume than MICE, the 4 x 3 minute protocol employed is comparable to other types of HIIE. Based on previous psycho-behavioural research, the authors hypothesise that the nadirs of negative affect are more likely to influence future participation in HIIE than the mean. Overall, this review does not paint a promising picture for adherence to HIIT. However, anecdotally, I found that participants’ perceptions of HIIE were negative before even having tried it; due to feelings of fear and lack of understanding. Future interventions therefore, should perhaps include prior education about vigorous-intensity exercise and the associated experience. This may reassure individuals and so improve their experience. This is something that I will raise in a planned PPI results dissemination event.

5.4.3 Could IT leave the lab?

5.4.3.1 Practicality

Just a few studies have tested HIIT on insulin sensitivity in high risk populations in community,[267] home,[413] or unsupervised settings[212, 213] (Chapter 2). These studies found increases in VO_{peak},[177, 267] but limited improvements in markers of insulin sensitivity, even in participants with T2DM. Allison et al.[414] recently found that stair climbing elicited similar responses to low-volume SIT and that six weeks of stair climbing and descending training increased VO_{peak} to a slightly lower, but still comparable extent as Wingate SIT in young, sedentary adults. They did not find improvements in markers of insulin sensitivity, although this could be because the normal-weight participants are unlikely to have been insulin resistant at baseline. More studies need to be conducted in order to confirm the efficacy of non-laboratory based interventions, which to date, have shown, albeit slightly attenuated, clinically significant improvements in cardiorespiratory fitness. However, the benefits to insulin sensitivity and glycaemic regulation are less clear. Importantly though, these studies show that, in principle, HIIT can be performed in every day settings.

5.4.3.2 Safety

A major criticism of the overall view that HIIT can be performed safely[415] by individuals at high risk or with chronic disease (few adverse events have been reported; Table 2.1 and Cassidy et al.[416]) is that almost without exception, participants have undergone rigorous health screening prior to taking part in HIIT. Therefore, any individuals for whom HIIT is most likely to be unsafe
have not been included in any research. Indeed, out of 30 individuals screened for the GO for IT study (Chapter 4), two (7%) had adverse reactions relating to the maximal exercise test. Although in one case angina pain was self-limiting and in the other atrial fibrillation was not repeated in a subsequent stress test and the participant able to complete the study, one could argue that this is a high incident rate in a relatively small, self-selected sample. It is well established that the risk of sudden cardiac death or acute myocardial infarction (AMI) is significantly increased during vigorous exertion compared to rest.\[417\] Arguably, this phenomenon was first noticed in firefighters\[418\] and “snow shovelers”.\[419\] Firefighters have a higher level of fitness and are exposed to more hazards than the general population, so this group will not be discussed. “Snow shovelers”, on the other hand, are typical of the general population. It was noticed that the rate of coronary artery disease death dramatically increased after a heavy snowfall, and that this relationship could not be explained by cold air. Inspection of the circumstances surrounding these events revealed that, in many cases, individuals, who were mostly men, had been shovelling snow in the preceding hours or days and that snow shovelling can elicit similar physiological responses as maximal treadmill exercise.\[419\] Further investigation into this paradox revealed that those at the highest risk of exertion-induced AMI were not those with traditional CVD risk factors such as hyperlipidaemia or hypertension, but those with low self-reported physical activity, a personal or family history of CVD and, to a lesser extent, diabetes (type 1 and 2) and renal disease.\[420\] Given that the risks of being inactive far outweigh those of engaging in vigorous physical activity, in conjunction with recommendations from other organisations e.g. American Heart Association, 2008 Physical Activity Guidelines Association, the American College of Sports Medicine (ACSM) state that exercise stress testing with ECG should not be conducted pre-participation in physical activity even in those with underlying health conditions. However, in the case of those with known cardiovascular, metabolic or renal disease, or those who experience symptoms associated with CVD or have NDH, should seek medical clearance from a health care professional. These individuals should then begin a light-moderate intensity exercise regime depending on the severity of their symptoms and the discretion of the health care professional. This is to reduce the number of false positives identified by screening and the barriers to physical activity. Therefore, in line with the ACSM guidelines, a simple strategy to ensure the safety of HIIT would be to implement more progressive exercise programmes. A few studies have gradually increased the length or number of intervals, but rarely has interval intensity been steadily raised throughout the intervention. Even though intensity is relative to an individual’s fitness and as fitness improves absolute intensity will increase for the same relative intensity, attempting to increase tolerance to increasing physical exertion, particularly in sedentary individuals who have a reduced heart rate reserve, may also mitigate any negative
feelings of affect associated with higher intensity exercise. This may mean that HIIT protocols in fact begin as “MIIT” (moderate-intensity interval training), but as the results of Study 2B (Chapter 3) suggest, any increase in physical activity intensity is likely to improve insulin sensitivity. Furthermore, given the differences in participation in VPA versus MPA,\(^{157, 421}\) this could help to maximise adherence.

5.4.3.3 Motivation

HIIT detractors also argue that given current participation in MVPA,\(^{145}\) and indeed, VPA specifically,\(^{157}\) that the especially high levels of motivation required to perform HIIT mean that individuals adverse to exercise will not regularly engage in HIIT by choice. As eloquently rebutted by Professor Batterham, this argument would only hold had the plethora of campaigns to promote MICT thus far been successful.\(^{198}\) Given the human precondition to expend energy only in the face of hunger, danger or other survival drive, the immediate necessity to move at all in the current environment is mostly absent on a day-to-day basis. Today, “reward” for performing physical activity is intrinsic (i.e. feelings of pleasure\(^{422}\)), or delayed relating to the avoidance of poor health. Motivation to engage in any physical activity therefore, must be high.

5.4.4 Will IT leave the lab?

There are two main audiences who need to be considered when addressing the potential for HIIT to become routine: those who would advocate HIIT and those who would take HIIT up.

Despite the overwhelming evidence for the role of physical activity in the prevention of a host of chronic diseases\(^ {423}\) and the effect increasing physical activity levels can have on those already suffering with T2DM,\(^ {243, 424}\) support for the intensive promotion of physical activity in preference to pharmaceutical therapy in healthcare settings is equivocal in terms of cost-effectiveness.\(^ {425-427}\) This is almost certainly due to the comparative adherence of taking tablets to participation in the recommended levels of physical activity, but nonetheless highlights the difficulty in “prescribing” physical activity. In a similar way that medications must be prescribed at a specific quantity in a way that is suitable for the patient i.e. dependent on co-morbidities and other medications, patients should be equally aware of the dose of physical activity they need to complete in order to improve their health. If there were a variety of options available for achieving this e.g. MICT or HIIT, physical activity can be prescribed in a personalised manner which should also help to address the aforementioned safety concerns with HIIT. In addition to general guidelines, which have merit in their simplicity, a range of activities with known outcomes should be available to patients in order to optimise adherence and effect.\(^ {151}\) Lack of knowledge about physical activity has been cited as a barrier to participation.\(^ {147}\) It appears that
“sit less, move more” is not an adequate instruction for those unaccustomed to physical exertion (see section 1.2.3.2). Given time restrictions within GP appointments, it is unlikely that prescribing physical activity will be practical in primary care. Ideally, referrals to clinical exercise physiologists should be as routine as those to other secondary care providers. With the recent investment in Diabetes Prevention Programmes which offers individuals with NDH a minimum of 16 hours of contact time over nine months with lifestyle professionals, there is the possibility that more detailed physical activity information could be included in education sessions. Providers have flexibility with which to tailor programmes to their target audience using evidence-based theory meaning that content can be updated as new evidence emerges. Furthermore, information should be delivered by experts so that more nuanced questions from patients can be answered.\cite{428}

In a similar way that LPA and MPA could be encouraged using “nudge” factors; increased green space,\cite{67} availability of standing desks,\cite{429} or town planning initiatives,\cite{430} VPA could be encouraged with safer, more extensive cycle paths,\cite{431} workplace showering and changing facilities, and normalisation of VPA e.g. Parkrun (\url{http://www.parkrun.org.uk}).\cite{432} Performing VPA must be made easy in terms of facilities and integration into daily routine. There is no reason that with a series of small societal changes, the attitude that VPA is for “fit people” cannot be countered.

Barriers to physical activity were summarised in Chapter 1 section 1.2.3.2. It is important to address these barriers directly, on an individual basis. However, what is striking is how these obstacles highlight the priority, or lack thereof, physical activity has in many people’s lives. A societal shift has to occur in order that physical activity is valued as much as other daily activities such as work and thus the motivation required to perform physical activity reduced.

5.5 Future directions

5.5.1 Next steps based on this thesis

The main question raised by this thesis relates to the potential for short-duration HIIT to improve insulin sensitivity and glycaemic variability in the long term, and ultimately whether this leads to prevention of T2DM. Using findings and observations from the studies conducted as part of this thesis as well as related literature, it would be possible to design a training intervention that employed a home-based, practical model of low-volume HIIT. Postprandial hyperglycaemia\cite{72,329} and glycaemic variability\cite{91,330} remain and emerge, respectively, as important independent predictors of T2DM incidence and complications and should therefore be focussed on as primary
outcomes. Combining robust laboratory techniques (i.e. glucose and meal tolerance testing) with developing technologies (i.e. CGM) will provide information on the accuracy of these new devices compared to gold-standard techniques, and accordingly, the potential for less invasive, self-monitored research design. I also believe we are at a stage where interventions should be implemented on discretion of a healthcare professional and without rigorous screening unless absolutely necessary. Using a progressive training programme as recommended by the ACSM, the time has come for unsupervised HIIT to be assessed in a relatively large cohort of high-risk individuals with a comprehensive range of outcomes encompassing psychological as well as physiological measures. Whether a pre-intervention education session improves efficacy and adherence should also be considered.

5.5.2 HIIT in the wider context

The benefits of HIIT on cardio-metabolic health outcomes such as cardiorespiratory fitness, cardiac structure and output and glycaemic regulation are becoming well established. However, many questions still remain. For instance, the effects of HIIT on blood pressure, endothelial function and inflammation and lipid profile are unclear. These measures are included as outcomes in much of the HIIT literature, with narrative reviews indicating positive effects, but as of yet, no large scale studies or meta-analyses have been conducted specifically on these outcomes. It is important to elucidate whether HIIT has the potential to improve these markers given the independent effects they have on morbidity and mortality. In addition, there are still many populations in which the evidence of the effects of HIIT specifically are lacking. One review highlighted the absence of research in brain health including stroke and dementia. HIIT may have differential effects to MICT on the brain as high-intensity physical activity (≥70% \( VO_{2\text{max}} \)) increases the risk of hyperperfusion in individuals with reduced neuroprotective mechanisms; such as older, sedentary individuals. There is also a distinct lack of research in individuals with impaired renal function.

5.6 Implications for physical activity guidelines

There is a balance between providing varied, detailed public guidelines, and ones which are clear and concise. Given the pluripotent effect of physical activity, not just on outcomes relating to T2DM, and with the current affinity for soundbites, I suggest that recommendations should be simple and free of superfluous caveats (such as to exercise prior to eating as suggested in Chapter 4). However, if exercise is to be valued as a therapeutic health tool for those with or at risk of T2DM, its effects should be as well understood as those of pharmaceutical therapies.
Health care professionals should be trained in exercise prescription and therefore detailed guidelines must exist. It is in this context where a recommendation to exercise prior to eating may be useful. Furthermore, understanding how the FITT elements (frequency, intensity, time and type; section 1.2.2.1) influence various physiological pathways e.g. cardiorespiratory versus metabolic, as well as how they affect people with different health characteristics in unique ways means that exercise therapy can be targeted. The main advantage of this would be to increase goal success which, in turn, should increase motivation and adherence.

This thesis provides a unique contribution towards this aim by generating evidence that HIIT is as effective as MICT at improving cardiorespiratory fitness, HbA1c and insulin sensitivity (Study 1, Chapter 2). The findings from Study 3 (section 4.3) provide evidence that HIIE improves insulin sensitivity in individuals at risk of T2DM, thus increasing the breadth of information available for precise exercise prescription. Finally, Study 2 (Chapter 3) adds to the growing body of literature that indicates that tangible health benefits can be gained with substantially lower volumes of physical activity than the guidelines state, as well as suggesting that thresholds for MVPA should be lower for older, sedentary populations at high risk of T2DM. This is all information that could lead to specificity in goal setting for particular populations, resulting in increased participation and improved health.

5.7 Closing remarks

This thesis has focussed on VPA for the prevention and management of T2DM. Here, I have shown that low volumes of VPA in the form of HIIT and habitual physical activity are sufficient to produce tangible benefits in insulin sensitivity and glucose regulation. It remains to be seen whether engagement in VPA will increase in high-risk populations from the near negligible levels it is currently at. However, I believe that with a holistic approach, the barriers to VPA can be overcome and far-reaching benefits can be achieved.
Appendix 1  Published version of the meta-analysis reported in Chapter two

Physical Activity/Metabolic Effects

The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis

C. Jolleyman1,2, T. Yatos1,6, G. O’Donovan1, L. J. Gray3, J. A. King2, K. Khunti1,2 and M. J. Davies1,2

Diabetes Research Centre, University of Leicester, Leicester, UK; *NHR
Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, Leicester & Loughborough, UK; †Department of Health Sciences, University of Leicester, Leicester, UK; #School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, UK; ‡NHS Collaboration for Leadership in Applied Health Research and Care – East Midlands (NHLA CLAHRC – EM), Leicester, UK

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Summary

The aim of this meta-analysis was to quantify the effects of high-intensity interval training (HIIT) on markers of glucose regulation and insulin resistance compared with control conditions (CON) or continuous training (CT). Databases were searched for HIIT interventions based upon the inclusion criteria: training 22 weeks, adult participants and outcome measurements that included insulin resistance, fasting glucose, HbA1c or fasting insulin. Dual interventions and participants with type 1 diabetes were excluded. Fifty studies were included. There was a reduction in insulin resistance following HIIT compared with both CON and CT (HIIT vs. CON: standardized mean difference [SMD] = -0.49, 95% confidence intervals [CI] = -0.87 to -0.11, P = 0.009; CT: SMD = -0.35, 95% CI: -0.68 to -0.02, P = 0.016). Compared with CON, HbA1c decreased by 0.19% (95% CI: -0.36 to -0.01, P = 0.021) and body weight decreased by 1.3 kg (95% CI: -1.9 to -0.7, P < 0.001). There were no statistically significant differences between groups in other outcomes overall. However, participants at risk of or with type 2 diabetes experienced reductions in fasting glucose (-0.92 mmol L-1, 95% CI: -1.22 to -0.62, P < 0.001) compared with CON. HIIT appears effective at improving metabolic health, particularly in those at risk of or with type 2 diabetes. Larger randomized controlled trials of longer duration than those included in this meta-analysis are required to confirm these results.

Keywords: High-intensity interval training, physical activity, weight loss, type 2 diabetes.
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Appendix 3  Funnel plots to show risk of publication bias

**HOMA-IR**

Figure A 6.1a. HIIT arms only  

- Studies with a non-exercising control group  
- Studies with a continuous training group

**HbA1c**

Figure A 6.2a. HIIT arms only  

- Studies with a non-exercising control group  
- Studies with a continuous training group
Fasting glucose

Figure A 6.3a. HIIT arms only

b. Studies with a non-exercising control group

c. Studies with a continuous training group

Fasting insulin

Figure A 6.4a. HIIT arms only

b. Studies with a non-exercising control group

c. Studies with a continuous training group
$VO_2\text{max}$

**Figure A 6.5a.** HIIT arms only  
**b.** Studies with a non-exercising control group  
**c.** Studies with a continuous training group

**Body mass**

**Figure A 6.6a.** HIIT arms only  
**b.** Studies with a non-exercising control group  
**c.** Studies with a continuous training group
### Figure A 6.7. Change in insulin resistance following high-intensity interval training (HIIT)

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### Figure A 6.8a. Change in insulin resistance after high-intensity interval training (HIIT) compared to control by time between last training session and blood sampling
b. Change in insulin resistance after high-intensity interval training (HIIT) compared to control by time between last training session and blood sampling

Figure A 6.9. Change in HbA1c following high-intensity interval training (HIIT)
Figure A 6.10. Change in fasting glucose following high-intensity interval training (HIIT)

Figure A 6.11. Change in fasting insulin following high-intensity interval training (HIIT)
Figure A 6.12. Change in cardiorespiratory fitness following high-intensity interval training (HIIT)

Figure A 6.13. Change in body weight following high-intensity interval training (HIIT)
**Appendix 5  MSSE confirmation of acceptance**

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**RE: MSSE-D-17-00215R1, "Associations of physical activity intensities with markers of insulin sensitivity"**

Miss Jolleyman,

I am pleased to inform you that your work is accepted for publication in Medicine & Science in Sports & Exercise. Congratulations to you and your colleagues in meeting the standards required for publication in the journal.

Pending a final format check, all manuscript materials will be forwarded to the production staff for placement in an upcoming issue. In due course you will receive further information and instructions from the Editorial Office about any final procedures for preparing the manuscript for publication.

Please be aware that there is usually a delay of a few months before the article will appear in print, due to the high demand for space in the journal.

**Open-Access Publication**

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   a. Article Title - Associations of physical activity intensities with markers of insulin sensitivity
   b. Manuscript Number - MSSE-D-17-00215R1

Thank you for submitting this study to Medicine & Science In Sports & Exercise and best wishes for your future work.

Regards,

Dr Glen P Kenny
Associate Editor
Medicine & Science in Sports & Exercise

**Reviewer Comments:**

Reviewer #1: The authors have carefully considered my comments. While it would have been optimal to perform some sort of adjustment for total physical activity, I appreciate the difficulties in undertaking this analysis with this data set and the authors have acknowledged the limitation in the discussion. The paper makes a valuable contribution to the literature.
Associations of Physical Activity Intensity with Markers of Insulin Sensitivity

Charlotte Jelleyman$^{1,2}$, Charlotte L. Edwardson$^{1,2}$, Drew Henson$^3$, Laura J. Gray$^{3,4}$
Alex V. Rowlands$^{1,5,6}$, Kaniela Khur$^{1,5,6}$, Melanie B. Dall$^{1,2,3,4}$, and Thomas Yates$^{1,2}$

$^1$Diabetes Research Centre, University of Leicester, Leicester, United Kingdom; $^2$National Institute for Health Research (NIHR) Leicester Respiratory Research Centre, Leicester, United Kingdom; $^3$Department of Health Sciences, University of Leicester, Leicester, United Kingdom; $^4$Leicester Diabetes Centre, University Hospitals of Leicester, Leicester General Hospital, United Kingdom; $^5$NIHR Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – East Midlands, United Kingdom; $^6$Alliance for Research in Exercise, Nutrition and Activity (ARENA), Sansom Institute for Health Research, Division of Health Science, University of South Australia, Adelaide, Australia

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Table A1 Associations of physical activity intensity with markers of insulin sensitivity

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<th>ES (%)</th>
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<td>28.58 (-12.89, 64.45)</td>
<td>0.000</td>
<td>2.97</td>
<td>20.04 (5.41, 36.69)</td>
<td>0.006</td>
<td>1.54</td>
</tr>
<tr>
<td></td>
<td>3000-3499</td>
<td></td>
<td>32.01 (-13.72, 53.25)</td>
<td>0.000</td>
<td>2.72</td>
<td>22.13 (5.25, 41.72)</td>
<td>0.009</td>
<td>1.42</td>
</tr>
<tr>
<td></td>
<td>3500-3999</td>
<td></td>
<td>34.66 (-13.85, 59.26)</td>
<td>0.001</td>
<td>2.52</td>
<td>23.02 (4.05, 45.46)</td>
<td>0.015</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>4000-4499</td>
<td></td>
<td>28.43 (-8.71, 51.74)</td>
<td>0.003</td>
<td>1.95</td>
<td>19.86 (1.69, 41.28)</td>
<td>0.031</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>≥4500</td>
<td></td>
<td>23.62 (-11.21, 37.41)</td>
<td>0.000</td>
<td>3.45</td>
<td>17.32 (5.60, 30.34)</td>
<td>0.003</td>
<td>2.08</td>
</tr>
</tbody>
</table>

Table displays back-transformed correlation coefficients and represent the factor by which the outcome is multiplied by (with 95% confidence intervals) for every 10 minutes of physical activity performed at each intensity per day. Model 1 was adjusted for age, sex, ethnicity, smoking status and β-blocker medication and accelerometer wear time. Model 2 was further adjusted for BMI.

cpm—counts per minute; CI—confidence intervals; HOMA-IS—homeostatic model assessment of insulin sensitivity; ISI—insulin sensitivity index
### Table A2 Baseline associations of total, continuous and sporadic bouts of MVPA with markers of insulin sensitivity

<table>
<thead>
<tr>
<th>N</th>
<th>Total ES (%)</th>
<th>Continuous ES (≥10min) (%)</th>
<th>Continuous with exception ES (≥10 min inc. ≤2 min break) (%)</th>
<th>Sporadic ES (0-10min) (%)</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>595</td>
<td>-0.19 (-0.58, 0.20)</td>
<td>0.16 (-1.07, 0.19)</td>
<td>3.2 (-0.37, -0.07)</td>
<td>0.29 (0.05, 0.74)</td>
</tr>
<tr>
<td>2 hour glucose</td>
<td>593</td>
<td>-0.65 (-1.79, 0.49)</td>
<td>0.22 (-3.33, 0.39)</td>
<td>0.41 (-3.01, 0.34)</td>
<td>0.42 (0.19, 2.23)</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>595</td>
<td>-2.05 (-4.17, -0.07)</td>
<td>0.62 (-7.28, -0.39)</td>
<td>0.82 (-6.53, -0.33)</td>
<td>0.81 (-4.08, 3.47)</td>
</tr>
<tr>
<td>2 hour insulin</td>
<td>531</td>
<td>-5.51 (-8.78, -2.33)</td>
<td>2.06 (-11.43, -1.13)</td>
<td>1.10 (-10.45, -1.17)</td>
<td>1.16 (-11.60, -0.49)</td>
</tr>
<tr>
<td>HOMA-IS</td>
<td>593</td>
<td>2.27 (0.01, 4.54)</td>
<td>0.66 (0.55, 7.96)</td>
<td>0.87 (0.46, 7.11)</td>
<td>0.86 (0.38, 4.43)</td>
</tr>
<tr>
<td>Matsuda ISI</td>
<td>531</td>
<td>4.30 (1.31, 7.30)</td>
<td>1.52 (0.83, 10.26)</td>
<td>1.03 (0.87, 9.36)</td>
<td>1.08 (3.51, 9.04)</td>
</tr>
</tbody>
</table>

Table displays back-transformed correlation coefficients and represent the factor by which the outcome is multiplied by (with 95% confidence intervals) for every 10 minutes of physical activity performed either continuously or sporadically.

Continuous and sporadic MVPA were entered into models together, total was added separately. Models were controlled for wear time, valid days, sedentary time, age, sex, BMI, ethnicity, smoking status beta-blocker, other anti-hypertensive and lipid lowering medication.

ES – Effect size; MVPA – moderate-vigorous physical activity; HOMA-IS – homeostatic model assessment of insulin sensitivity; ISI – insulin sensitivity index

Units: glucose – mmol·L⁻¹; insulin – μU·L⁻¹
Table A 3 Associations of total, continuous and sporadic bouts of MVPA with markers of insulin sensitivity for baseline, 12 and 36 month data combined

<table>
<thead>
<tr>
<th>MVPA</th>
<th>N</th>
<th>% change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td><strong>Fasting glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol·L⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs</td>
<td>1550</td>
<td>730</td>
</tr>
<tr>
<td><strong>2 hour glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmol·L⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs</td>
<td>1526</td>
<td>727</td>
</tr>
<tr>
<td><strong>Fasting insulin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(μU·L⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs</td>
<td>1000</td>
<td>677</td>
</tr>
<tr>
<td><strong>2 hour insulin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(μU·L⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs</td>
<td>882</td>
<td>662</td>
</tr>
<tr>
<td><strong>HOMA-IS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs</td>
<td>1550</td>
<td>730</td>
</tr>
<tr>
<td><strong>Matsuda ISI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obs</td>
<td>1394</td>
<td>697</td>
</tr>
</tbody>
</table>

Table displays back-transformed correlation coefficients and represent the factor by which the outcome is multiplied by (with 95% confidence intervals) for every 10 minutes of physical activity performed either continuously or sporadically.

Continuous and sporadic MVPA were entered into models together, total was added separately. Models were controlled for wear time, valid days, sedentary time, age, sex, BMI, ethnicity, smoking status beta-blocker, other anti-hypertensive and lipid lowering medication.

MVPA – moderate-vigorous physical activity; CI – confidence interval; HOMA-IS – homeostatic model assessment of insulin sensitivity; ISI – insulin sensitivity index
Study Title: The effect of a single bout of high intensity interval training on glucose responses in white European and south Asian patients at risk of type 2 diabetes
Reference: UHOLE 0521/CRN 167329

MODEL AGREEMENT FOR NON-COMMERCIAL RESEARCH IN THE HEALTH SERVICE

This Agreement dated of October 2015 is between

University Hospitals of Leicester NHS Trust
Trust Headquarters
Level 3, Estoril Building
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
United Kingdom

(referred to as the "NHS Organisation")

AND

The University of Leicester
University Road
Leicester
LE1 7RH
United Kingdom

(referred to as the "Sponsor")

Which are collectively referred to as the "Parties" or individually referred to as a "Party"

The above Parties agree to the following obligations, terms and conditions when carrying out the clinical research study entitled: The effect of a single bout of high intensity interval training on glucose responses in white European and south Asian patients at risk of type 2 diabetes

Page 1 of 22
28 July 2015

Professor Melanie Davies
Leicester Diabetes Centre
Leicester General Hospital
Leicester
LE5 4PW

Dear Professor Davies,

**Study title:** The effect of a single bout of high-intensity interval training on glucose responses in white European and south Asian patients at risk of type 2 diabetes.

**REC reference:** 15/EM/0259

**Protocol number:** UNOLE 9521

**IRAS project ID:** 157328

Thank you for your letter of 15th July 2015, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Ms Rachel Nelson, at NRESCommittee.EastMidlands-Nottingham1@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the
GO FOR IT

Ethnic differences in glucose regulation following interval training

Research Protocol

The effect of a single bout of high-intensity interval training on glucose responses in white European and south Asian patients at risk of type 2 diabetes

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust(s), regulatory authorities, and members of the Research Ethics Committee.
Dear «Title» «Surname»,

You are being invited to participate in a study supervised by Prof. Kamlesh Khunti investigating the effects of different forms of exercise on blood sugar.

Enclosed is a leaflet giving details of the GO for IT study. Please take the time to read through this as it explains what the study involves.

If you would like to participate in the study, please complete and sign the enclosed reply slip and questionnaire and return it in the pre-paid envelope provided. The study team will then contact you directly to arrange an appointment.

If you feel that you would like any further information before completing the forms, please contact the study team on 0116 258 4394 or email Charlotte at c136@she.ac.uk.

Yours sincerely

Charlotte Jolleyman
Study co-ordinator
GO FOR IT

Leicester Diabetes Centre
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Charlotte Jolleyman
(study coordinator)
☎ 0116 258 4364
✉ c136@le.ac.uk

PARTICIPANT INFORMATION SHEET

You are being invited to take part in a research study but before you make a decision, it is important that you understand why the research is being carried out and what it involves. The study is being conducted by a student, Charlotte Jolleyman, as part of her research degree (PhD) and this information sheet is designed to help you decide whether you would like to take part. You can talk it over with your family or friends, and if anything is not clear, or you would like to know more, we have put a contact number on this leaflet allowing you to talk to us directly.

BACKGROUND

What is the purpose of the study?

Research shows that moderate-intensity continuous exercise helps to control blood sugar levels. However, many people do not have time to do the amount required to produce health benefits. Interval training is a type of exercise that involves performing several short bursts of more intense exercise (60 sec), but with rest periods in between (60 sec). It requires less physical activity and less overall time than moderate continuous exercise. We want to know if interval training has similar benefits as traditional exercise on blood sugar regulation.

Why have I been invited?

You have been invited because you are aged 50-74 and have had a blood test done and the results indicate that you might meet the inclusion criteria for the study.

What if I do not meet the other inclusion criteria?

We will see whether you meet our full inclusion criteria on your first visit to the Leicester Diabetes Centre. If it is found that you do not meet the criteria for this study we will give you general
PSYCHOLOGICAL MOOD AND AFFECT SCALE

Felt Arousal Scale

Please indicate on the scale below how aroused you feel at the moment. By aroused we mean how “worked-up” you feel. You might experience high arousal in one of a variety of ways, such as excitement, anxiety or anger. Low arousal might be experienced as relaxation, boredom or calmness.

<table>
<thead>
<tr>
<th>Low Arousal</th>
<th>High Arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Feeling Scale

It is common to experience changes in mood and feelings across time. Please indicate the number on the scale below that best corresponds with how you feel at the moment.

<table>
<thead>
<tr>
<th>Very bad</th>
<th>Bad</th>
<th>Fairly bad</th>
<th>Neutral</th>
<th>Fairly good</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>-4</td>
<td>-3</td>
<td>-2</td>
<td>-1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Mood, affect and sleepiness questionnaires
REAGENT PREPARATION

➢ To be completed 1 month prior to 1st participant’s 1st treatment and then monthly

PHMB solution (for phrelin samples)

1. Add one PBS tablet to 200ml analytical grade water in a bottle.
   ➢ Put on rollers to dissolve (This will take about 15 minutes)
   ➢ Label Cl PBS GO for IT DD/MM/YY
2. Prepare PBS/NaOH solution
   ➢ Wearing PPE, weigh 1.2g NaOH pellets into a 7ml Bijou tube.
   ➢ Add 3ml analytical grade water, place on roller mixer and allow solid to dissolve. This generates 10M NaOH solution- take care.
   ➢ Add 1ml 10M NaOH to 99ml PBS, this generates 100ml of 100mM NaOH in PBS.
   ➢ Label Cl NaOH/ PBS GO for IT
3. Prepare PHMB solution
   ➢ In a fume cupboard and wearing appropriate PPE, weigh out ~0.5g PHMB
   ➢ Add sufficient of the PBS/NaOH solution to give 100mM i.e. make to 35mg/ml (~12ml)
   ➢ Gently mix to dissolve the PHMB. This generates a 100x solution.
   ➢ Label Cl PHMB
   ➢ Put in -20°C freezer

Hydrochloric Acid (for phrelin samples)

1. Aliquot 50ml 1M HCl into 250ml Duran bottle
   ➢ Label Cl HCl GO for IT

DPP-IV (PYY<sub>3-36</sub>/GLP-1)

1. Aliquot 1ml DPP-IV into 30 x 1.5ml tubes
   ➢ Label Cl GO for IT DPP-IV
   ➢ Put in -20°C freezer


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