The impact of time of the day on muscle and metabolic responses to resistance exercise in healthy adults

By

Anas Dighriri

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i. THESIS STRUCTURE.

The current thesis includes five chapters:

A. **Chapter one** includes general background and context of the thesis, the study aims and hypotheses.
B. **Chapter two** includes the impact of the time of day on metabolic responses to exercise in adults: systematic review and meta-analysis.
C. **Chapter three** includes the impact of the time of the day on insulin sensitivity in response to a single resistance exercise session in adults: randomised cross-over study.
D. **Chapter four** includes the impact of the time of day on muscle and metabolic responses to resistance exercise in healthy adults: a randomised controlled trial
E. **Chapter five** includes a general discussion, limitations of the current thesis and conclusions.

ii. Abstract

Metabolic disorders is a term used for a group of diseases including obesity, insulin resistance and type 2 diabetes. Today more than 537 million adults (age: 20–79 years) worldwide are living with diabetes, with a prevalence of 10%. This number is projected by international diabetes federation to reach 643 million by 2030 and 784 million by 2045 (Al Ozairi et al., 2023, Federation, 2021). Regular exercise is a powerful strategy for the treatment and prevention of metabolic disease with previous studies demonstrating that this improves insulin sensitivity over time. Concurrently there are data indicating there are circadian rhythms in metabolism and that these might interact with exercise performance. However, data remains unclear on the impact of time of the day at which exercise is performed and how this influences metabolic responses.

Therefore, the aim of Chapter 2 is to systematically review and carry out a meta-analysis on the impact of exercise timing on metabolic responses to exercise in adults, considering both acute and more chronic studies and those with and without disease. The narrative analysis showed that the time of the day at which the exercise is performed does not have a clear impact on metabolic responses. Furthermore, the quantitative analysis found no significant difference in 24-hour CGM measured glucose levels, on the day of exercise or the following day regardless of whether the exercise was performed either in the morning or afternoon/evening.

Although aerobic exercise can improve insulin sensitivity acutely, resistance exercise has been less well studied in that regard. Therefore, the aim of Chapter 3 is to determine whether the time of the day has an effect on insulin sensitivity, measured during an oral glucose tolerance test, in response to a single resistance exercise session in healthy adults in a cross over study. The two-way repeated measures ANOVA revealed no significant effect of time ($p=0.586$), group ($p=0.720$) or time*group interactions ($p=0.511$) for glucose

area under the curve. Similarly, insulin area under the curve revealed no significant effect of time (p=0.735), group (p=0.663) or time*group interaction (p=0.973). Finally, insulin sensitivity revealed no significant effect of time (p=0.134), group (p=0.780) or time*group interactions (p=0.250). This finding indicate that a single session of resistance exercise has little effect on insulin sensitivity in healthy young adults, with no differences if this was performed in the morning or afternoon.

One of the main benefits of regular resistance exercise is that it increases muscle strength and mass which are important for maintenance of physical function, glucose control, and morbidity/mortality risk. However, the time at which resistance exercise is performed may be related to in improvements in muscle strength, muscle mass and metabolic responses. Therefore, the aim of Chapter 4 is to determine the effect of time of day at which resistance exercise is performed on the muscle and metabolic responses in healthy adults. We recruited 38 participants (30±7 years old; and 28±4 kg/m^2) who were randomised to either a control, exercise in the morning (6:00-10am) or exercise in the evening (4:00-8:00pm) group. Those in the exercise groups performed 8 resistance exercises 3 times a week for 6 weeks, at their allocated time of day. The findings demonstrated that over the 6-week intervention period there were effects of time on insulin sensitivity (p<0.001), muscle thickness (p=0.008) and knee extensor maximal torque (p<0.001) but no interactions with time of day. Post-hoc tests revealed increases in insulin sensitivity and knee extensor maximal torque in the morning group (+7.55 [3.33 to 11.77] mg l^2 $mmol^{-1}$ mU^{-1} min^{-1} p=0.003), with increases in muscle thickness (+1.17 [0.37 to 1.97] mm p=0.009) and knee extensor maximal torque in the evening group (+5.68 [2.36 to 8.99] Nm p=0.003). However, there was no clear effect of time of day. These results suggest that the benefits of resistance exercise may be achieved regardless of the time of day for healthy young adults and this should be the focus of public health strategies.

Overall, the current thesis demonstrated that there was no clear effect of the time of day on metabolic responses with exercise, the benefits of resistance exercise may be achieved regardless of the time of day for healthy young adults, and this should be the focus of public health strategies. Limitations, such as, a small sample sizes mean that further work is needed to corroborate these findings.

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vii. Publications and conference presentations:

- **The impact of the time of day on metabolic responses to exercise in adults: A systematic and meta-analysis review** (Dighriri et al., 2024).

- **The impact of the time of day on metabolic responses to resistance exercise in healthy adults: a randomised controlled trial** (The physiological Society conference 2023).

- **The impact of the time of day on muscle and metabolic responses to resistance exercise in healthy adults: a randomised controlled trial** (ECSS conference 2024).

viii. Acknowledgements

First and foremost, I would like to say I am grateful to Allah because I was able to finish and complete my research study successfully.

I would like to express my sincere gratitude to my supervisor, **Professor Stuart Gray (THE BOSS),** who has been an exceptional mentor throughout my research journey. His prompt responses to my emails and constant availability demonstrated his genuine commitment to my success. His guidance gave me the confidence I needed to complete my research, and his wonderful sense of humour made the challenging PhD journey more manageable, transforming what could have been an intimidating academic experience into an engaging and enjoyable pursuit. I could not have asked for a better mentor to guide me through this academic journey.

My deepest appreciation goes to my beloved **family**, whose unconditional love and support have been my pillar of strength throughout this challenging journey. Their constant encouragement, patience, and understanding have made it possible for me to pursue and complete this research. Their unwavering belief in my abilities has been a source of motivation during both the difficult and rewarding moments of this academic pursuit.

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I am profoundly grateful to all the research **participants** who dedicated their time and effort to this study, whether arriving early in the morning or staying late into the evening to complete the exercise protocols. Your commitment and enthusiasm were vital to the

success of this research. A special note of appreciation goes to **Lynsey Johnston, Greig Logan, Hannah Lithgow, and Emma Dunning**, whose invaluable assistance in conducting the research was instrumental to its completion. Your dedication and professional support significantly enhanced the quality of this study.

Lastly, but certainly not least, I want to thank me, I want to thank me for believing in me, I want to thank me for doing all this hard work. Indeed, I want to thank myself for the countless late nights spent writing, analysing data, and working with participants. For pushing through the challenging times, for staying dedicated when motivation was low, and for maintaining the passion for research throughout this journey. While this thesis represents just the first step in my research career, I am proud of the determination, resilience, and commitment I have demonstrated throughout this process. This achievement is not just a culmination of research, but a testament to personal growth and academic development, and yes - I want to thank me for that.

ix. AUTHOR'S DECLARATION

I declare that the work presented in this thesis is original and has been conducted by me, **Anas Dighriri**. I have been fully responsible for the organisation and execution of the studies, including clinical measurements, laboratory analyses, and data processing, except where explicitly stated otherwise.

I certify that the work reported in this thesis has been performed by **Anas Dighriri**

x. LIST OF ABBREVIATIONS

1RM	One Repetition Maximum
24H SD	Glycaemic Variability Over 24 H
ANOVA	Analysis Of Variance
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BEBG	Before Exercise Blood Glucose
BIA	Bioelectrical Impedance Analysis
BMAL1	Brain And Muscle Arnt-Like1
BMI	Body Mass Index
CENTRAL	Cochrane Central Register of Controlled Trials
CGM	Continuous Glucose Monitoring
CI	Confidence Intervals
CLOCK	Circadian Locomotor Output Cycle Kaput
CONGA	Continuous Overall Net Glycaemic Action
CRY	Cryptochrome
EIGR	Exercise Induced Glucose Response
FADH2	Flavin Adenine Dinucleotide
FG	Fasting Glucose
FGM	Flash Glucose Monitor
G-6-P	Glucose 6-Phosphate
GH	Growth Hormone
GRADE	Grading Of Recommendations Assessment, Development And Evaluation
GSK3	Glycogen Synthase Kinase
HBA(1C)	Haemoglobin A(1c)
HDL	High-Density Lipoprotein
HEC	Hyperinsulinaemic Euglycemic Clamp
HIIT	High Intensity Interval Training
HKII	Hexokinase II
HOMA	Homeostasis Model Assessment
HOMA2-IR	Insulin Resistance
IDDM	Insulin Dependent Diabetes Mellitus
ISI	Insulin Sensitivity Index
ISR	Insulin Secretion Rates
LDL	Low-Density Lipoprotein
MAGE	Mean Amplitude Of Glucose Excursions
MCTQ	Munich Chronotype Questionnaire
MD	Standardised Mean Differences
MSFSC	Mid Sleep On Free Days
MVC	Maximal Voluntary Contraction
NADH	Nicotinamide Adenine Dinucleotide
OGTT	Oral Glucose Tolerance Test
PDH	Pyruvate Dehydrogenase
PEBG	Post Exercise Blood Glucose
PER	Period
PKA	Protein Kinase A
PPG	Postprandial Glucose
PTH	Parathyroid Hormone
ROR	Retinoid-Related Orphan Receptor

RTFGM	Real Time Flash Glucose Monitoring
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SMBG	Self-Monitored Blood Glucose
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TCA	The Tricarboxylic Acid
TSH	Thyroid Stimulating Hormone
TTFL	Transcription-Translation Feedback Loop
VO2MAX	Maximal Oxygen Uptake
VO2PEAK	Peak Oxygen Uptake
ZEITGEBERS	External Timing Cues

CHAPTER I: Introduction

1 Background and context:

1.1 Chronobiology an overview

Chronobiology is the study of the effects of circadian rhythm on biological systems in living organisms (Caliyurt, 2017, Mina, 2023, Rietveld, 1990). Scientists have known about circadian rhythms for centuries, with Jean Jacques d'Or Tous de Mairan observing biological timekeeping for the first time in 1729. He observed that the leaves of a plant moved within an approximately 24-h cycle, even in the absence of sunlight, suggesting the existence of an internal clock (Roenneberg and Merrow, 2005). It is now established that in almost all living organisms, these circadian rhythms are driven by an endogenous timing system called the circadian clock (Dibner et al., 2010). Bacteria, plants and humans all display cycles in their physiology and behaviour over periods that last from seconds to months (Wulund and Reddy, 2015). Since then, our understanding of clock genes has expanded along with the interaction between the circadian clock and various aspects of physiology. However, many of these genes have been discovered in bacteria but are still under investigation in humans.

The circadian clock is an internal regulator of cells that coordinates physiological and behavioural activities with changes in daily environmental conditions in approximately 24 hours (Farhud and Aryan, 2018, Gabriel and Zierath, 2019). Furthermore the circadian clock consists of the central and peripheral clocks (Schibler and Sassone-Corsi, 2002). The central clock is also known as the central pacemaker of the circadian system and it is located in the hypothalamic suprachiasmatic nucleus (SCN) which is the anterior part of the hypothalamus, and it acts as a regulator that synchronises the rest of the cellular clocks, including the peripheral clocks (Gerhart-Hines et al., 2015, Hastings et al., 2018). Moreover, the peripheral clocks may be connected among themselves and may communicate back to the SCN. Metabolites, hormone cascades, or other circulating factors

can all play a role in this process (Richards and Gumz, 2012). Exposure to light daily is important for adjusting the circadian rhythm to 24 hours (Duffy and Wright, 2005). However, a lack of light in the suprachiasmatic nucleus causes people with blindness to become desynchronised (Andrews et al., 2019, Atan et al., 2023). While other drugs have been shown to shift the timing of the clock, melatonin appears to be the most promising therapeutic treatment (Lockley et al., 2007, Mistlberger and Skene, 2005).Unlike the central clock, which responds primarily to the light signals from the eye, peripheral clocks are found in nearly all tissues including the liver, heart and muscles, and they regulate tissue specific function and respond to local cues such as feeding and physical activity (Bass and Takahashi, 2010, Green et al., 2008). The presence of circadian clocks in almost all life forms highlights their fundamental importance in evolution, allowing organisms to adapt to and anticipate daily environmental changes. In most people circadian rhythms are slightly longer than 24 hours, which are adjusted daily based on environmental cues to match the solar rhythm of 24 hours (Atan et al., 2023). It is common for shift workers to experience poor sleep quality and duration, and symptoms of insomnia, especially those who work at night, early in the morning, or rotate shifts (Akerstedt and Wright, 2009, Moreno et al., 2019, Kecklund and Axelsson, 2016). This complex system of central and peripheral clocks working together ensures that physiological processes are optimally timed throughout the 24-hour day.

1.1.1 Chronobiology and its role in physiology:

At the physiological level, circadian rhythms regulate many processes such as feeding, hormone secretion, body temperature regulation and the sleep wake cycle within approximately 24-hour periods (Brown et al., 2002, Buhr et al., 2010). Previous studies demonstrated that light serves as the primary environmental cue for the SCN, which as

mentioned is responsible for the synchronisation of peripheral clocks and many physiological processes (Quintero et al., 2003). Light is, therefore, one of the chief Zeitgebers (external timing cues) and is sensed by photoreceptors located in the retina (Guler et al., 2008, Provencio et al., 1998). In brief, the process begins when light enters the eye via specialised photoreceptors in the retina, and these signals then travel through the retinohypothalamic tract to reach the master clock coordinator in the SCN (Dibner et al., 2010). Once these signals from the light reach the SCN, they have many effects including triggering the release of hormones such as cortisol (peaks in the morning) to promote arousal and alertness and melatonin (peaks at night) to promote sleep. This helps synchronise peripheral clock in the tissues, such as skeletal muscles, liver, heart and adipose tissue (Figure 1-1) (Aoyama and Shibata, 2017, Panda, 2016).

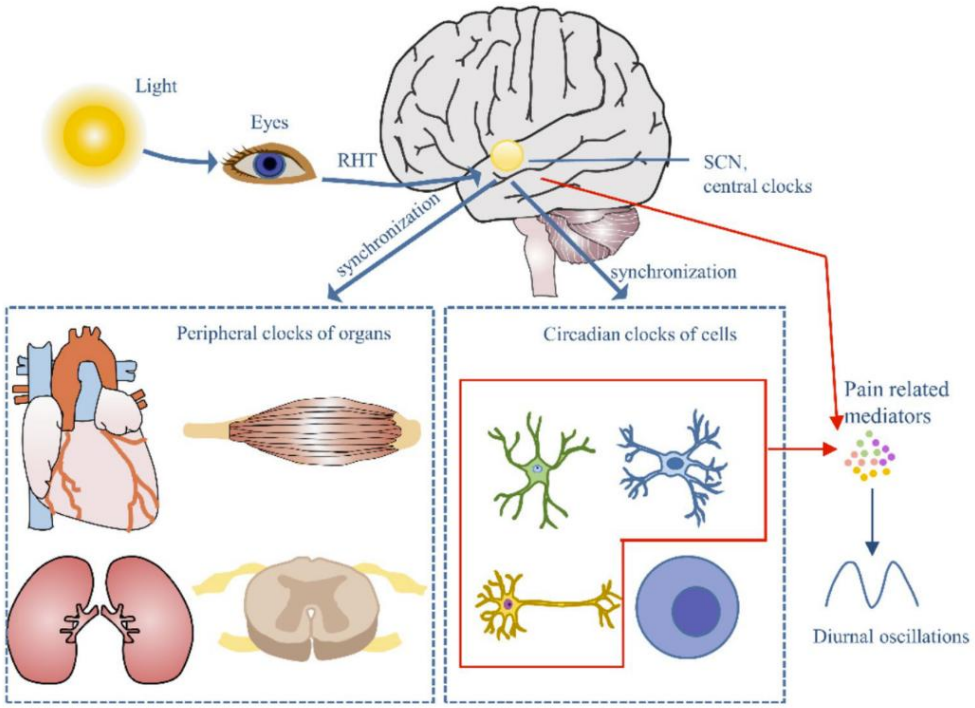


Figure 1-1: The circadian system in humans. Light signals detected by the retina travel to the brain's master clock (SCN), which then coordinates daily rhythms through hormones. These hormones help synchronize peripheral clocks in tissues such as muscle, liver, hear and fat tissue. Retinohypothalamic (RHT), diurnal oscillation (a cyclical pattern or rhythm that occurs approximately once every 24 hours). Figure adapted from (Chu et al., 2023).

Furthermore, body temperature varies throughout the day, and it has been shown the SCN contributes to the regulation of body temperature to a set point of around 37°C (Waterhouse et al., 2005). This plays an important role in the resetting of peripheral timekeepers such as in the liver, kidney and lungs which are sensitive to temperature changes (Brown et al., 2002, Buhr et al., 2010, Mohawk et al., 2012). As mentioned, body temperature varies throughout the day and follows a 24-hour cycle, peaking in the afternoon or early evening and decreasing after the mid-point of sleep (Waterhouse et al., 2005, Edwards et al., 2002). These variations in body temperature play an important role in multiple physiological functions including regulating sleep patterns.

Temperature is monitored by specialised sensory neurons in the brain, specifically in the preoptic area of the hypothalamus and also in other parts of the body such as skin, muscle. These sensory neurons have cell bodies located the peripheral ganglia and axons that extend out to monitor temperature in key tissue such as skin and spinal cord (Tan and Knight, 2018). While in rodents the preoptic area is the location resulting in the largest effector response to either warming or cooling, the skin itself experiences the greatest temperature fluctuations throughout the day (Tan and Knight, 2018). However, it is important to acknowledge that there are differences between humans and rodents in both genetics and structure. Studies in laboratory mammals have shown that during low amplitude temperature pulses that mimic circadian body temperature rhythms, these peripheral tissues can be reset, while temperature profiles that closely match circadian body temperature strongly entrain the peripheral clocks (Brown et al., 2002, Buhr et al., 2010, Mohawk et al., 2012). Furthermore, it has been shown that these daily temperature variations contribute significantly to human metabolism (Vetter et al., 2018, Bescos et al., 2018); this highlights the relationship between circadian rhythm and metabolic processes.

1.1.2 Chronobiology and metabolism:

The term energy metabolism can be defined as the chemical reactions occurring within each cell of the body in order to supply the body with energy (Judge and Dodd, 2020, Sanchez Lopez de Nava and Raja, 2025). The primary goal of metabolism is to provide Adenosine Triphosphate (ATP) which serves as the central link between the energy production and energy demands, fuelling processes such as muscular contraction (Corriden and Insel, 2010, Bonora et al., 2012). In humans, metabolism primarily relies on nutrients such as carbohydrates, fatty acids and amino acids, which are necessary for ATP synthesis. Additionally, metabolic pathways can be separated into three types: a) anabolism, which is the synthesis of simple molecules into more complex macromolecules, b) catabolism, which is the process of breaking down molecules to release energy or recycle components**.** For example, protein catabolism is important for several reason such as helping to mobilise essential amino acids for resynthesis (Gurina and Mohiuddin, 2025). c) waste disposal, which is the process that ensures to elimination of toxic waste production (DeBerardinis and Thompson, 2012). Glucose is the main energy source of the cell (Brouzgou and Tsiakaras, 2015, Soty et al., 2017), and it is catabolised through three processes - glycolysis, the tricarboxylic acid cycle (TCA) and oxidative phosphorylation for ATP production (Figure 1-2) (Bonora et al., 2012). However, this is dependent on the duration and intensity of exercise. For example, phosphocreatine (PCr) utilisation is the major ATP source in the first few seconds of exercise(Gaitanos et al., 1993, Sahlin, 2014).

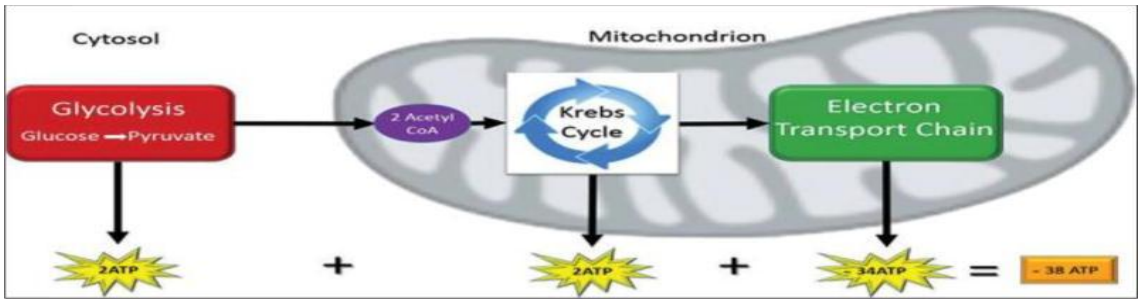


Figure 1-2: An illustrates the cellular respiration process. Glycolysis, occurring in the cytoplasm, breaks down glucose into pyruvate. The tricarboxylic acid (TCA) cycle, also known as the Krebs cycle, comprises a series of reactions within the mitochondria that generate ATP. The final step, oxidative phosphorylation, produces the majority of cellular ATP (Fernie et al., 2004, Bonora et al., 2012, Martinez-Reyes and Chandel, 2020). Figure adapted from (Mahoney et al., 2018) .

Like other physiological processes, metabolism displays distinct circadian rhythms that are important for metabolic health. For example, studies in mice have shown that mitochondria exhibit daily variations in their function and morphology, though their abundance remains stable throughout the day (Peek et al., 2013, de Goede et al., 2018). Furthermore, in human studies PGC1A, the marker of mitochondrial biogenesis, was not found to be rhythmically expressed(de Goede et al., 2018). However, studies using synchronised immortalised human hepatic cells found rhythmic mRNA levels of PGC1A with peak expression occurring near the peak of BMAL1(de Goede et al., 2018). In animal models, approximately 38% of mitochondrial annotated proteins exhibit oscillations over a 24-hour basis, suggesting that these mitochondrial protein oscillations may impact mitochondrial function (Kim and Sun, 2024, Neufeld-Cohen et al., 2016). The SCN plays a crucial role in the circadian regulation of metabolism by maintaining an approximately 24-hour rhythm during rest, activity, fasting and feeding cycles.

As a result, critical metabolic processes such as glucose utilisation, lipid metabolism and energy expenditure are influenced by output from the SCN (Panda, 2016, Gerhart-Hines et al., 2015) and it has been suggested that understanding the mechanistic basis of diurnal metabolic physiology might lead to prevention and treatment of metabolic diseases (Gabriel and Zierath, 2019, Staels, 2006, Smolensky et al., 2007).

In general, both the central circadian clock and peripheral clocks regulate, either directly or indirectly, the synthesis and release of several molecules. For example, Growth Hormone (GH) follows a circadian pattern that peaks during sleep (Van Cauter et al., 1991, Linkowski et al., 1987). Studies in rats support the notion that GH secretion is synchronised to occur at the same time each day during the light-dark cycle (Willoughby and Martin, 1978). Metabolically, GH is known as a counterregulatory hormone that increases glucose production through gluconeogenesis (synthesis of glucose) and glycogenolysis (breakdown of glycogen to glucose), from the liver and the kidneys, in healthy adults (Hoybye et al., 2008, Kim and Park, 2017). Since GH is a counterregulatory hormone, it also inhibits insulin action in the liver and muscle (Moller and Jorgensen, 2009). Additionally, plasma melatonin concentrations follow a circadian pattern that increases in the evening to promote sleep, while cortisol peaks in the early morning to promote wakefulness (Figure 1-3) (Aoyama and Shibata, 2017, Panda, 2016). Insulin secretion is affected by both hormones, but their effects vary by context, dose and genetic factors (van Raalte and Diamant, 2014, Tuomi et al., 2016). It is important to note that the Tuomi study included both human and rodent experimental observations, and this highlights the complexity in the translation of these findings.

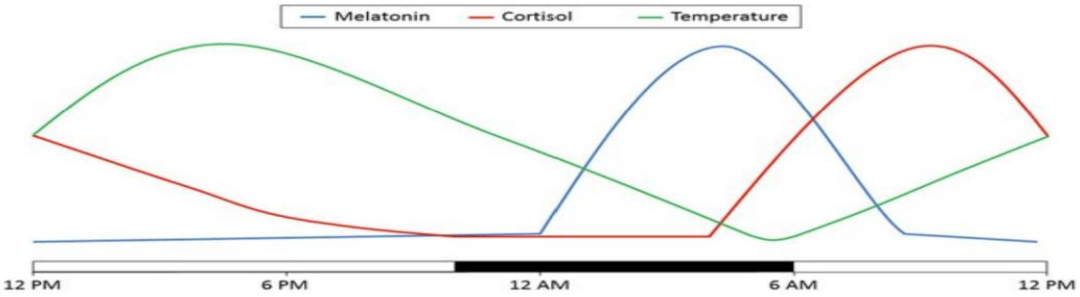


Figure 1-3: Daily patterns of two key hormones (melatonin and cortisol) regulated by the circadian clock. Melatonin levels rise in the evening to promote sleep, while cortisol peaks in the early morning to promote wakefulness. This 24-hour pattern helps coordinate our sleep-wake cycle. Figure adapted from (Jobanputra et al., 2020).

Studies have reported that, in response to a meal, insulin secretion rate and total insulin secreted peak later in the day at 20:00 rather than the morning at 08:00. (Van Cauter et al., 1992, Saad et al., 2012). Additionally, studies reported that fasting insulin was 21% lower in the evening around 8:00 PM than the morning around 8:00 AM (Morris et al., 2015). These daily variations can influence several key metabolic processes, specifically glucose metabolism. Insulin sensitivity, which refers to the ability of insulin to stimulate glucose uptake and suppress hepatic glucose production (Sanchez, 2020, Albaugh et al., 2023), shows distinct daily variations. Studies have shown that in healthy individuals, insulin sensitivity was greater in the morning [20 ± 7 µmol/L/min] than in the evening [12 ± 2 µmol/L/min](Morgan et al., 1999). Furthermore, numerous human studies have reported diurnal variation in glucose tolerance, via oral glucose tolerance test (OGTT), in the late 1960s and 1970s as evidence for circadian regulation of glucose metabolism (Jarrett and Keen, 1969, Aparicio et al., 1974). Recent studies using advanced methodologies, such as continuous glucose monitoring and molecular circadian markers, provide stronger evidence that glucose metabolism is regulated by circadian rhythms and this will be covered in more detail in subsequent sections of the thesis (Yardley, 2019, Moholdt et al., 2021a, Savikj et al., 2019).

In mice, ATP oscillations in the rat SCN peaks at night in advance of the daytime peaks in SCN neural activity and glucose utilisation (Inouye and Kawamura, 1982, Klein et al., 1991, Womac et al., 2009). In mammals, circadian clock controlled feeding and fasting cycle (Sancar and Brunner, 2014). During fasting conditions, gluconeogenesis is increased to maintain blood glucose levels (Sancar and Brunner, 2014). The process starts through glucagon signalling to activate protein kinase A (PKA), which promotes glycogenolysis and gluconeogenesis to supply glucose to tissues (Mayr and Montminy, 2001, Panda, 2016). Also, studies have reported that glucose tends to peak in the morning and decrease in the afternoon and evening in a fasting condition (Bowen, 1967, Hulman et al., 2013). Additionally, as a result of a meal ingestion plasma glucose concentration showed statistically significant across morning, lunch and dinner times ($P= 0.004$), with a mean value of 5.2 mmol/L in the morning compared to 5.0 (mmol/L) at both lunch and dinner times (Saad et al., 2012, Van Cauter et al., 1992).

In addition, in the fed condition, insulin activates glycogenesis via the inhibition of glycogen synthase kinase (GSK3), promoting glucose storage as glycogen in the liver and skeletal muscle (Kanungo et al., 2018, Panda, 2016). Glucose oxidation is essential because it involves ATP generation from glucose and glycolysis is the initial step involved in this process. There are ten steps in this enzyme-catalysed pathway prior to the Krebs cycle and the electron transport chain. In glycolysis, glucose is first converted into glucose-6-phosphate by hexokinase and glucokinase, then into fructose-6-phosphate by phosphoglucoisomerase. Pyruvate is then formed and enters the Kreb cycle in the mitochondria. As the Kreb cycle generates NADH and FADH2, they are finally oxidised in the inner mitochondrial membrane to generate ATP (Figure 1-4) (Ighodaro, 2018, Pelicano et al., 2006, Kruger and von Schaewen, 2003, Allard et al., 1994, Carracedo et al., 2013). Studies have shown that glucose oxidation displays daily rhythms, specifically through the activity of pyruvate dehydrogenase (PDH), that usually peaks during the transition from

rest/fasting to active/feeding phase (Dyar et al., 2014). In rodent work, this temporal regulation is a major role of the muscle clock, which is to prepare the muscle cells for daily metabolic transitions by optimising glucose uptake and facilitating to the switch from lipid to glucose metabolism at the light/dark transition (Dyar et al., 2014) These molecular mechanisms may have a direct impact on human muscle metabolism, but their exact function remains unclear.

There is evidence that the SCN has role in regulating the whole body glucose metabolism, independent or through the effect of behavioural feeding fasting cycle and sleep-waking cycle. Several human studies have reported that glucose tolerance tends to peak in the morning at 09:00 h with an impairment in glucose tolerance in the afternoon 15:00 h and evening 20:00 h (Jarrett et al., 1972). Similarly, circadian variation occurred in blood glucose level with lower values early morning at 06:00 AM and higher values at evening 06:00 PM and midnight 00:00 in normal subject (Aparicio et al., 1974). More recently, studies reported higher oral glucose tolerance of 203 ± 71 mg/dl at 19:00 h than 163 ± 62 mg/dl at 7:00 h in adults with prediabetes (Sonnier et al., 2014). However, these findings should be interpreted cautiously given the small sample size (n=10) and large standard deviations, which may reflect the low sample size rather than true population variability.

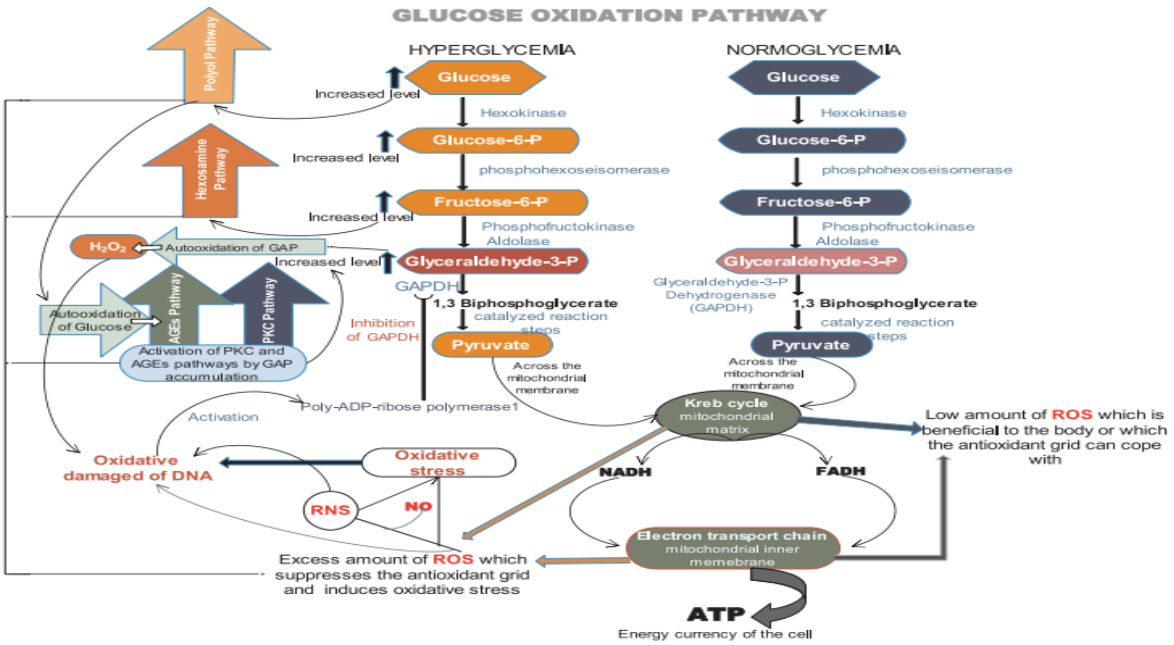


Figure 1-4: An illustration of gluocse oxidation pathway, the process of glycolysis starts with the phosphorylation of glucose by hexokinase, proceeds through fructose-6-phosphate and glyceraldehyde-3-phosphate, eventually producing pyruvate. As pyruvate enters the mitochondria, it proceeds through the Kreb cycle, generating NADH and FADH2, which are used to produce ATP through the electron transport chain. The figure adapted form (Ighodaro, 2018).

Skeletal muscle has the largest tissue mass in the human body, also it is responsible for approximately 80% of postprandial glucose disposal (Ferrannini et al., 1988, Defronzo et al., 1981). In order to understand how circadian rhythms regulate muscle metabolism, it is essential to examine the fundamental molecular mechanisms that generate these daily rhythms. The majority has been conducted in rodents, with minimal studies performed in humans. In mammalian cells, transcriptional and/or translational autoregulatory feedback loops function as molecular clock (Sukumaran et al., 2010, Gabriel and Zierath, 2019). Transcriptional and translational feedback loops between the circadian clock genes and their protein products create circadian oscillations (Buijs et al., 1999, Schibler and Sassone-Corsi, 2002, Gabriel and Zierath, 2019). Cell-autonomous circadian rhythms are produced by transcriptional activators, circadian locomotor output cycle kaput (*Clock*) and brain and muscle arnt-like1 (*BMAL1*) and their target genes period (*PER*), cryptochrome (*CRY*) and NR1D1 (which encodes *REV-ERBα*) at the molecular level, which form a

repressor complex that interacts with Clock and Bmal1 to inhibit transcriptional activity (Gerhart-Hines et al., 2015, Robinson and Reddy, 2014, Gabriel and Zierath, 2019). These clock genes are in the SCN which acts as the master clock. (Gerhart-Hines et al., 2015, Panda, 2016). This mechanistic understanding is well-supported by experimental evidence, primarily from animal studies with limited human validation.

Furthermore, these circadian rhythms are mainly generated by two interactive transcription-translation feedback loops (Reppert and Weaver, 2002). In the first loop, the mechanism begins when Bmal1 and Clock proteins combine together as paired complexes within the cytoplasm. These pairs move into the nucleus where they bind to specific DNA sequences called E-boxes. Within the nucleus, these Bmal1-Clock complexes initiate a positive feedback loop by activating the transcription of several genes, including period (*Per1*/2/3) and cryptochrome (*Cry1/2*) (Konopka and Benzer, 1971, Gekakis et al., 1998). The formation of the negative feedback loop starts when Per and Cry proteins are translated in the cytoplasm. They then form a regulatory complex and move back to the nucleus to inhibit Bmal1-Clock through the transcription process (Hurley et al., 2016, Preitner et al., 2002). This process of activation and inhibition helps to create a rhythmic cycle that takes approximately 24 hours to be completed. Furthermore, a second major loop occurs when Bmal1-Clock complex enters the nucleus and triggers nuclear receptor subfamilies (*REV-ERBs*) and retinoid-related orphan receptor (*ROR*) gene transcription via E-box. As a result, *ROR* proteins act as transcription factors, which activate *Bmal1* transcription. Where *REV-ERB* proteins inhibit the transcription of *Bmal1* forming a negative feedback loop (Figure 1-5) (Preitner et al., 2002).

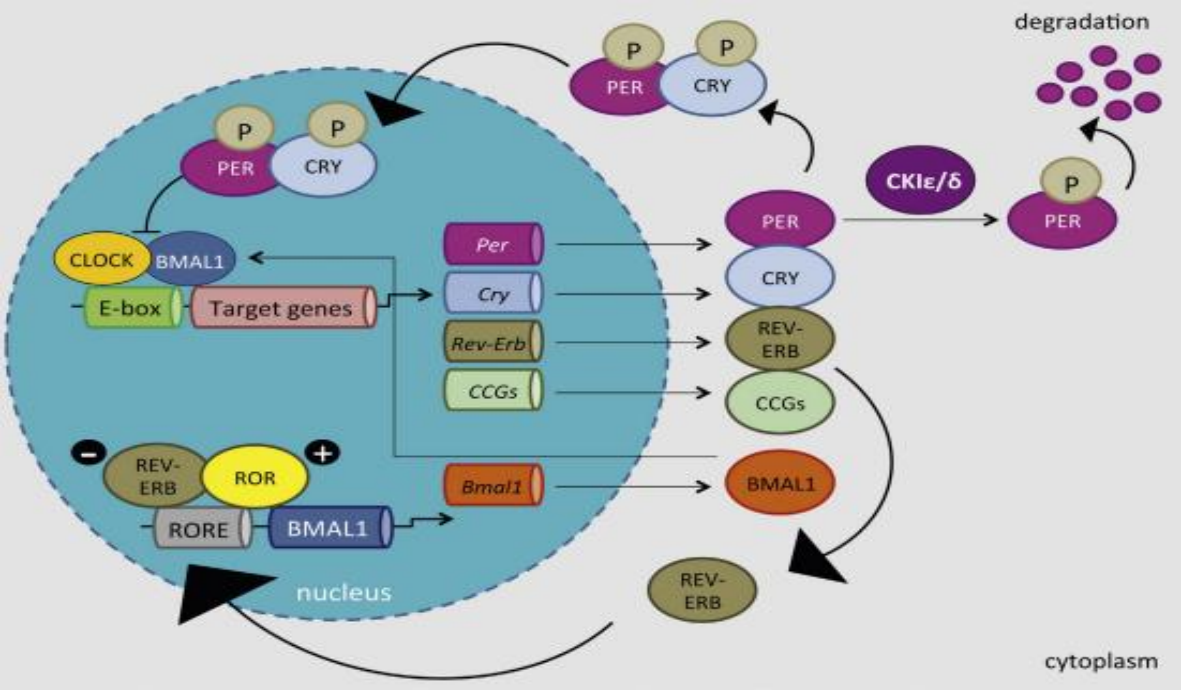


Figure 1-5: The core clock consists of transcriptional activators CLOCK and BMAL1, which form heterodimers and activate transcription of target genes including Per, Cry, and Rev-erb via E-box elements. *PER* and *CRY* proteins form repressor complexes that inhibit *CLOCK-BMAL1* activity, creating a negative feedback loop. A second feedback loop involves *REV-ERB* and *ROR* proteins regulating Bmal1 transcription (Pickel and Sung, 2020). The figure adapted form (Bartlang and Lundkvist, 2017)

In skeletal muscle, circadian rhythms and molecular clocks modulate a substantial number of genes that play an important role in metabolism (Rudic et al., 2004, Shimba et al., 2005, McCarthy et al., 2007, Lamia et al., 2008). This is essential for organisms to anticipate circadian rhythms. For example, studies have reported that loss of the molecular clock gene *Bmal1* results in impaired mitochondrial respiration and severe muscle pathology (Dyar et al., 2014, Andrews et al., 2010). Additionally, there is evidence that skeletal muscle possesses its own internal timing system that directly influences muscle metabolism throughout the day (Hodge et al., 2015), dependent on the energetic demands of skeletal muscle across the 24 hour period as the cycle transitions from a resting/fasting phase to an active/feeding phase. During this process, skeletal muscle clock fine tunes transcriptional control of metabolic genes (Erickson et al., 2021). For example, during the

resting/fasting phase, a peak in fatty acid uptake and β-oxidation genes occurs (Hodge et al., 2015, Dyar et al., 2014) while during the active/feeding phase, skeletal muscle clock shifts utilisation towards carbohydrate metabolism promoting genes involved in the regulation of insulin sensitivity and glucose utilisation while simultaneously inhibiting genes involved in lipid oxidation and amino acids transport (Dyar et al., 2014, Hodge et al., 2015, Erickson et al., 2021). As skeletal muscle contracts and/or is stimulated by insulin, glucose uptake and utilisation are rapidly modulated (Romijn et al., 1993, Abdulla et al., 2014, Hodge et al., 2015). The primary purpose of muscle metabolism is to generate ATP needed to produce work. While skeletal muscles at rest utilise approximately 30% of ATP, this increases to approximately 90% during exercise (Blanco and Blanco, 2017).

This flexibility in substrate utilisation is particularly evident in how skeletal muscle handles lipid metabolism throughout the day. During periods of low glucose availability or prolonged exercise, muscle tissue increasingly relies on fatty acid oxidation as an alternative energy source. While human studies of circadian lipid metabolism are limited, (Poggiogalle et al., 2018) In human studies it has been shown that approximately 13% of plasma lipid metabolites are rhythmic, in that they vary throughout the day, for example triglycerides plasma concentration exhibited peak levels in the morning (39.1% higher than other groups), where a small number of phophatidylcholines plasma concentration peak in the evening (11.3% higher than other groups) (Chua et al., 2013).

Lipid metabolism is regulated by the circadian rhythm (Petrenko et al., 2023), which orchestrates metabolic processes through complex molecular mechanisms. Clock genes oscillate throughout the 24-hour cycle, influencing how the body processes and uses lipids. When feeding and fasting naturally alternate between the day and night. Several interactions occur, among this interaction feeding and fasting driven regulation maintains normal physiology. Understanding these mechanisms is essential for comprehending lipid metabolism. The process begins with lipolysis, a process in which stored triglycerides in

adipose tissue are converted into free fatty acids and glycerol (Lass et al., 2011). Previous studies have shown diurnal regulation of triglyceride and cholesterol, with a peak near midnight in rats (Pan and Hussain, 2007). Additionally, in healthy humans, studies reported that triglyceride levels were higher in response to a single meal eaten at night at 01:00 h compared to during the daytime at 13:00 h (Romon et al., 1997).

Energy production is generated by the breakdown of fatty acids, and this process occurs in the mitochondria, where it is known as fatty acid oxidation or beta (β)-oxidation. A major regulator of human lipid metabolism is the nuclear receptor REV-ERBα, which maintains the circadian activity of enzymes and transcription factors (Sinturel et al., 2022). Furthermore REV-ERBα plays a crucial role in regulating metabolism through its gene repression activity, which operate in both in a circadian and tissue- specific manner (Everett and Lazar, 2014, Gerhart-Hines et al., 2013) Additionally, studies have shown that REV-ERBα directly controls the circadian expression of several genes involved in fatty acid biosynthesis (Grechez-Cassiau et al., 2015, Zhang et al., 2015). As result, REV-ERBα is essential for the complex interactions between the core clock and metabolism.

1.1.3 Summary of glucose and fat metabolism throughout the day:

- Human studies show a circadian rhythm in lipid metabolism which is independent of food intake and sleeping pattern (Loizides-Mangold et al., 2017, Chua et al., 2013).

- In healthy humans, studies have reported that triacylglycerides plasma concentration (also known as triglycerides), diacylglycerides and glycerophospholipids plasma concentrations share a similar pattern of variation across the day, they appear to be the lowest at 1 PM (afternoon) and peaks at 4 AM (morning) (Figure 1-6)(Held et al., 2020).

- In healthy human, studies have shown that oral gluocse tolerance tends to peak at 09:00 h with an impairment in glucose tolerance in the afternoon 15:00 h and evening 20:00 h (Jarrett et al., 1972).

- In people with impaired gluocse tolerance, studies have reported that people with impaired gluocse tolerance (IGT) showed higher glucose responses after breakfast than people with normal glucose tolerance (NGT). Furthermore data reveals a lower glucose tolerance in the evening in people with IGT but not those with NGT (Figure 1-7) (Dos Santos et al., 2006).

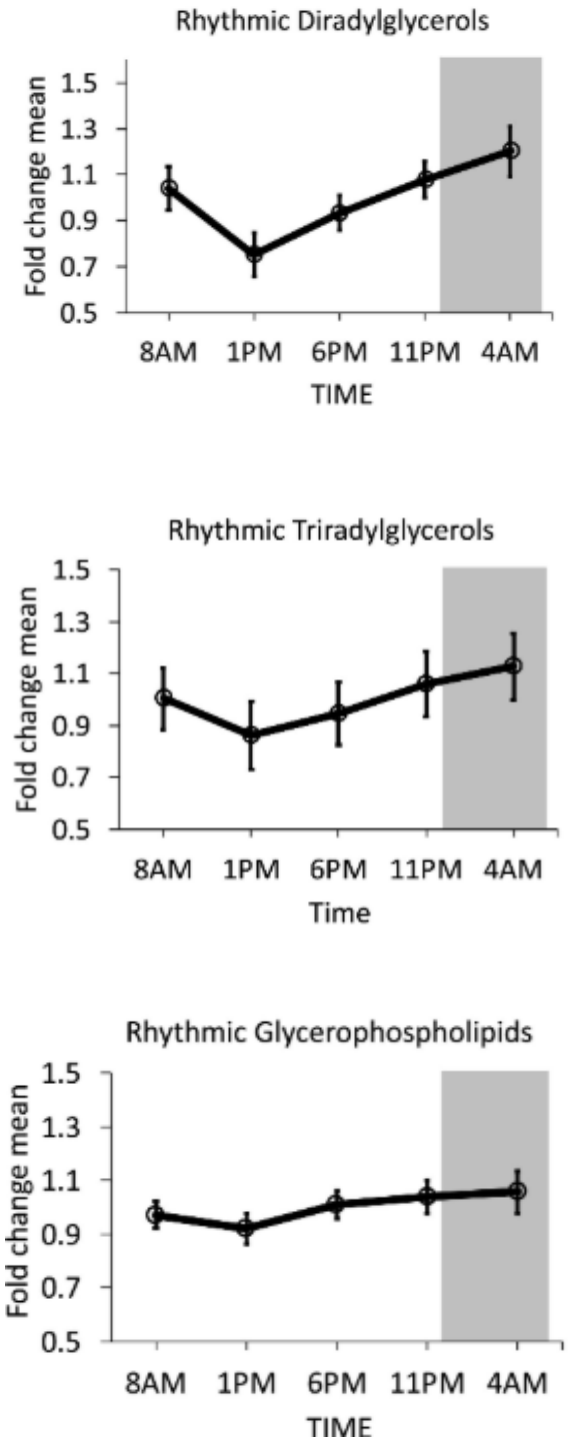


Figure 1-6: An illustration of rhythmic regulation of skeletal muscle lipidome through the day. Diradylglycerols, triradylglycerols and glycerophospholipids have a similar pattern with low point at 1 PM (afternoon) and peaks at 4 PM (morning).This figure adopted from (Held et al., 2020).

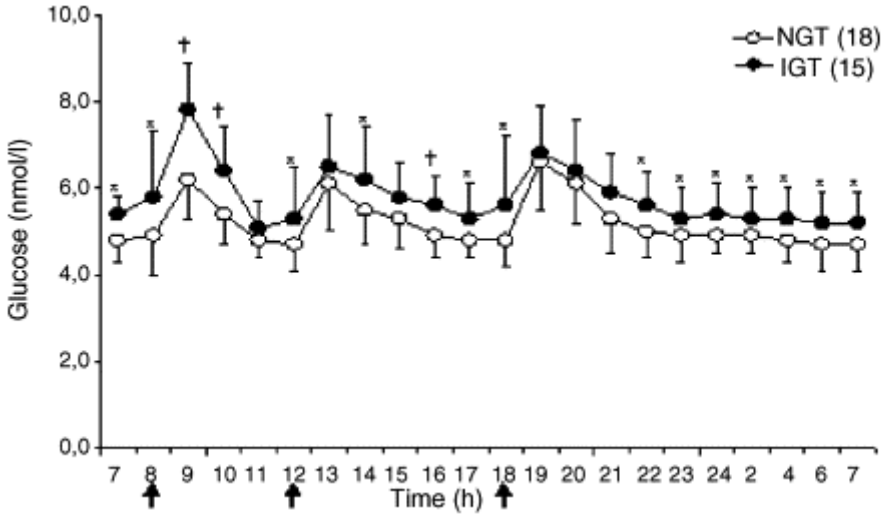


Figure 1-7: An illustration of plasm glucose during a 24h cycle in individuals with impaired and normal glucose tolerance. The arrows under the x-axis show the meals time, breakfast was served at 8 AM, lunch at 12 PM and dinner at 6 PM. This figure adopted from (Dos Santos et al., 2006).

1.2 Importance of metabolism for health:

In a healthy body, insulin is produced by the pancreatic β-cells in response to elevated blood gluocse levels following food intake and functions to promote anabolism and suppresses catabolism (Wendt and Eliasson, 2020, Lee et al., 2022). Insulin plays a crucial role in regulating glucose metabolism by stimulating glucose uptake in insulin sensitive tissue, particularly the skeletal muscle which is, as mentioned above, responsible for approximately 80% of postprandial glucose disposal (Ferrannini et al., 1988, Defronzo et al., 1981). Insulin resistance is a complex metabolic disorder that occurs when insulin's ability to stimulate glucose uptake in key metabolic tissues, particularly skeletal muscle liver, adipose tissue (Czech, 2017, Defronzo et al., 1981). This condition affects both oxidative and nonoxidative pathways of glucose disposal (Bonadonna et al., 1990, Golay et al., 1988). Target tissues do not respond appropriately to normal insulin concentrations leading to hyperinsulinemia as the pancreas attempts to maintain normal glucose homeostasis (Moore et al., 1991, Defronzo et al., 1981, Lee et al., 2022, Zhao et al., 2023). On top of this decrease in glucose uptake, there are also defects in glucose oxidation and

glycogen synthesis, with a smaller effect in a decrease in the ability for insulin to suppress lipid oxidation (DeFronzo and Tripathy, 2009, Kelley and Mandarino, 2000, Shulman et al., 1990).

Research has demonstrated that individuals with diabetes, hypertension and obesity have been shown to have insulin resistance and concomitant hyperinsulinemia (Bogardus et Ormazabalal., 1984; Defronzo et al., 1981; Modan et al., 1985; Saad et al., 1989). This insulin resistance has several consequences, with the resulting hyperglycaemia resulting in the development of oxidative stress and inflammation, and the inhibition of lipid oxidation resulting in hypertriglyceridemia, and low HDL and high LDL cholesterol levels (Ginsberg et al., 2005, Ormazabal et al., 2018). There is also evidence that there is insulin resistance of the vasculature, cumulating in endothelial dysfunction, which alongside the aforementioned metabolic defects can result in atherosclerotic plaque formation and an increased risk of CVD (Ormazabal et al., 2018). Several studies have suggested that fasting blood glucose might be a powerful predictor of mortality in high-risk patients (Watanabe et al., 2021) and that there is a strong link between mortality and blood glucose levels (Zhao et al., 2020, Watanabe et al., 2021, Martín-Timón et al., 2014).

Insulin resistance is sometimes known as prediabetes (Merz and Thurmond, 2020) and research shows that there is 50% chance of someone with prediabetes developing type 2 diabetes within 5 years of diagnosis (American Diabetes, 2017), with insulin resistance often preceding development by 10 to 15 years (Freeman et al., 2025). Type 2 diabetes is characterised by two factors, defective insulin secretion by pancreatic β-cells and/or an insulin resistance, and over time insulin production decreases resulting in type 2 diabetes (Figure 1-8)(Galicia-Garcia et al., 2020). Type 2 diabetes, increases the risk of microvascular diseases, such as neuropathy, nephropathy, and retinopathy, and macrovascular diseases, such as coronary artery disease, peripheral arterial disease, stroke, and other related complications (Al Ozairi et al., 2023). Indeed, people with type 2 diabetes

have a 2- to 3-fold higher risk of CVD, which accounts for 80% of deaths in patients with type 2 diabetes (Al Ozairi et al., 2023, Morrish et al., 2001) Diabetes accounted for 6.7 million deaths in 2021(Federation, 2021).

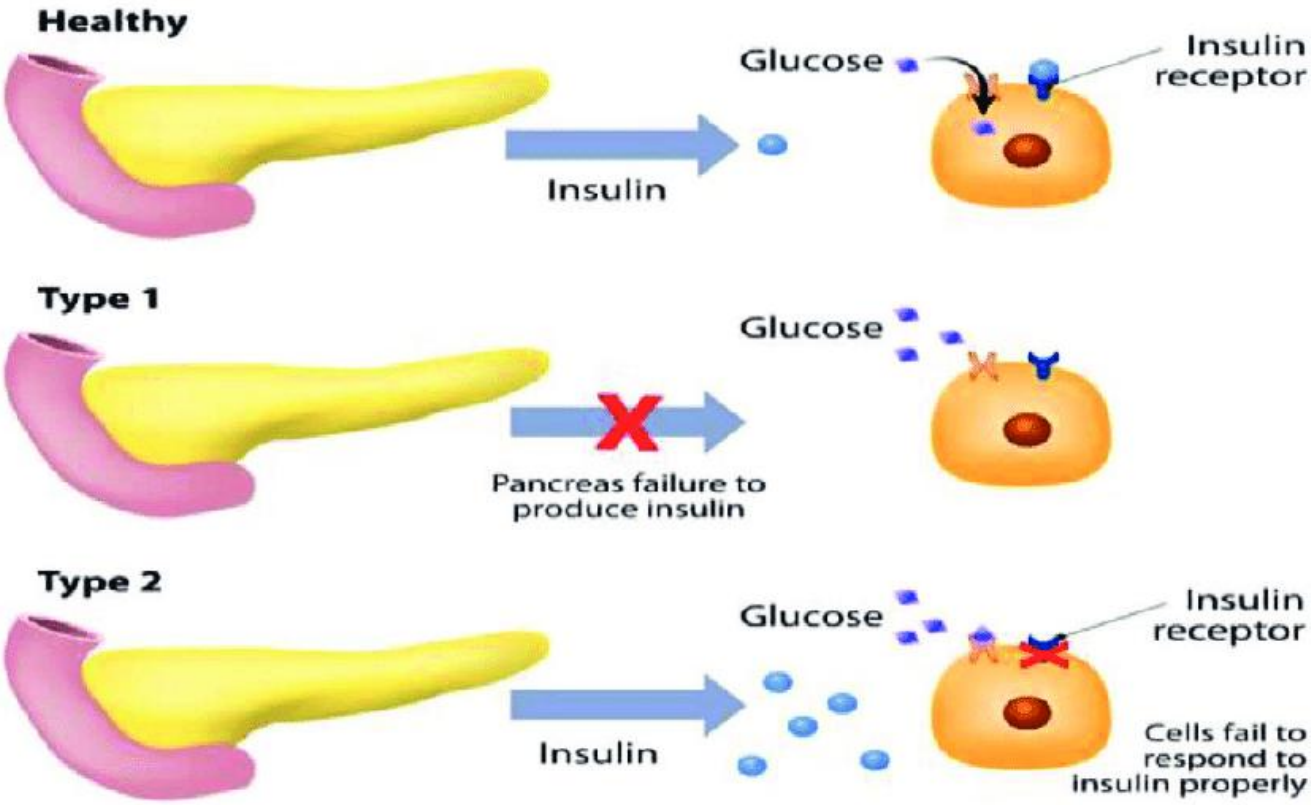


Figure 1-8: An illustration of insulin signalling in healthy individuals and diabetes. The top photo shows normal insulin production by the pancreas and gluocse uptake through insulin receptors in healthy individuals. The middle photo illustrates type 1 diabetes, where the pancreas fails to produce insulin, preventing glucose uptake by the cell. The last photo shows insulin (insulin resistance), leading to impaired glucose uptake. This figure adopted from (Sanusi-Olubowale, 2022).

Current prevalence of poor metabolic health and obesity:

In the U.S, the prevalence of insulin resistance among young adults (18 to 44 years) was 40.3% during 2015-2018 (Parcha et al., 2022). While in Italy 22.3% of adult men and 27.2% of adult women were found to be insulin resistant between 1997-1999 (Magi et al., 2005). On top of this, currently, 537 million adults (age: 20–79 years) worldwide are living with diabetes, with a prevalence of 10%. This number is projected to reach 643 million by

2030 and 784 million by 2045(Federation, 2021). Approximately 90%–95% of people with diabetes have type 2 diabetes.

Insulin resistance and type 2 diabetes are commonly associated with obesity (Krentz, 1996, Abate et al., 1995, Despres and Lemieux, 2006, Van Gaal et al., 2006) and research has demonstrated that tissue sensitivity to insulin decreases by approximately 30-40% when an individual exceeds their ideal body weight by 35-40% (Defronzo et al., 1981, Bonadonna et al., 1990, Golay et al., 1988, Bogardus et al., 1984). Obesity is one of the most pressing public health problems globally and is often defined by Body mass index (BMI), a measurement of individuals weight and height by calculating weight (kg)/height (m^2). The World Health Organisation defines overweight as a BMI greater than or equal to 25 (WHO, 2023) and obesity is defined as a BMI of 30 or greater. Obesity currently affects 800 million people worldwide (WHO, 2023). Furthermore, recent data from England shows that 64.0% of adults aged 18 or older classified as overweight or obese between 2022 and 2023 (Office for Health Improvement & Disparities, 2024) The classifications are based on BMI cutoffs, which may not be accurate or take individual variations into account. Similarly, in Scotland around 67% of all adults were living with overweight or obesity, with a higher prevalence observed in men than women (Scottish Government, 2023) .

1.2.1 Management of insulin resistance and obesity:

The primary approach to managing insulin resistance begins with obesity management, as research has shown that 5-10% weight loss may reduce blood pressure and cardiovascular risk (Jensen et al., 2014, Ryan and Yockey, 2017). Importantly, weight loss exceeding 15% has shown to be associated with lower rates of all-cause mortality and improved quality of life (Ryan and Yockey, 2017).

Current guidelines indicate that obesity treatment primarily involves weight management through a combination of diet modification, physical activity, and behavioural

interventions and more recently anti-obesity medications (National Institute for Health and Care Excellence, 2025). It is now possible to treat obesity with GLP-1 receptor agonists, but questions remain regarding long-term safety, cost-effectiveness, and optimal patient selection. And this raise the a question A comprehensive meta-analysis compared over 14 types of popular dietary programmes for weight and cardiovascular risk factors concluded that over a six-month period most macronutrient diets result in modest weight loss, such as Atkins diet (weight loss of 5.5 kg, reduction in systolic blood pressure of 5.1 mm Hg, and diastolic blood pressure of 3.3 mm Hg) (Ge et al., 2020). Although dietary modifications are important, further benefit can be gained from the inclusion of physical activity, which not only enhances weight loss efforts but also independently improves insulin sensitivity and metabolic health (Blair et al., 1989, Brouwers et al., 2016, Phielix et al., 2012, Conn et al., 2014). While a comprehensive meta-analysis provides a robust statistical power, they may be limited by heterogeneity in study design and follow-up duration across included research.

1.3 Physical activity exercise: An overview:

The term physical activity refers to any body movement produced by the skeletal muscles that results in energy expenditure (Caspersen et al., 1985), including activities such as walking, running and swimming. Exercise is defined as physical activity that is planned, structured, and repeated in order to maintain physical fitness (Caspersen et al., 1985, Sodergren et al., 2008). It is well established that physical activity is beneficial for one's health (Warburton et al., 2006, Reiner et al., 2013, Piercy et al., 2018) with regular exercise and physical activity providing multiple health benefits including improved cardiovascular fitness, enhanced muscular strength, weight management, and enhanced mental well-being (Brown et al., 2020, Sigal et al., 2004b). Additionally, it has been reported that physical activity is associated with reduced mortality (Abell et al., 2017, Anderson et al., 2014) and improved bone strength (Adsett et al., 2015, Rowlands et al., 2020), with benefits

extending to all body systems including musculoskeletal (Hagen et al., 2012), immunological (Sellami et al., 2018) and hormonal (Kraemer and Ratamess, 2005). Notably, exercise has a significant positive impact on metabolic processes and is a key factor in the regulation of glucose control and, thus, reducing the risk of metabolic disorders such as diabetes (Thyfault and Bergouignan, 2020) and improving glycaemic control (Aljawarneh et al., 2019, Chastin et al., 2019, Posadzki et al., 2020)

Exercise encompasses various types such as aerobic exercise, which is defined as physical activity involving large muscle groups and rhythmical movements that increases heart rate and breathing rate above resting levels (Donatelle and Kolen-Thompson, 2015, Bidonde et al., 2017). Resistance exercise is defined as planned repeated muscle movements against external resistance or one's own body weight (Nuzzo et al., 2024). In the United Kingdom, current physical activity guidelines for adults aged 19 to 64 recommend both aerobic and resistance exercise, performing at least 150 minutes of moderate-intensity activity per week or 75 minutes of vigorous intensity activity. Additionally, adults should perform strengthening activities targeting all major muscle groups (legs, hips, chest, shoulder and arms) at least two days per week (NHS, 2019). For optimal exercise prescription, it is important to understand the specific mechanisms through which physical activity affects metabolic health.

1.3.1 Benefits of general physical activity on muscle and metabolic health

Physical activity induces a number of adaptations that enhance metabolic health and muscle function (Lewis and Hennekens, 2016, Caro et al., 2013, Thyfault and Bergouignan, 2020). There are three main metabolic processes that can be regulated by exercise to influence glucose uptake and utilisation: 1) glucose delivery to muscle, 2) glucose transport into muscle and 3) glucose metabolism (Figure 1-9)(Richter and Hargreaves, 2013).

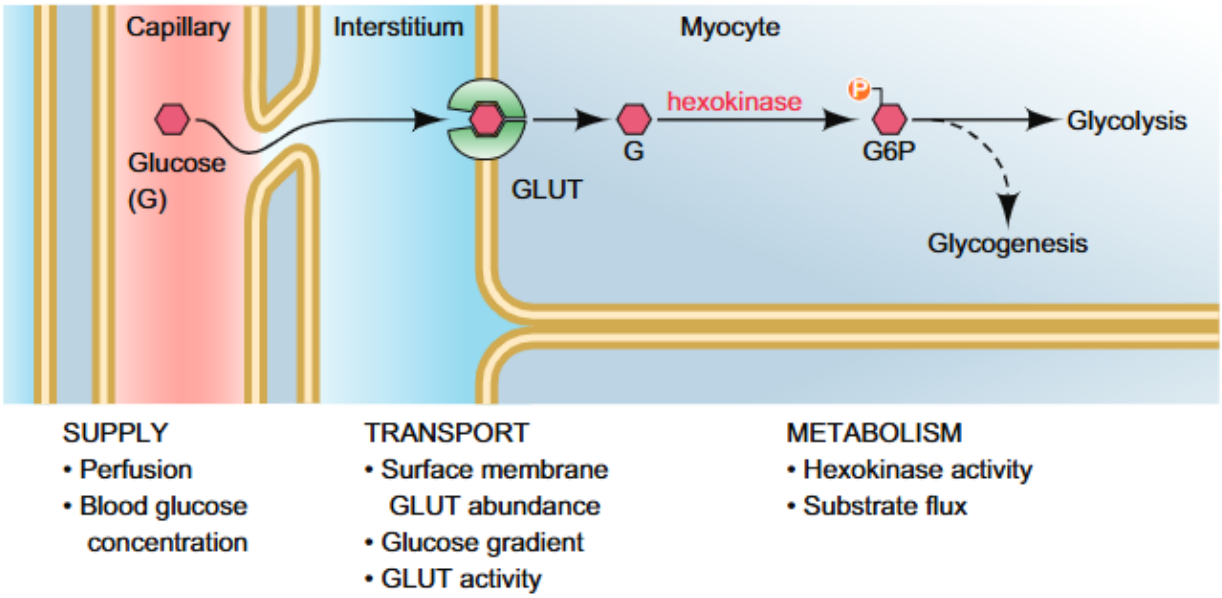


Figure 1-9: Rate-limiting steps of glucose uptake by skeletal muscles; There are three main metabolic processes that can be regulated by exercise to influence glucose uptake and utilisation from the blood stream: 1) glucose delivery to muscle 2) glucose transport into muscle by GLUT transport-mediated uptake across all cell membrane, 3) glucose metabolism converted via hexokinase to glucose-6-phosphate (G6P), which can enter either the glycolysis or glycogenesis pathways in the cell. This figure adopted from (Rose and Richter, 2005).

Concerning glucose delivery, it has been shown that during exercise, muscle blood flow increases, up to 20 fold, and this increase is quantitively the largest contributor to increasing muscle glucose uptake during exercise (Richter and Hargreaves, 2013, Ahlborg et al., 1986). This increase in glucose delivery occurs due to changes at both the macro and microvascular levels, during exercise, with both vasodilation of arteries and the recruitment of further capillaries which increases the available surface area for glucose delivery and exchange (Rose and Richter, 2005).

Concerning glucose transport, exercise results in insulin independent GLUT4 translocation from intracellular storage site to sarcolemma and T-tubules to increase skeletal muscle gluocse uptake (Richter and Hargreaves, 2013, Kristiansen et al., 1997). The translocation of GLUT4 is regulated by two key signalling molecules: AMPK, which acts as an energy

sensor when ATP levels drop, and calcium, which is released during muscle contractions (McGee and Hargreaves, 2024). GLUT4 is then translocated to the surface of cells and inserted into the sarcolemma by activated kinases such as Ca^{2+} and APMK in both rodent and human (McGee and Hargreaves, 2024, Sylow et al., 2017, Douen et al., 1990, Kristiansen et al., 1997, Kennedy et al., 1999). Physical activity is, therefore, particularly appropriate to address metabolic diseases such as insulin resistance and type 2 diabetes (DiMenna and Arad, 2018). Exercise impacts insulin sensitivity through acute (single session) and chronic (training) adaptations. During exercise, there is an increase in insulin-independent glucose uptake, while post-exercise insulin sensitivity can improve by more than 50% and last up to 72 hours (Roberts et al., 2013).

The acute response to exercise occurs in distinct phase. Insulin-independent glucose uptake during exercise usually reverses ~ 2-3 hours postexercise, whereas enhanced muscle and whole body insulin sensitivity, it can be detectable at ~ 1-4 h postexercise, and can persist for 24-48 hours (Arias et al., 2007, Cartee and Holloszy, 1990, Koopman et al., 2005, Mikines et al., 1988, Perseghin et al., 1996). These effects have been demonstrated in various populations. For example, in a prediabetic individuals, aerobic exercise showed an improvement in insulin sensitivity by approximately 50% 1-hour post-exercise (Rynders et al., 2014). Additionally, research demonstrated in individuals with type 2 diabetes, a single bout of cycle exercise improved insulin stimulated glucose disposal when measured 12-16 h post-exercise (Devlin et al., 1987).

The effect of exercise on insulin sensitivity depends on various factors including the type, intensity, frequency and gluocse levels (Motahari-Tabari et al., 2014). Research indicated that 8 weeks of aerobic exercise improved insulin sensitivity in women with type 2 diabetes (Motahari-Tabari et al., 2014). Additionally, improvements in insulin sensitivity was observed following six weeks of aerobic exercise (Damirchi et al., 2014), however,

these improvement returned to baseline following a determining period (Damirchi et al., 2014).

Physical activity is associated with an increase in insulin effectiveness in the skeletal muscle (Teixeira-Lemos et al., 2011, Guyton, 2006). A part of this effect is the promotion of glucose uptake in the skeletal muscles, as well as the loss of body fat in the central part of the body (Praet and van Loon, 2009, Guyton, 2006, Teixeira-Lemos et al., 2011, Turcotte and Fisher, 2008), and reduced lipid products and increased lipid oxidative capacity (Turcotte and Fisher, 2008). Several mechanisms contribute to the enhancement of lipid oxidation, including increased mitochondrial density, increased enzyme activity, and enhanced substrate delivery to skeletal muscles (Holloszy and Coyle, 1984). In response to these adaptations, the body is more likely to rely on fat oxidation during submaximal exercise (Horowitz and Klein, 2000). Additionally, physical activity can lead to modest reductions in adiposity even in the absence of weight loss (Wilmore et al., 1999). These metabolic improvements are partly mediated through enhanced mitochondrial biogenesis and function (Sutherland et al., 2009, Stallknecht et al., 1991).

The level of insulin sensitivity correlates with changes in body fat as well as anti-inflammatory factors (Bluher et al., 2005, Weyer et al., 2001, Nicklas et al., 2004). Low-to moderate intensity uses lipid as a source of energy which increases the work capacity of the skeletal muscles, increases blood supply to different parts of the body, enhances vessels' ability to respond efficiently to blood demand, and reduces peripheral vascular resistance (Albarrati et al., 2018).

Concerning gluocse metabolism, once the glucose enters the muscle cells it is phosphorylated to gluocse 6-phosphate (G-6-P) by an enzyme called Hexokinase II (HKII) (Richter and Hargreaves, 2013). The regulation of glucose metabolism depends on several factors such as intensity and duration. During maximal exercise, increased intramuscular

glucose levels suggest hexokinase inhibition and limited glucose phosphorylation and utilisation, associated with elevated intramuscular G-6-P concentration, indicative of increased muscle glycogenolysis rates (Katz et al., 1986). As well, G-6-P-mediated inhibition of hexokinase limits glucose uptake and utilization during early exercise (Katz et al., 1986, Richter and Hargreaves, 2013). With continued exercise, glucose uptake and intramuscular glucose concentration decrease as G-6-P reduces hexokinase inhibition (Katz et al., 1986).

The majority of research in this area has been carried out on aerobic exercise, but there is emerging evidence of the metabolic benefits of resistance exercise. The reason may be that aerobic exercise is easier to standardise in research settings and its cardiovascular benefits were recognised earlier.

1.3.2 Benefits of specifically resistance exercise on muscle and metabolic health:

One of the main benefits of regular resistance exercise is that it increases muscle strength and mass (Thyfault and Bergouignan, 2020), which are important for maintenance of physical function, blood pressure and glucose control, and morbidity/mortality risk (Celis-Morales et al., 2018, Kirwan et al., 2017, Colberg et al., 2010). Compared to aerobic exercise, however, there is a relative dearth of research investigating the metabolic effects and benefits of resistance exercise.

Resistance exercise provides multiple benefits metabolically, involving both acute and chronic adaptions. Acute adaptions of resistance exercise include enhanced glucose uptake and insulin sensitivity (Koopman et al., 2005, Black et al., 2010b). Similar to aerobic exercise, resistance exercise results in increased blood flow and glucose extraction (Dela et al., 1995, Holten et al., 2004). The insulin response to resistance exercise shows distinct temporal phases: during the early phase (0–10 min) of hyperglycaemic stimulus, bouts of

exercise to exhaustion increase pancreatic insulin secretion, and during the late phase (15–180 minutes), they increase insulin clearance (Kirwan et al., 1991). Additionally, whole body glucose disposal calculated at (30 min) intervals didn't show any significant difference between phases (Kirwan et al., 1991). Moreover, studies reported in one legged resistance exercise insulin more rapidly activated gluocse uptake by two to four-fold higher compared to with resting leg in healthy men (Wojtaszewski et al., 2000).

Previous research has demonstrated that when six male individuals perform 60 minutes of repeated knee extension exercise on one leg at 75% of their maximum, insulin sensitivity improved. While repeated knee extension exercise may could be consider as aerobic, it is fundamentally a resistance exercise that targets a specific muscle group. The differences in leg glucose uptake between the rested and exercised thigh at the highest insulin-infusion was 20% 4 hours post-exercise (Richter et al., 1989). Moreover, studies have demonstrated that a single session of resistance exercise performed at 75% of individual one repetition maximum (1RM), comprising three sets of ten repetitions on three resistance exercise machines targeting the upper body, improved insulin sensitivity by 13.4 ± 4.8% for at least 24 hours in healthy men (Koopman et al., 2005).

Although the data on the intensity, duration and volume of resistance exercise required to improve insulin sensitivity acutely are limited, Black et al, evaluated the effect of various resistance exercise protocols on 24 h post-exercise insulin sensitivity. The researchers recruited seventeen participants with impaired fasting glucose, all of whom were classified as sedentary. The intervention comprised of 4 separate bouts of resistance exercise under either moderate intensity (65% of 1RM), at this intensity participant performed 12 to 15 repetitions for all for 8 exercises targeting major muscle groups. Or high intensity (85% of 1RM), at this intensity participants required to complete 6 to 8 repetitions of each exercise. The study measured fasting insulin sensitivity using the Homeostasis Model Assessment (HOMA). A minimum washout of 72 hours was used between test days to prevent a

carryover effect from previous testing. This result indicated that there were significance differences between pre and post measures with moderate intensity (65% of 1RM). However, the results revealed an improvement in insulin sensitivity 24 h post-exercise with 85% 1RM of multiple sets (Black et al., 2010b). These results showed that high intensity exercise up to 85% of 1RM may be more effective to improve insulin sensitivity. Previous studies using aerobic exercises have provided a number of evidence to the current data, which showed intensities between 70% and 90% may be more efficient to improve glycaemic control (Houmard et al., 2004, Koval et al., 1999, Braith and Stewart, 2006)

Furthermore, a research study evaluated the effects of acute and chronic resistance training on glucose and insulin responses, during an OGTT, in women with type 2 diabetes. After familiarisation, subjects participated in resistance training three times per week for six weeks. An OGTT was performed 12 to 24 hours after the first exercise session to assess the acute response, while an OGTT was performed 60 to 72 hours after the last training program to assess the chronic effects. The study revealed a significant strength increase ranging from 19% to 57% in all exercises. Additionally, the acute response to exercise improved integrated glucose concentration, as measured by the Area Under the Curve (AUC) during the OGTT after the acute bout of exercise (AUC: 2,868 ± 324.0 mmol/L · min), and the after the chronic training (3,206.0 ± 337.0 mmol/L). However, there were no significant changes in insulin AUC after either the acute or the chronic exercise (Fenicchia et al., 2004).

The repeated acute responses to resistance exercise appears to lead to chronic adaptations, such as increased insulin sensitivity and improved glycaemic control. A recent study reported that ten overweight men who participated in a single set of 80% of 1RM of resistance training for six weeks showed improvements in insulin sensitivity and muscle mass adaptation, although the lack of a control group is a clear limitation of this study. The results indicated an improvement in vastus lateralis muscle thickness by 10.3 ± 2.5% and

in insulin sensitivity, measured during an OGTT, by 16.3 ± 18.7% in overweight men (Ismail et al., 2019b). It important to notice that the very large standard deviation, due to the relatively low sample size, for insulin sensitivity makes interpretation difficult and limits confidence in these findings. Moreover, resistance exercise is a powerful tool for managing type 2 diabetes, as demonstrated in a systematic review and meta-analysis examining the association between structured exercise training (aerobic, resistance or both) and physical advice only on changes in haemoglobin A(1c) (HbA(1c)) in type 2 diabetes. The results indicated that eighteen studies of aerobic structured exercise training were associated with a reduction in HbA1c by 0.73% (95% CI, −1.06% to −0.40%). Four studies of resistance exercise training were associated with a reduction in HbA1c by 0.57% (95% CI, −1.14% to −0.01%). While a seven studies of a combination of aerobic and resistance exercise training were associated with a reduction in HbA1c by 0.51% (95% CI, −0.79% to −0.23%). The author concluded that structured exercise of more than 150 minutes per week was associated with a reduction in HbA1c by 0.89% (Umpierre et al., 2011).

1.4 Interactions between chronobiology, exercise and muscle and metabolic health:

Summarising the preceding sections, the beneficial effects of exercise for muscle and metabolic health are well established (Kirwan et al., 2017, Ismail et al., 2019b), but more recent and emerging evidence suggests that these adaptations may be influenced by time of the day at which exercise is performed (Bruggisser et al., 2023). As mentioned above, the circadian rhythm is approximately a 24 h transcription-translation feedback loop (TTFL) which drives metabolism (Gabriel and Zierath, 2019). In skeletal muscle, CLOCK and BMAL1 and their target genes directly control metabolic transcription through this molecular machinery (Gabriel and Zierath, 2019, Gerhart-Hines et al., 2015). Additionally, a key component of metabolic homeostasis is circadian rhythm regulation in skeletal muscle (Zhou et al., 2014).

Metabolic disorders reveal the significance of this clock-metabolism interaction. Changes in circadian rhythms can increase the risk for chronic disease such as hypertension, diabetes, and cancer risk (Schernhammer et al., 2001, Forman et al., 2010). For example, metabolic disease has been associated with a disruption of mammals' circadian clocks (Panda, 2016). Additionally, variations in glucose tolerance and insulin action throughout the day suggest that circadian rhythms influence glucose metabolism (Van Cauter et al., 1997, Gagliardino et al., 1984). In mice, disruption of both *Cry1* and *Cry2* results in glucose intolerance and impaired body growth (Bur et al., 2009). Additionally, the development of metabolic disturbances and diseases is more common among subjects with perturbed circadian rhythms and mice with disrupted central clocks (Coomans et al., 2015). Researcher demonstrated that insulin sensitivity can be reduced in healthy adults by only four nights of simulated night shift work, and this will increase the risk of type 2 diabetes (Bescos et al., 2018).

Research demonstrated the exercise modulates the molecular clock in the skeletal muscle affecting both the phase and the amplitude of circadian rhythm (Peek et al., 2017, Saner et al., 2018). This modulation is evident from molecular studies to whole-body performance. At a molecular level, Exercise-induced gene signatures were changed in mice with Cry1 and Cry2 genetic ablation (Jordan et al., 2017). A few studies have indicated that exercise modifies the rhythm of the clock machinery in the skeletal muscle (Peek et al., 2017, Saner et al., 2018, Wolff and Esser, 2012, Gabriel and Zierath, 2019). In humans, resistance exercise of ten sets of eight repetitions at 80% 1RM on one leg alters circadian gene expression, causing a phase shift in core clock genes in comparison with contralateral control legs in healthy men (Zambon et al., 2003).

Furthermore, it appears that these molecular adaptations affect athletic performance throughout the day. For example, data on the interactions between diurnal timing and exercise performance showed that the number of world records are broken by athletes was

higher during early evening compared to morning (Atkinson and Reilly, 1996). Additionally, a time of the day effect in healthy individuals aged 19-36 years for back and leg strength peaked between 16:53 h and 18:20 h. the strength have been found to range between 17.9% and 21.1% (Coldwells et al., 1994). there is, however, no consensus on the precise effect of preforming exercise at different types of day and how this may influence metabolism (Gabriel and Zierath, 2017), and this is an area where further research is needed.

1.4.1 Theoretical underpinnings:

Circadian rhythm influences many physiological functions including core body temperature (Hiddinga et al., 1997, Kusumoto et al., 2021), endocrine factors including insulin, cortisol and GH (Gamble et al., 2014, Avram et al., 2005, Kalsbeek et al., 2014). These circadian-controlled processes fundamentally affect exercise response. For example, in healthy people under resting conditions, gluocse tolerance and insulin sensitivity are optimal in the morning (Van Cauter et al., 1997). It has previously been demonstrated that the molecular clock facilitates metabolic homeostasis by regulating insulin sensitivity. For example, a diurnal pattern of glucose tolerance has been observed in humans (Saad et al., 2012, Lee et al., 1992). Additionally, a study has shown that forced desynchronisation induces pre-diabetic conditions in healthy young men (Scheer et al., 2009). Since exercise is known to modify the rhythm of the clock machinery (Gabriel and Zierath, 2019), this suggests that the timing of exercise might be able to be optimised in order to coincide with optimal physiological and molecular responses, thereby enhancing its therapeutic potential.

This theoretical framework has important practical implications. While the current physical activity recommendations identified the frequency, type, intensity and the duration of physical activity (NHS, 2019). However, the optimal time of the day at which to perform exercise is still unknown. This question becomes particularly relevant given that disruption

of the circadian rhythm is linked to the increase of the risk of developing metabolic disease (Vetter et al., 2018, Bescos et al., 2018). The complexity of these interactions is further demonstrated by the fact that eating patterns and other behaviours might significantly affect sleep patterns and circadian rhythm (Manoogian and Panda, 2017). Understanding the diurnal feeding patterns and exercise interventions is important to better under the metabolic regulation (Gabriel and Zierath, 2019). Further research is needed to fully understand the interaction between exercise timing and metabolic benefits.

1.5 Aims and hypotheses

Chapter 2 is entitled “the impact of the time of day on metabolic responses to exercise in adults: A systematic and meta-analysis review” and this study aims to systematically review the literature to investigate whether the time of day at which exercise is performed affects metabolic, glucose and insulin responses to exercise in adults. The In chapter 2 the hypothesis tested was that exercise in the morning would result in improved glucose and insulin responses than when exercise was performed in the afternoon/evening, in adults

Chapter 3 is entitled “the impact of the time of the day on insulin sensitivity in response to a single resistance exercise session in adults: randomised cross-over study” and this study aims to compare the effects of single session of resistance exercise training performed in the morning vs the afternoon on insulin sensitivity. The hypothesis tested in chapter 3 was that a single bout of resistance exercise performed in the morning will elicit greater improvements in insulin sensitivity compared to a single resistance exercise bout performed in the afternoon, in adults.

Chapter 4 is entitled “the impact of the time of day on metabolic responses to resistance exercise in adults with a BMI greater than 23kg/m^2: a randomised controlled trial” and this study has the following aims. 1) to compare the effects of resistance exercise training

performed in the morning vs the evening on insulin sensitivity, 2) to compare the effects of resistance exercise training performed in the morning vs the evening on gains in muscle mass and strength and 3) to compare the acute glucose responses to resistance exercise performed in the morning vs the evening. The hypotheses tested in chapter 4 are that resistance exercise training performed in the morning will result in greater improvements in muscle mass, muscle strength and insulin sensitivity, compared to resistance exercise training performed in the afternoon/evening, in in adults with a BMI greater than 23kg/m^2.

CHAPTER II

2 The impact of the time of day on metabolic responses to exercise in adults: systematic review and meta-analysis

2.1 Abstract

2.1.1 Background

The benefits of regular physical exercise are manifold, and data indicates that these may vary depending on the time of day at which it is performed. To our knowledge, there has been no systematic review which has explored the effect of the time of day at which exercise is performed on glucose/metabolic responses to exercise. Therefore, the aim of the current study is to investigate whether the time of day at which exercise is performed affects metabolic, glucose and insulin responses to exercise in adults.

2.1.2 Methods:

The databases: PubMed, EMBASE, CINAHL, Scopus, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomised controlled (parallel and crossover) trials. Studies were included if the population was aged from 18-65 years, with an intervention of any exercise carried out a specific time of the day and compared to any exercise carried out at a different time of the day. The main outcomes were markers of metabolic control, such as blood glucose and insulin levels.

2.1.3 Results:

From 2458 screened articles, 12 studies were included in the systematic review of which 5 studies were included in the meta-analyses. The meta-analysis compared 24-hour continuous glucose monitoring (CGM) data, between morning and evening exercise, on the day on exercise day was performed (SMD = 0.12 [-0.22 to 0.46] P =0.76) and the day after exercise was performed (SMD = -0.02 [-0.36 to 0.33] P=0.94. Similar findings were observed in the wider systematic review. Overall, several studies exhibited an unclear risk of bias, while other studies demonstrated a low risk of bias.

2.1.4 Conclusions:

The results indicate that there is no clear effect of the time of the day on metabolic responses to exercise. As the data stands performing exercise at any time of day should be the goal of public health strategies. Studies were limited in this area and further work is required to confirm these assertions.

Registration: PROSPERO (ID:CRD42021266494)

Keywords: Adult; Circadian Rhythm; Exercise; Exercise Therapy; Humans; Metabolism; Physiological Phenomena; Public Health; Time Factors

2.2 Introduction:

Regular exercise and physical activity provide a multiplicity of health benefits including improved cardiovascular fitness, enhanced muscular strength, weight management, and enhanced mental well-being (Brown et al., 2020, Sigal et al., 2004b). Notably, exercise has a significant positive impact on metabolic processes and is a key factor in glucose control and, thus, reducing the risk of metabolic disorders such as diabetes (Thyfault and Bergouignan, 2020). This is exemplified by the benefits of acute exercise, which include: increased uptake of glucose by skeletal muscle independent of insulin action (Frampton et al., 2021); enhanced post-exercise insulin sensitivity; and reduced postprandial glucose levels in healthy individuals and in those with impaired glucose tolerance (Bird and Hawley, 2016). Extensive research has analysed the impacts of exercise on glucose control and revealed that aerobic exercise, resistance exercise, and high-intensity interval exercise, can improve glycaemic control and enhance insulin sensitivity, for example, among individuals with diabetes (Sigal et al., 2004b, Frampton et al., 2021). It has been shown that, in people with type 2 diabetes, whole body insulin sensitivity can be improved by just one week of aerobic exercise (Winnick et al., 2008). Collectively, these results, amongst others, concur that regular exercise is an effective strategy for the management and

prevention of metabolic disorders such as diabetes (Myers et al., 2019). In addition, there is emerging data which suggests that the benefits of exercise may vary depending on the time of day at which physical activity is performed.

The circadian rhythm (a 24-hour internal body clock) responds to changes in environmental light and regulates the cycles of alertness and sleepiness. At a cellular level, the majority of cells express clock genes which are part of an autoregulatory, transcription-translation feedback loop (TTFL) that includes transcriptional activators CLOCK and BMAL1(Reddy et al., 2025). Circadian cycles of behaviour and physiology are controlled by the suprachiasmatic nucleus (SCN), located in the hypothalamus, which is the pacemaker for the circadian rhythm. At a physiological level, the circadian rhythm regulates processes including blood pressure control, lipid and carbohydrate metabolism, and feeding behaviours and may interact with exercise responses (Gabriel and Zierath, 2019, Wefers et al., 2018). Whilst there has been some study of how these circadian rhythms interact with metabolic responses to exercises, these have yet to be systematically reviewed. Therefore, the current study aims to systematically review the literature to investigate whether the time of day at which exercise is performed affects metabolic, glucose and insulin responses to exercise in adults.

2.3 Methods:

2.3.1 Registration:

The current study protocol was registered in 2021 with the International Prospective Register of Systematic Reviews (Appendix 2-A) (Bracci et al., 2007), ID:CRD42021266494. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report this systematic review (Appendix 2-B)(Page et al., 2021).

2.3.2 PICOS:

This review included the following, population: adults aged from 18 to 65 years of age; intervention: any exercise carried out a specific time of day, including both acute (i.e. single bout) and longer term (i.e. training) exercise; comparator: any exercise carried out at a different time of day; outcomes: metabolic markers such as blood glucose and insulin levels; and study types: randomised controlled trials, crossover trials.

2.3.3 Inclusion/Exclusion Criteria:

Our analysis was confined to studies published in English language peer-reviewed journals that met the following criteria: (a) an experimental trial involving aerobic or resistance exercise performed in mornings compared with afternoons or evenings (with or without a no-exercise control group); (b) measurement of blood or interstitial glucose or blood insulin; (c) the study involved participants aged 18 to 65 years of age; (d) a randomised control (parallel and crossover) trials were included, studies published as abstracts or conference presentation were included if enough details were available to allow analysis.

2.3.4 Search strategy and study selection:

A search was performed in the following databases: PubMed, EMBASE, CINAHL, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL). And to minimise publication bias and relevant unpublished findings. grey literature (non-commercially published materials including conference abstracts, theses, and institutional reports) was searched using (OpenGrey). The terms circadian rhythm, exercise, glucose and insulin resistance were used and combined with AND & OR. An example of the search strategy is detailed in Appendix 2-C. To reduce the potential for selection bias, each of these studies were independently screened by 2 of the investigators (AD and MT) for inclusion. Any disputes were resolved by discussion with a third reviewer (SRG). Of the studies initially reviewed, 42 were determined to be potentially

relevant to the topic based on information contained in the abstracts. Full texts of these articles were then screened, and 12 studies were regarded as suitable for inclusion based on the criteria outlined (Figure 2-1).

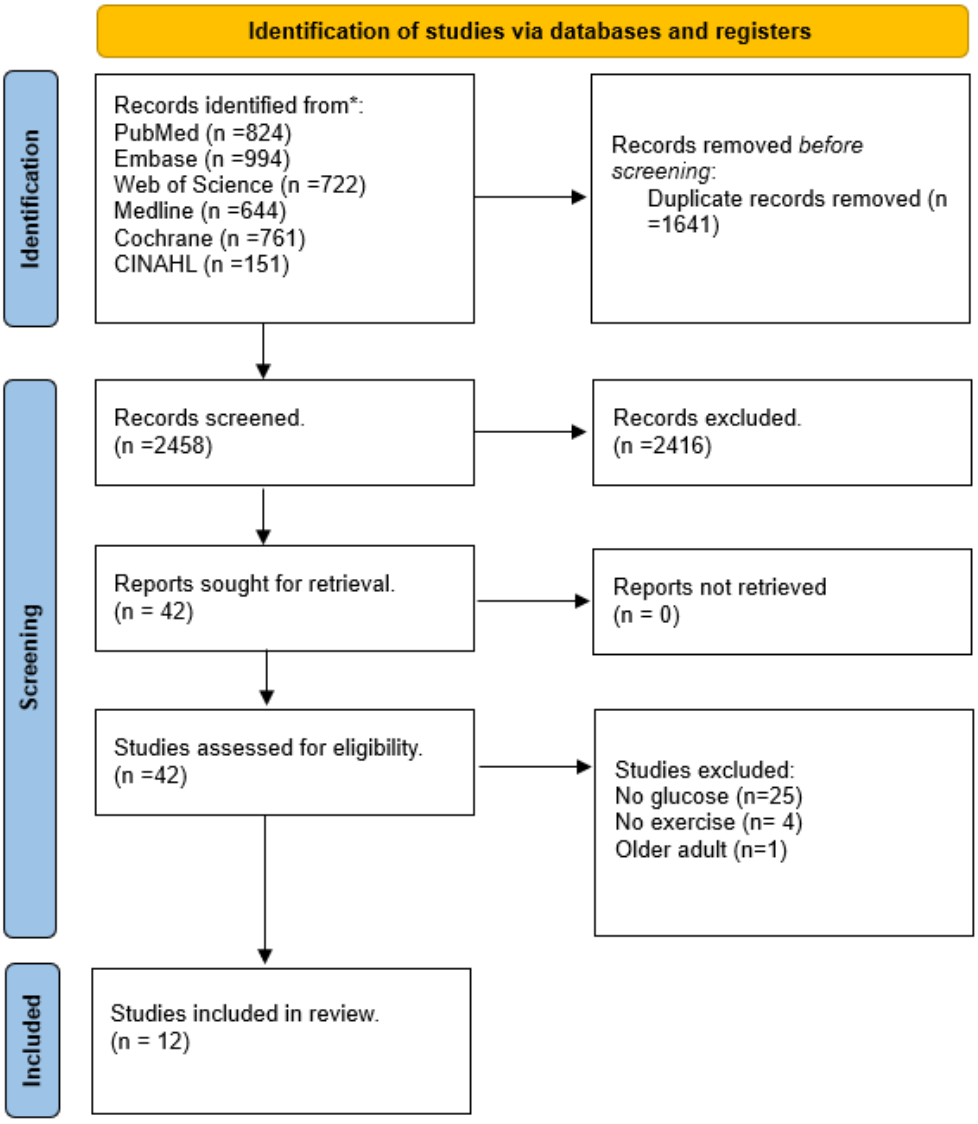


Figure 2-1: Flow diagram illustrating the study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021) guidelines.

2.3.5 Methodological Quality:

The quality of each study in the meta-analysis was independently assessed by 2 of the authors (AD and MT) and agreement was mutually determined for any observed discrepancies. Study quality was evaluated by use of the 11-point Physiotherapy Evidence Database scale, which has been shown to be a valid measure of the methodologic quality of randomised trials and displays acceptable interrater reliability (Moseley et al., 2020). Given that the assessors are rarely blinded, and that is impossible to blind the participants and investigators, in supervised exercise interventions, we elected to remove items 5–7 from the scale, which are specific to blinding. With the removal of these items, the maximum result on the modified PEDro 8-point scale (i.e., items 5-7 are not included in the total score). The qualitative methodology ratings were adjusted similar to that used in previous exercise-related systematic reviews (26) as follows: 6–8 = “excellent”; 5 = “good”; 4 = “moderate”; and 0–3 = “poor.”.

2.3.6 Data extraction and risk of bias assessment

A data extraction form was used in the meta-analysis, and information included bibliometric data, study characteristics (duration, setting, and location), participants information, exercise intervention characteristics (type and modality of exercise, frequency, intensity, and time of day), comparator and outcome (Appendix 2-D). Two authors (AD and MT) extracted the data independently and differences were discussed and resolved with a third reviewer (SRG). Risk of bias was assessed using the Cochrane risk of bias tool for randomised controlled trials. The form evaluates selection bias, performance bias, detection bias, attrition bias and reporting bias. Risk of bias scores were low, high or unclear. Two reviewers (AD and MT) scored this independently and conflicts were resolved by a third reviewer (SRG).

2.3.7 Grade assessment:

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is an approach to evaluate the certainty of evidence in systematic reviews and clinical practice and was applied in the current review.

2.3.8 Meta-analysis:

Due to differences in outcomes used between studies, we chose to meta-analyse five studies who had all measured glucose using CGMs in similar way. The RevMan manger version 5.4 software was used to perform meta-analysis (The Cochrane Collaboration Review Manager, 2020) comparison between the different times of days with data of the days 24-hour period during which exercise was performed and the following day's 24-hour period without exercise. Mean values and SDs were used, when the data were not available, authors were contacted to request the information.

2.4 Results:

2.4.1 Characteristics of the included studies

A total of twelve studies were included, with participants having type 2 diabetes (Four studies), type 1 diabetes (two studies) or no health conditions (six studies). The twelve studies compared morning exercise versus afternoon (n=8) or evening (n=4) exercise, with two studies also having a control group with no exercise. The type of exercise varied across the studies with aerobic exercise (n=6) and resistances exercise (n=2) and one study did not mention what type of exercise they did. The duration of the interventions varied across the studies, ranging from single-session interventions to multi-session interventions lasting 11 days to 12 weeks. Key outcomes assessed in all nine studies included continuous glucose monitoring (CGM) interstitial glucose, and blood glucose and insulin data.

2.4.2 Narrative synthesis:

A total of 12 studies were included with details provided in (Table 4). Savikj in 2019 and recruited 11 men with type 2 diabetes aged between 45-68 years old with a BMI between 23 and 33 kg/m^2. All participants participated in high intensity interval training (HIIT) for 2 weeks in the morning and in the afternoon, in a crossover design, and they found that afternoon exercise was more efficacious than morning exercise in lowering blood glucose (Savikj et al., 2019). 2. Another study was conducted by Munan in 2020, and they recruited 14 participants with type 2 diabetes aged between 30 and 90 years old. Individuals were randomised into morning exercise, afternoon exercise, evening exercise and control, in a crossover design, and they performed a single session with 50 min of aerobic exercise. They found no effect of exercise or time of day on 24-hour glucose data (Munan et al., 2020). 3. Tanaka in 2021 and recruited 11 healthy adults aged between 22 to 30 to do a single session of 1h aerobic exercise, in a crossover design, in the morning, afternoon, or a session with no exercise (control). They found that glucose levels decreased during exercise in the afternoon but not in the morning resulting in less stable glucose fluctuations over 24 hours (Tanaka et al., 2021b). 4. Chiang in 2019, recruited 20 participants aged between 40 to 60 years old with type 2 diabetes. All participant participated aerobic exercise either in the morning, afternoon, or evening, in a prospective longitudinal study, The 12-week study of moderate-intensity exercise demonstrated feasibility and a progressive reduction in blood sugar levels. Interestingly, morning exercise led to a greater decrease in blood sugar compared to afternoon or evening exercise in participants with type 2 diabetes, all while maintaining their current medications (Chiang et al., 2019). 5. Gomez conducted a study in 2015 and recruited 35 patients with type 1 diabetes with median age was 30 years old and BMI of 23.3 kg/m^2. All participants did a total of 2 sessions of aerobic exercise either morning or afternoon, in a crossover design. And they found that exercise in the morning reduces the risk of late-onset hypoglycaemia and improves metabolic control (Gomez et al., 2015).

6. Hobson did a study in 2009, and they recruited 9 individuals aged 22 years old. All individuals did a single session of endurance exercise in both morning and evening. And they found that endurance exercise in the heat was significantly greater in the morning than the evening (Hobson et al., 2009). 7. Toghi-Eshghi in 2019 and recruited 12 participants with type 1 diabetes aged between 18 to 50 years old, all participants did a randomised crossover session, in both morning and in the afternoon. They found that resistance exercises performed early in the morning during fasting are associated with a different post exercise blood glucose response (Toghi-Eshghi and Yardley, 2019). 8. Teo in 2020, and they recruited 40 overweight adults aged between 18 to 65 years old. All participants were randomly allocated into 12 weeks multimodal exercise either morning or in the evening, in a parallel study design, and they found that despite improved glycemic control after 12 weeks of exercise, there were no differences in circadian rhythm between morning and evening exercise (Teo et al., 2020).

9. Moholdt in 2021, they recruited 25 overweight/obese men. All participants were randomised into three groups morning, evening and control group. Exercise was performed on cycle ergometer and they found that an improvement in glycaemic control only occurred (Moholdt et al., 2021b). 10. Weydahl in 1995, and they recruited 20 athletes aged between 18-38 years old to do aerobic exercises. All participants were randomly divided into 2 groups, morning and evening. They found that glucose response was lowest when exercised in the morning compared to afternoon (Weydahl et al., 1995) 11. Scheen in 1998, and they recruited 22 young men. All participants were divided into three groups morning, afternoon, and evening exercise. The training session included 15 min of cycling and 15 min of arm exercise. And they found that there was no relation between time of day and insulin secretion decrease during exercise (Scheen et al., 1998). 12. Ruegemer in 1990, and they recruited 6 aged 30 years old with an insulin dependent diabetes mellitus to do moderate aerobic exercise for four occasions. And they found that there was no significant

change in mean plasma glucose during afternoon exercise, but three out of six patients had mild hypoglycaemia (Ruegemer et al., 1990).

2.4.3 Meta-analysis:

The meta-analysis compared 24-hour continuous glucose monitoring (CGM) data on the day on which exercise was performed and the day after exercise was performed, comparing morning and evening exercise. On exercise days there were no differences in CGM measured glucose between morning and afternoon/evening groups (SMD = 0.12 [-0.22 to 0.46] P =0.76) (Figure 2-2). Similarly on the day after exercise there were no differences in CGM measured glucose between morning and afternoon/evening groups (SMD = -0.02 [-0.36 to 0.33] P =0.94) (Figure 2-3).

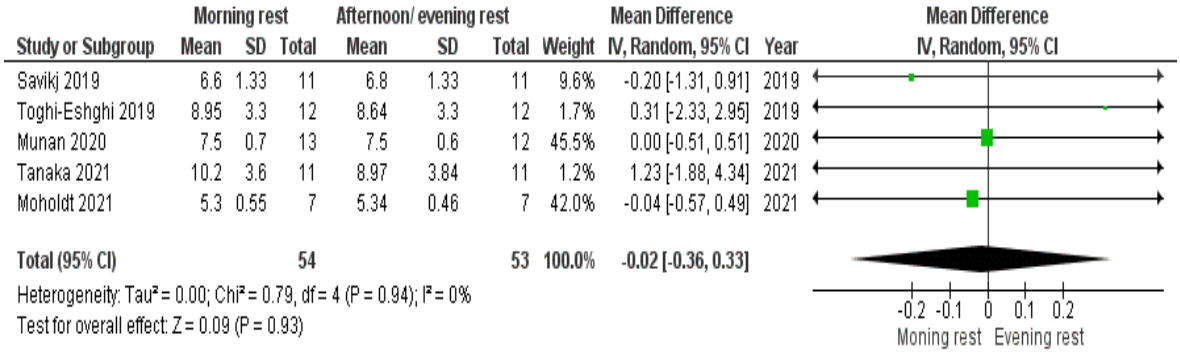


Figure 2-2: Forest plot displaying the Standardized Mean Differences (MD) and 95% confidence intervals (CI) comparing CGM measured glucose on exercise days performed in the morning or the afternoon/evening. The forest plot shows: individual study effects (squares) with horizontal lines representing 95% CIs; study weights (%) indicating relative contribution to the pooled estimate based on inverse variance weighting; the overall pooled effect (diamond); and the vertical line at zero indicating no effect. IV (inverse variance) weighting gives more weight to studies with greater precision (smaller standard errors).

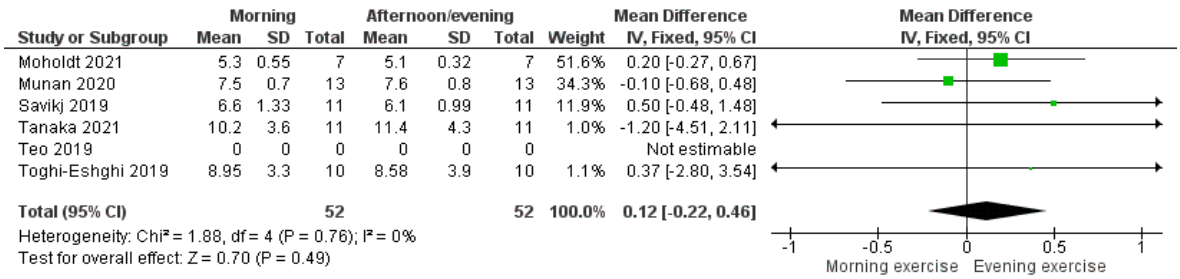


Figure 2-3: Forest plot displaying the Standardized Mean Differences (MD) and 95% confidence intervals (CI) comparing CGM measured glucose on the day after exercise when performed in the morning or afternoon/evening. The forest plot shows: individual study effects (squares) with horizontal lines representing 95% CIs; study weights (%) indicating relative contribution to the pooled estimate based on inverse variance weighting; the overall pooled effect (diamond); and the vertical line at zero indicating no effect. IV (inverse variance) weighting gives more weight to studies with greater precision (smaller standard errors).

2.4.4 Risk of bias:

The results of the risk of the assessment for each study are presented in (Figure 2-4) and (Figure 2-5). Overall, several studies exhibited an unclear risk of bias, while other studies demonstrated a low risk of bias. All studies showed a high risk of bias for participant blinding, as volunteers cannot be blinded to whether they are performing morning versus evening exercise. The search was conducted across multiple databases as well as grey literature to minimise publication bias, which occurs when studies with positive or significant results are more likely to be published than those with negative or non-significant findings.

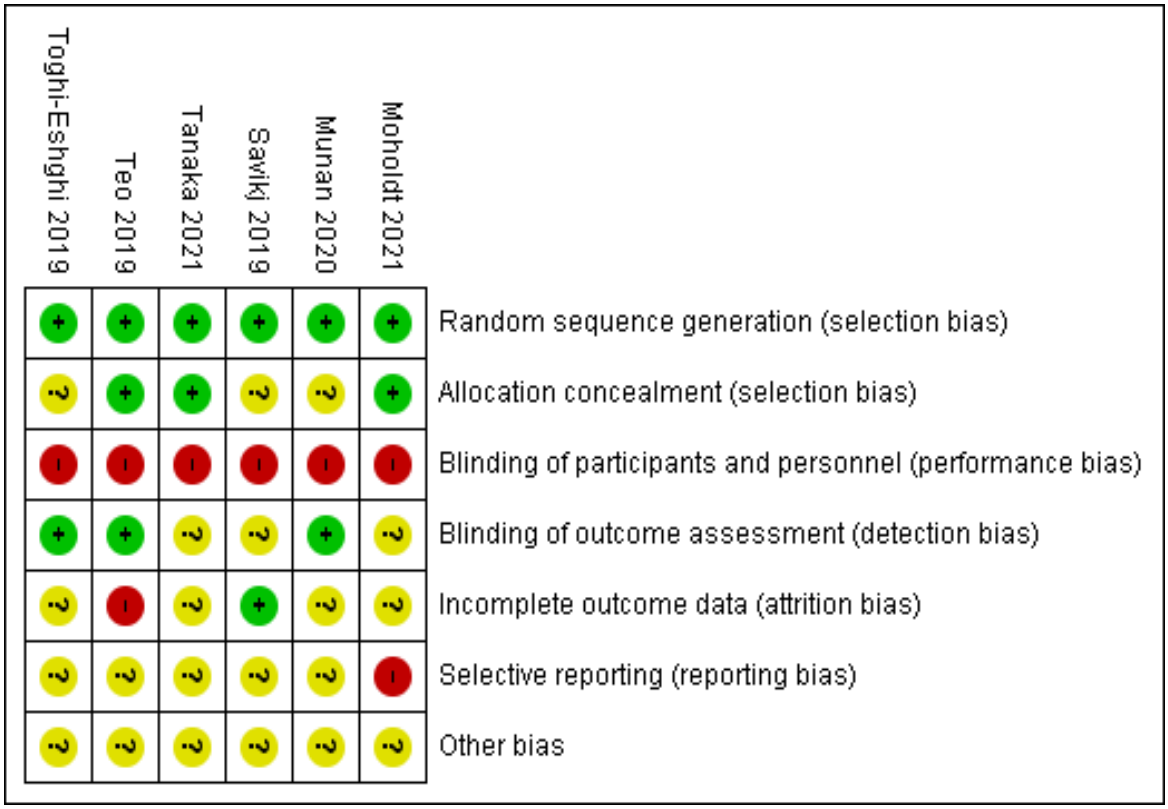


Figure 2-4: Risk of bias summary: review authors' judgements about each risk of bias item for each included study, the red dots represent high risk and the green dots a low risk and unclear represented with no dots.

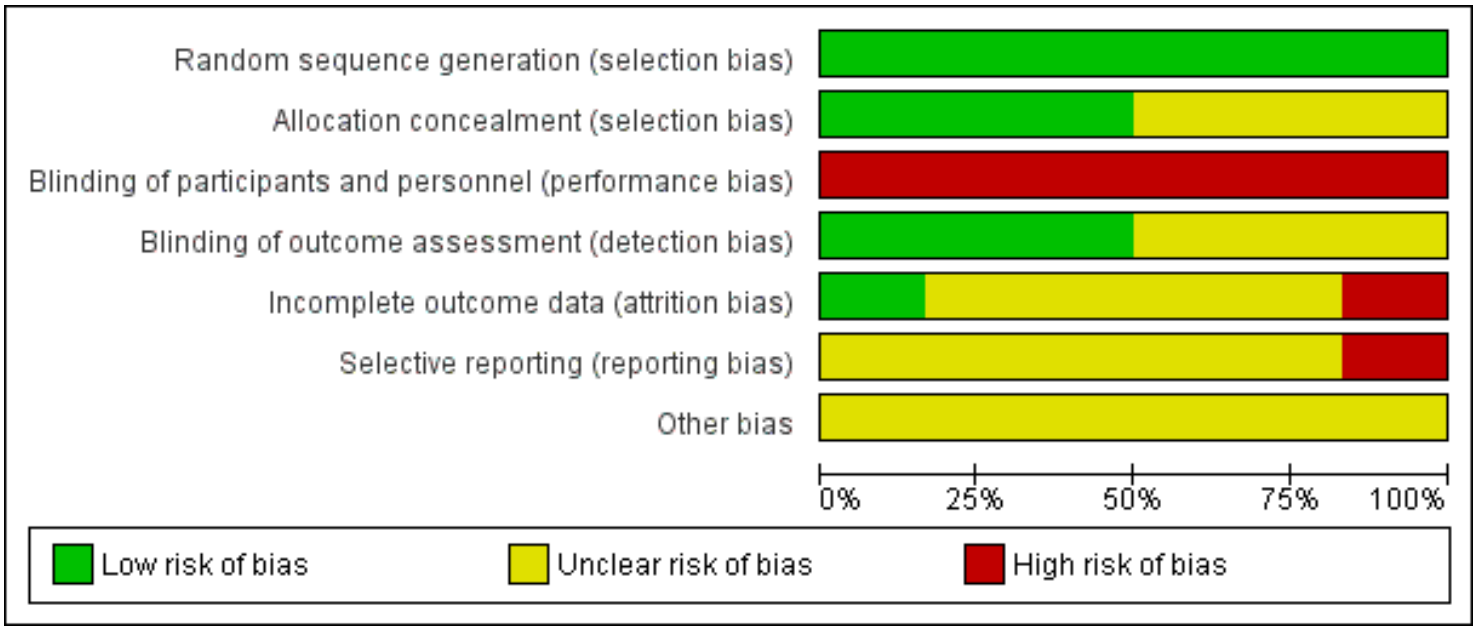


Figure 2-5: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

2.4.5 PEDro scale:

The overall observed across all studies was good and it ranged from 4-8. According to the individual studies, the main reasons why are studies are rated low was because concealed allocation, baseline comparability, adequate follow-up, and intention-to-treat analysis (Table 2-1).

Table 2-1: PEDro 8-point scale (i.e., items 5-7 are not included in the total score) as follows: 6–8 = "excellent"; 5 = "good"; 4 = "moderate"; and 0–3 = "poor.

	Savikj et al, 2019	Munan et al, 2020	Tanaka et al, 2021	Toghi-Eshgi et al, 2019	Moholdt et al, 2021
1.Eligibility criteria specified	1	1	1	1	1
2.Random allocation	1	1	1	1	1
3.Concealed allocation	0	0	1	1	1
4.Baseline comparability	0	0	0	0	0
5.Adequate follow-up	0	0	0	0	0
6.Intention-to-treat analysis	0	0	0	0	0
7.Between-group comparisons	1	1	1	1	1
8. Point measures and variability data	1	1	1	1	1
Score	4/8	4/8	5/8	5/8	5/8
Quality	**Good**	**Good**	**Good**	**Good**	**Good**

2.4.6 Grade assessment:

(**Error! Reference source not found.**) presents the results of GRADE assessment for the comparison of CGM measured glucose on exercise days comparing between morning

exercise and evening exercise. Based on the evaluation, the certainty of evidence in this comparison was categorized as a low. Similarly, (Table 2-3) displays the GRADE assessment outcomes for the comparison of CGM measured glucose on the days after exercise comparing between morning exercise and afternoon/evening exercise and the certainty of evidence was also a low.

Table 2-2: GRADE Assessment for a comparison between morning exercise vs. afternoon/ evening exercise for continues glucose monitoring (CGMs) for five studies included in the meta-analysis. CI: confidence interval; MD: mean difference; a. all studies have high performance bias while few studies have an incomplete outcome data; b. All studies have different protocols which includes different population such as (type 1 diabetes, type 2 diabetes, and healthy adults

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morning exercise	evening exercise	Relative (95% CI)	Absolute (95% CI)		
CGM concentration												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	52	52	-	MD **0.12 SD more** (0.22 fewer to 0.46 more)	⊕⊕◯◯ Low	IMPORTANT

Table 2-3: GRADE Assessment for a comparison between morning rest vs. afternoon/ evening rest for continues glucose monitoring (CGMs) for five studies included in the meta-analysis. CI: confidence interval; MD: mean difference; a. all studies have high performance bias while few studies have an incomplete outcome data; b. All studies have different protocols which includes different population such as (type 1 diabetes, type 2 diabetes, and healthy adults).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Morning Rest	Evening Rest	Relative (95% CI)	Absolute (95% CI)		
CGM concentration												
5	randomised trials	serious[a]	not serious	not serious	serious[a]	none	52	52	-	MD **0.02 SD fewer** (0.36 fewer to 0.33 more)	⊕⊕◯◯ Low	IMPORTANT

2.5 Discussion:

This systematic review and meta-analysis aimed to evaluate the impact of exercise timing on metabolic responses to exercise, considering both acute and more chronic studies. However, it is important to acknowledge that the evidence is limited by the small sample size included in this review. Giving these limitations, the narrative analysis suggests there is currently no evidence that the time of day at which exercise is performed affects metabolic response. Additionally, our quantitative analysis found that there was no significant difference in 24-hour CGM measured glucose levels, on the day or the day following the performance of exercise either in the morning and afternoon/evening.

The interplay between circadian rhythms and physical activity is a complex area of research, while the interaction between the molecular clock within skeletal muscle and cellular physiology is established (Gabriel and Zierath, 2019). Although our findings did not reveal a significant effect of the time of exercise on metabolic responses, previous work had suggested that circadian rhythms and diurnal exercise responses are influenced by the physiological regulation of glucose and triglycerides, which are controlled by the intrinsic clock (Gabriel et al., 2018). Studies using tissue specific *Bmal1*, a clock gene ablation models in mice have been used to demonstrate this concept with liver-specific ablation of *Bmal1* resulting in hypoglycemia during the fasting phase (Lamia et al., 2008). This highlights its importance in regulating blood glucose levels during this period. Although these rodent studies provide an important mechanistic insights, the focus of this review is on human research. Likewise, loss of *Bmal1* results in impaired glucose uptake with a concomitant decrease in muscle glucose in adults (Harfmann et al., 2016). This observation underlines the significance of muscle clocks in these processes. The mechanisms by which clock genes regulate human physiology remain unknown. Several factors, including sleep (Johnson et al., 2008, Yardley et al., 2013), food intake (Johnston,

2014), and core body temperature (Hobson et al., 2009), are demonstrably influenced by the time of day. It is important to note that not all studies included in this review controlled for these confounding factors and understanding how these factors interact with exercise timing can provide valuable insights into optimizing exercise strategies for improved health outcomes. On top of this, in humans, glucose tolerance tends to be higher in the morning than in the evening (Johnston, 2014). these findings highlight the influence of time of day on glucose metabolism. Additionally, exercise capacity is known to vary throughout the day (Aloui et al., 2017). Together this indicated that there may be an interaction between time of day exercise is performed and glucose metabolism. However, the current findings indicate that metabolic responses to exercise are not influenced by the time of day at which it is performed, although data was limited.

Interestingly, a meta-analysis found a significant difference related to power output in the jump height and handgrip strength in the late afternoon compared to the morning (Knaier et al., 2022). However, while they included 29 studies in this review, meta-analyses of small heterogeneous studies may not improve the reliability of conclusions. Unlike said exploratory meta-analysis, this review indicates that exercise timing may not significantly impact metabolic responses. In this study there were five studies included in meta-analysis. However, a clear limitation is the type of exercise across all studies. The included studies have different approaches, including high intensity interval (HIIT) exercise (Savikj et al., 2019), aerobic exercise (Munan et al., 2020) endurance exercise (Tanaka et al., 2021a) and resistance exercise (Toghi-Eshghi and Yardley, 2019). These forms of exercise target different muscle groups and different aspects of metabolism, i.e. anaerobic vs aerobic metabolism, which could potentially influence metabolic responses at different times of day. In addition, the exploratory meta-analysis provided only five studies, which were conducted with a total of 52 participants; the majority of which were men. Therefore, these findings should not be generalised to females. The studies involved a mix of young

healthy adults or people with diabetes and so there is considerable metabolic heterogeneity in the samples included, which would undoubtedly influence our findings. Larger studies within each different population are needed.

From a methodological perspective, this review exhibits numerous strengths: the review was registered in PROSPERO; conducted per PRISMA guidelines; and carried out a robust systematic search of the relevant databases. As mentioned, research on the effects of exercise timing on blood glucose control would be strengthened by additional high-quality studies with an increased sample size were conducted. Future investigations should explore the effects of distinct types of exercise on metabolic responses (including resistance exercises, with both acute and longer durations). This would provide valuable insights into how exercise timing interacts with varying exercise to regulate blood glucose. An understanding of how exercise types affect timing could result in bespoke exercise recommendations.

In conclusion, this systematic review and meta-analysis did not find a significant effect of exercise timing on metabolic responses to exercise. Due to the limited number of included studies and the heterogeneity between studies, interpretation of these findings should be approached with caution. Even though exercise timing had no influence on 24-hour blood glucose control in our study, it is essential to stress the established benefits of exercise for metabolic health.

Table 4: Summary of Included Studies that investing the effect of the exercise on the time of the day.

Author	Intervention	Comparison	Duration	Population	Outcome	Main findings
(Savikj et al., 2019)	Morning exercise	Afternoon exercise	2 weeks	T2D (11 men), Age (60 ± 2), BMI (27.5 ± 0.6)	-Glucose (mmol/l), -Insulin (pmol/l), -HbA1c (mmol/mol), -HbA1c (%) -Total cholesterol, (mmol/l) -HDL-cholesterol, (mmol/l) -LDL-cholesterol, (mmol/l) Triacylglycerol (mmol/l), -PTH (pmol/l), -TSH (mU/l), -T4 (pmol/l), -T3 (pmol/l)	Afternoon HIIT was more efficacious than morning HIIT at improving blood glucose in men with type 2 diabetes.
(Munan et al., 2020)	Morning exercise (fasting)	Afternoon exercise	12 days	T2D 14 (8 men, 6 women), Age	-Mean 24-hour glucose,	50mins of walking at 3 different times of

				(Men 65± 9.0),(Women	-24-hour MAGE, -Mean 2-hour postprandial -Time >10 mmol/L (min) -Fasting glucose	day and at different timing in relation to meals did not lower 24-hour glucose concentrations in people with T2D.
(Tanaka et al., 2021a)	Morning exercise	Afternoon exercise + control	Single session	Young men (11), Age (24.5 ± 2.8)	Glycaemic variability over 24 h (24h SD), J-index, mean amplitude of glucose excursions (MAGE), continuous overall net glycaemic action (CONGA), and detrended fluctuation analysis(Goldfarb et al.).	Glucose levels were slightly less stable when the exercise was performed in the afternoon, with higher insulin levels than morning.
(Chiang et al., 2019)	Morning exercise	Afternoon exercise + evening exercise	12 weeks	T2D, 20 (men 13, women 7), Age men (47.8 ±3.7), women	-Blood glucose, BEBG=before exercise blood glucose, EIGR=exercise induced blood glucose	Time of day for exercise, baseline VO2max, and baseline metabolic control may

					response, PEBG=post exercise blood glucose. VO2max, HgbA1c	influence the impact of exercise for individuals with T2DM.
Gomez et al., 2015)	Morning exercise	Afternoon exercise	2 sessions (morning, afternoon)	T1D (male 35), Age (30.31 ± 12.66)	-SMBG, self-monitored blood glucose, rate of hypoglycaemic episodes during exercise	Exercise in the morning confers a lower risk of postexercise hypoglycaemia than does afternoon exercise.
(Hobson et al., 2009)	Morning exercise	Afternoon exercise	Single exercise	Male (9), Age (24 ± 2),	-$VO_{2peak,}$ thermoregulatory measures, Changes in plasma volume, Sodium, Potassium, Chloride, Blood glucose	Endurance exercise capacity in the heat was significantly greater in the morning
(Toghi-Eshghi and Yardley, 2019)	Morning exercise	Afternoon exercise	Single exercise	12 participants with type 1 diabetes mellitus [nine females; aged 31 ±	-6-h Mean glucose mmol/L, 6-h MAG, mmol/L, Nocturnal mean glucose, mmol/L,	Morning resistance exercise was associated with distinctly different blood

				8.9 years; diabetes duration, 19.1 ± 8.3 years	Nocturnal MAG, hyperglycaemia, VO_{2max} ,HbA1c	glucose responses and postexercise profiles
(Teo et al., 2020)	Morning exercise	Evening exercise	12 weeks	Forty sedentary, overweight adults (mean ± SD, age = 51 ± 13 yr.; body mass index = 30.9 ± 4.2 $kg \cdot m^{-2}$; women, n = 23) with and without (n = 20) T2D	-VO_{2peak}, HbA1c (%), Insulin resistance (HOMA2-IR), peripheral skin temperature, Changes in FG and PPG and insulin responses, one-repetition maximums (1RM).	Twelve weeks of multimodal exercise training improved glycaemic control and postprandial glycaemic responses in overweight non-T2D and T2D individuals.
(Mohol dt et al., 2021b)	Morning exercise	Evening exercise + control	11 days	Twenty-five participants were randomised (morning exercise n = 9; evening exercise n =8; no exercise n =8), age 30–45 years,	-Peak oxygen uptake (VO_{2peak}) and PPO, continuous glucose monitor (CGM), Insulin (pmol/l), HOMA-IR, Cholesterol (mmol/l), HDL-cholesterol	Improvements in glycaemic control and partial reversal of HFD-induced changes were only observed in the evening.

				BMI 27.0–35.0 kg/m^2	(mmol/l), LDL-cholesterol (mmol/l), Triacylglycerol (mmol/l)	
(Weydahl et al., 1995)	Morning exercise (11:30)	Evening exercise (16:30)	2 sessions (December and April)	20 (12 men, 8 women), Age (18-38), (23.5 ± 4.7)	- VO_{2max}, Blood glucose concentration (fingertip)	Exercise in the morning produced the smallest glucose response for both sexes and faster recovery compared with exercise in the afternoon.
(Scheen et al., 1998)	Morning exercise	Afternoon exercise + midnight exercise	Single session for 3h of exercise	Twenty-two normal young men.	-Body temperature, plasma glucose, insulin secretion rates (ISR), and plasma cortisol, growth hormone (GH) and thyrotropin (TSH).	The results demonstrate the existence of circadian variations in neuroendocrine and metabolic responses to exercise.
(Ruegemer et	Morning exercise	Evening exercise	30 min of exercise	6 insulin-dependent diabetes mellitus	-$Vo_{2max,}$ plasma glucose, lactate,	Mean plasma glucose did not change

al., 1990)				(IDDM) patients	acetoacetate, (3-hydroxybutyrate, free fatty acids, human growth hormone, cortisol, glucagon, free insulin, epinephrine, and norepinephrine	during afternoon exercise

CHAPTER III

3 The impact of the time of the day on insulin sensitivity in response to a single resistance exercise session in adults: a randomised cross-over study

3.1 Abstract

3.1.1 Background

Studies have shown that in healthy individuals, insulin sensitivity is greater in the morning than in the evening and this may have interactions with exercise relevant for health. However, little is known about the acute effects of resistance exercise in healthy population, with measures of glucose and insulin responses to an oral glucose load unknown.

3.1.2 Aim:

This study aim is to determine whether the time of the day has an effect on insulin sensitivity in response to a single resistance exercise session in adults.

3.1.3 Methods:

Six participants (2 males, 4 females: age 25.3 ± 3.5 years old) who met the inclusion criteria were recruited. Participants then completed 4 further study visits with the order randomised in blocks (block 1: morning exercise (8:00-10am) then morning rest at the same time as exercise session, block 2: evening exercise (4:00-8:00pm) then evening rest at same time as exercise session. 2 hours after completion of the intervention we measured insulin sensitivity via oral glucose tolerance test (OGTT).

3.1.4 Results:

Two-way repeated measures ANOVA showed no significant effects of time, group, or time*group interactions for glucose area under the curve (AUC) ($p=0.586$, $p=0.720$, $p=0.511$), insulin AUC ($p=0.735$, $p=0.663$, $p=0.973$), or insulin sensitivity ($p=0.134$, $p=0.780$, $p=0.250$).

3.1.5 Conclusion:

The findings of this pilot study indicate that the time of day at which a single session of resistance exercise is performed has no effect on insulin sensitivity, although the study has clear limitations. However, this study provides novel insight into the acute effect of resistance exercise timing on insulin sensitivity and highlights important methodological considerations for future research.

3.2 Introduction:

Insulin resistance occurs when the ability of insulin to stimulate glucose uptake into tissues such as liver, adipose tissue, and muscle is attenuated (Czech, 2017). Whilst this is commonly associated with excess body weight, this is not always the case, with for example a high liver fat content, in the absence of obesity, linked to insulin resistance (Hazlehurst et al., 2016, Bays et al., 2004). The prevalence of insulin resistance, in the USA is 20.8 to 40%, varying by age, while in Italy 22.3% of adult men and 27.2% of adult women are insulin resistant (Ford et al., 2002, Magi et al., 2005). However, comprehensive prevalence data is only available for a limited number of countries such as Italy and the USA, with surprisingly limited data available for other nations. Importantly, insulin resistance increases the risk of developing conditions such as type 2 diabetes, often preceding development by 10 to 15 years (Freeman et al., 2025). Previous studies have shown that people with type 2 diabetes have lower muscle strength compared to healthy adults (Sayer et al., 2005, Cetinus et al., 2005) and it is associated with physical inactivity (Biswas et al., 2015, Brocklebank et al., 2015).

Regular exercise is a powerful strategy for the treatment and prevention of metabolic disease (Blair et al., 1989) with previous studies demonstrating that this improves insulin sensitivity over time (Brouwers et al., 2016, Phielix et al., 2012). In particular, there is a wealth of evidence that regular aerobic exercise is valuable first line treatment to improve insulin sensitivity and reduce the risk of diabetes (Conn et al., 2014). Furthermore, studies have shown that acute responses to exercise occur in distinct phases. Elevated insulin-independent glucose uptake is observed 2 to 3 hours after exercise, whereas increased muscle and whole body insulin sensitivity is detectable 1 to 4 hours after exercise and is persistent for 24 to 48 hours after exercise (Arias et al., 2007, Cartee and Holloszy, 1990, Koopman et al., 2005, Mikines et al., 1988, Perseghin et al., 1996, Cartee, 2015). Whilst many benefits of exercise are due to the associated chronic adaptation, there are clear acute

effects of exercise which are important for its health benefits. Previous studies have shown that a single bout of aerobic exercise results in an increase in insulin sensitivity in untrained adults (Young et al., 1989). Furthermore, following a single bout of aerobic exercise improves insulin sensitivity by more than 50% for up to 72 hours after exercise (Roberts et al., 2013, Rynders et al., 2014).

While the acute effects of aerobic exercise on insulin sensitivity are well documented, less is known about the acute effects of resistance exercise on insulin sensitivity. Although, there are some studies that report a decline in blood glucose levels after acute resistance exercise (Toghi-Eshghi and Yardley, 2019, Yardley et al., 2013) these studies were relatively small and restricted to people with type 1 diabetes. Less is known about the acute effects of resistance exercise in healthy population, with measures of glucose and insulin responses to an oral glucose load unknown.

On top of this, the time at which exercise is performed may modulate metabolic responses, as it has been demonstrated that insulin sensitivity of healthy humans varies throughout the day (Van Cauter et al., 1991, Kalsbeek et al., 2014) with higher insulin-stimulated glucose uptake in the morning compared to the evening (Verrillo et al., 1989). There are very few studies which have investigated the effects of timing of exercise, particularly resistance exercise, on its acute effects on insulin sensitivity, with mixed responses (Dighriri et al., 2024). Therefore, this study aim is to determine whether the time of the day has an effect on the acute insulin sensitivity in response to a single resistance exercise session in adults.

3.3 Methodology:

3.3.1 Participants:

Participants were recruited through flyers and social media posts (Appendix 3-AE). Inclusion criteria were: age between 18-50 years old and body mass index (BMI) between

20 kg/m² - 40 kg/m². Exclusion criteria were: unable to exercise, or if they (I) had undergone surgery for weight loss; (ii) had prior history of heart, lung, cancer, kidney, endocrine, or liver disease (Appendix 3-BF). The study was approved by the ethical review committee of the College of Medical Veterinary and Life Sciences at the University of Glasgow (No. 200220303) and all participants provided written informed consent, with the study adhering to the guidelines of the Declaration of Helsinki (Appendix 3-CG) & (Appendix 3-DH).

The current study is a pilot study, and was aim to recruit 10 participants, primarily as this is a feasible number to complete during the timeframe of this PhD. However, recruitment challenges resulted in finishing the study with six participants. As result this represents a significant limitation and therefore the result should be interpreted cautiously as preliminary findings.

3.3.2 Study Design:

Eligibility was confirmed during an initial visit, where height, weight and BMI were also measured. Participants then completed 4 further study visits with the order randomised in blocks (block 1: morning exercise then morning rest, block 2: evening exercise then evening rest). The four study visits were 1) A session of resistance exercise in the morning (8:00-10:00am) and oral glucose tolerance test (OGTT) 2 hours after completion of the exercise. 2) An OGTT at the same time of the day as in 1). 3) A session of resistance exercise in the evening (2:00-4:00pm) and OGTT 2 hours completed after completion of the exercise. 4) An OGTT at the same time of the day as in 3). The study flow chart, including recruitment, randomisation, is illustrated in (**Error! Reference source not found.**).

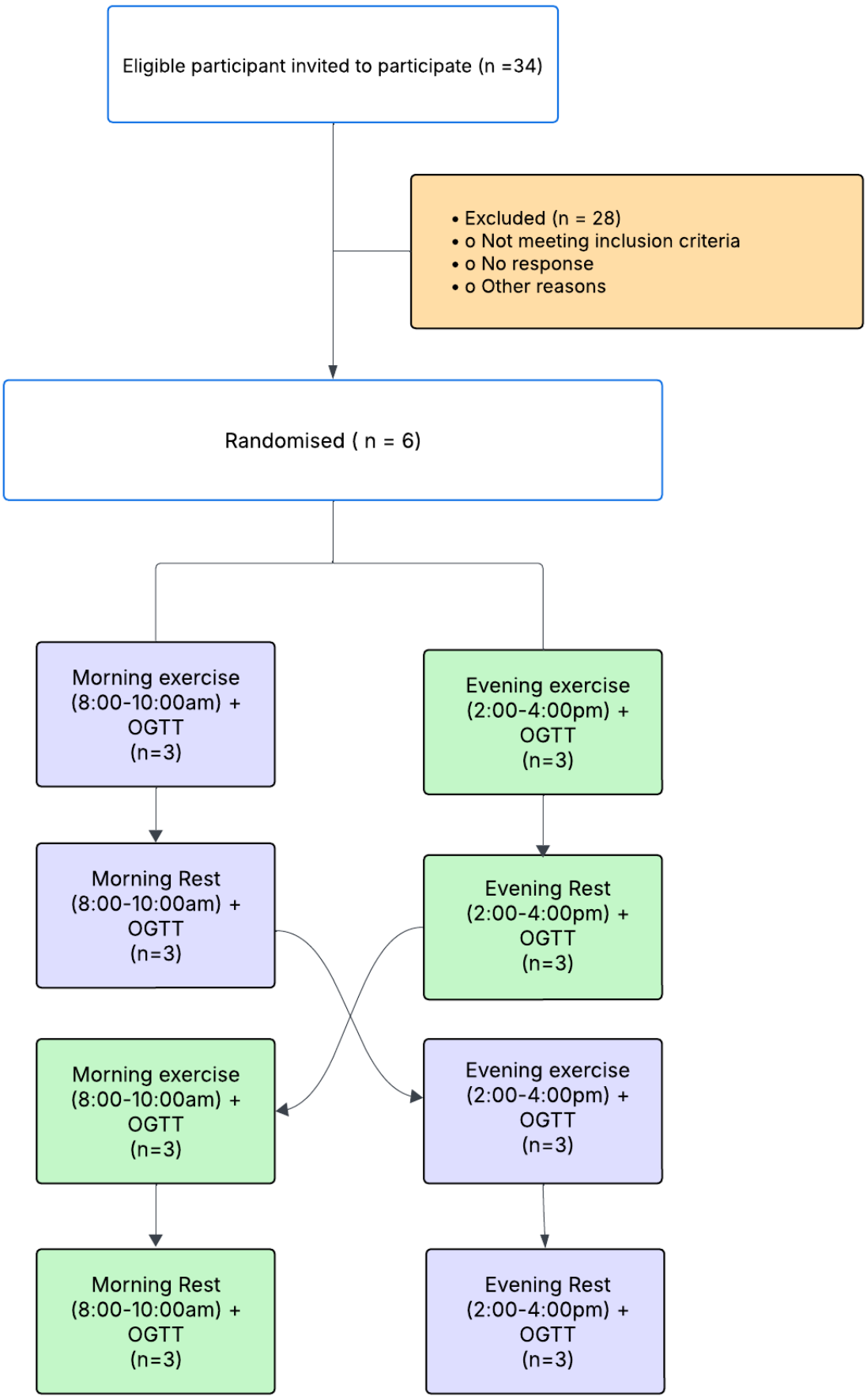


Figure 3-1: Flow diagram of participant recruitment, randomisation, and the study visits. Oral glucose tolerance test (OGTT)

3.3.3 Exercise:

Exercise consisted of 5 sets of 8 exercises to volitional failure at a load of 80% of 1RM. Prior to the experimental sessions, participants were familiarised with each resistance exercise by starting with light weights and progressively increasing the load until failure, to determine their 1RM. During the actual experimental sessions, participants performed the exercises at the predetermined 80% of their established 1RM. All exercise sessions were supervised by a researcher and the following exercises were performed: Bench press, overhead press, biceps curl, late pull down, leg press, squat, leg extension, leg curl and calf raise. Smith machine was used for bench press, overhead press, squat and calf raises, while biceps curl, lit-pull down, leg extension and leg curl were done via pully. All participants successfully completed all exercises across both experimental sessions with no reported injuries or adverse events.

3.3.4 Outcome measurements:

Insulin sensitivity (oral glucose tolerance test) - OGTT: A cannula was inserted into an antecubital vein and a resting blood sample collected. Participants consumed 75 g of glucose made up to 300 ml with water, and further blood samples were collected after 30-, 60-, 90- and 120-min. Blood samples were analysed for glucose and insulin levels in our clinical biochemistry laboratory.

3.4 Data and Statistical analysis:

Glucose and insulin area under the curve was calculated during the OGTT using the trapezoid rule. On top of this glucose and insulin data were also used to estimate insulin sensitivity via Matsuda index (Matsuda and DeFronzo, 1999) as follows:

$$Insulin\ sensitivity = \frac{10000}{\sqrt{(FPG * FPI) * (Mean\ OGTT\ glucose * mean\ OGTT\ insulin)}}$$

A two-way (group*time) repeated measures analysis of variance (ANOVA) was conducted to compare data by group (exercise, rest) and time (morning, evening). A p-value of < 0.05 being used to determine statistical significance. Data are presented as mean ± standard deviation (SD). Statistical significance was set at a P=≤0.05.

3.5 Results:

3.5.1 Participants recruitment and characteristic:

Six participants completed all study visits (2 males, 4 females: age 25.3 ± 3.5 years old) met the inclusion criteria and were randomised into either morning exercise or evening exercise (Table 5). It is important to note that in this analysis the mean was combined for both men and women, which increases the statistical power but may mask sex-specific differences in circadian responses to exercise. However, with only 6 participants it would be challenging to conduct separate analyses for each sex, which would lack sufficient power to detect meaningful differences.

Table 5: Baseline characteristics of the participants. Body Mass index (BMI). Data are mean ± SD

Study characteristics	
Variable (n=6)	Baseline data
Male/ Female	2/4
Age (years)	25.3 ± 3.5
Height (cm)	165.5 ± 5.4
Weight (kg)	65.5 ± 6.1
BMI (kg/m^2)	24.3 ± 2.1

3.5.2 Metabolic data:

Glucose and insulin AUC, and insulin sensitivity, data are presented in (Table 6). The two-way repeated measures ANOVA revealed no significant effect of time (p=0.586), group (p=0.720) or time*group interactions (p=0.511) for glucose area under the curve. Similarly, analysis of insulin area under the curve revealed no significant effect of time (p=0.735), group (p=0.663) or time*group interaction (p=0.973). Finally, a two-way repeated measures ANOVA revealed no significant effect of time (p=0.134), group (p=0.780) or time*group interactions (p=0.250) for insulin sensitivity. The plasma glucose and insulin responses during the OGTT are shown in (**Error! Reference source not found.**).

Table 6: Table 6 shows glucose and insulin area under the curve (AUC) and insulin sensitivity index (ISI) values comparing no exercise versus exercise conditions in the morning (AM) and evening (PM). The change values represent the difference between exercise and no-exercise conditions, with 95% confidence intervals indicating the precision of these estimates.

	AM (n =6)		**Change (95% CI)**	**PM (n=6)**		**Change (95% CI)**
	No Exercise	**Exercise**		**No Exercise**	**Exercise**	
Glucose AUC	4.97 ± 0.73	5.28 ± 1.22	0.32 (-0.72, 1.35)	5.28 ± 1.07	5.23 ± 0.83	-0.05 (-0.76,0.66)
Insulin AUC	34.13 ± 17.89	32.87 ± 16.08	-1.27 (-16.80, 14.27)	38.37 ± 35.08	37.32 ± 36.5	-1.05 (-5.37, 3.27)
ISI (mg l^2 $mmol^{-1}$ mU^{-1} min^{-1})	136.75 ± 55.89	169.35 ± 103.63	32.6 (-40.43, 105.63)	102.83 ± 62.70	163.32 ± 76.20	60.5(-80.64, -201.14)

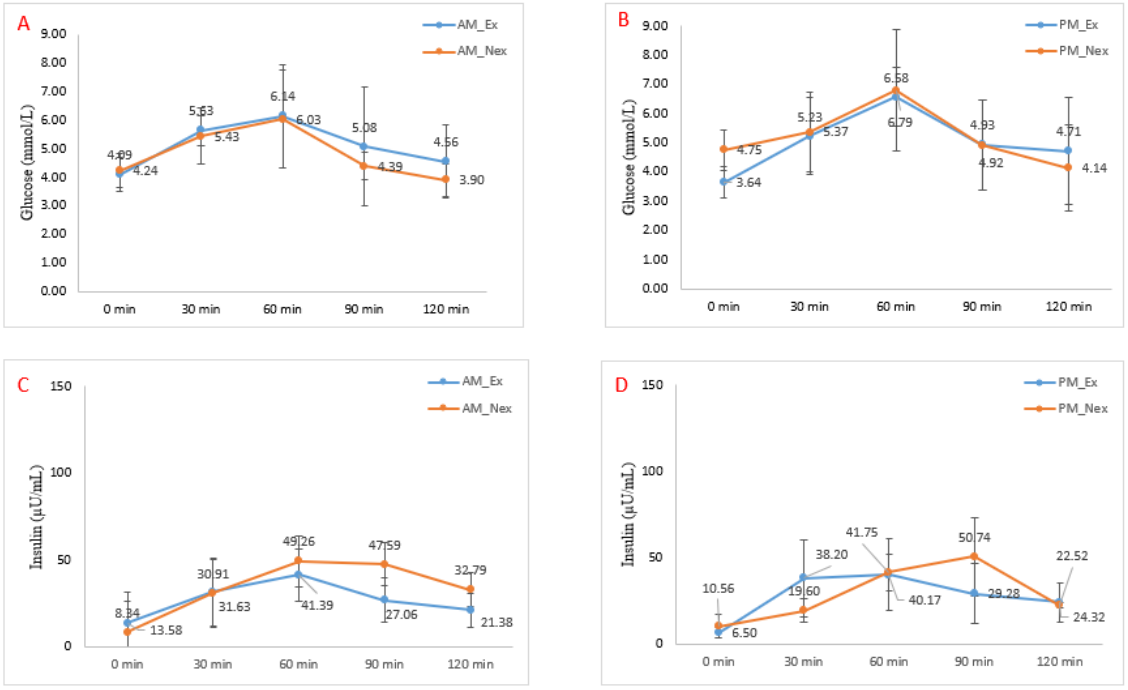


Figure 3-2: Plasma glucose and insulin responses during oral glucose tolerance tests (OGTT). (A) Morning glucose responses, (B) Evening glucose responses, (C) Morning insulin responses, and (D) Evening insulin responses. Data shown for exercise (Ex) and no exercise (NEx) conditions in morning (AM) and evening (PM) trials. Values are presented as mean ± SD.

3.6 Discussion:

The current study investigated whether the time of the day at which exercise is performed has an effect on insulin sensitivity in response to a single bout of resistance exercise in healthy adults. The findings indicate that a single session of resistance exercise has little effect on insulin sensitivity in healthy young adults, with no differences if this was performed in the morning or evening. The current study is, however, not without limitations and so further work is required to confirm these findings. One of the main limitations in the current study is that the small sample size (n=6) resulted in wide confidence intervals and limited statistical power to detect meaningful differences.

The findings from the current study showing little effect on insulin sensitivity contrast with previous research examining the acute exercise responses. For example, Koopman et al

(2005) found that a single session of resistance exercise improved insulin sensitivity 24 hours after exercise in healthy young men (Koopman et al., 2005). It is important to note that the differing results might be explained by the methodological variations between the two studies. In the current study insulin sensitivity was measured 2 hours post-exercise, whereas Koopman et al measured this 24 hours post-exercise. Additionally, Koopman et al included only men (n=12) while the current study included both and women (n=6). Lastly, their study performed resistance exercises at 75% of 1RM, while the current study used 80% of 1RM. This is considered unlikely, as the effects of resistance exercise on insulin sensitivity can be seen immediately post-exercise (Howlett et al., 2007). Further studies, have also confirmed the acute effects of resistance exercise on insulin sensitivity. (Wojtaszewski et al., 2000, Koopman et al., 2005, Howlett et al., 2007, Black et al., 2010a). For example, studies reported in one legged resistance exercise insulin more rapidly activated gluocse uptake by two to four-fold higher compared to with resting leg in healthy men (Wojtaszewski et al., 2000). It is contended that the lack of effect of resistance exercise seen in the current study is most likely due to a lack of statistical power due to the small sample size, a suggestion supported by the magnitude of effect of exercise on insulin sensitivity seen in the current study, which although not significant, is in the order of approximately 20% which is similar to that seen in other exercise studies (Richter et al., 1989, Magkos et al., 2008).

As there was no clear effect of resistance exercise observed in the current study it is perhaps no surprising that no effect of time of day was observed, and again it is likely the study was underpowered in this regard. This aligns with previous research indicating that there is no clear effect of the time of the day on metabolic responses to exercise (Dighriri et al., 2024). It is important to note that the majority of studies examining an acute exercise timing have primarily focused on glucose, rather than insulin, responses with insulin more

informative in healthy populations where blood glucose levels are still tightly regulated. There are some differences when comparing the current data to other research in this field.

Tanaka et al (2021) found that a single bout of exercise on a cycle ergometer, in the afternoon resulted in lower 24 h glucose levels compared to when performed in the morning, in healthy young adults (Tanaka et al., 2021b). While the current study and the work of Tanaka and colleagues both examined healthy young adults, the contrasting results might be explained due to the variation in the exercise type. Specifically, their study used aerobic exercise at 60% of VO2max and measured glucose levels via continuous glucose monitoring, with no measure of insulin levels. The current study employed resistance exercise and measured insulin sensitivity through glucose and insulin responses to an oral glucose tolerance test. Whilst the data on acute effect of resistance exercise to insulin sensitivity are limited the current findings also contrast with those of Toghi-eshghi and Yardley who found that morning resistance exercise was associated with increased blood glucose (from 9.5 ± 3.0 to 10.4 ± 3.0 mmol/L), while afternoon exercise resulted in decreased blood glucose (from 8.2 ± 2.5 to 7.4 ± 2.6 mmol/L) in individuals with type 1 diabetes (Toghi-Eshghi and Yardley, 2019). While their study considered the influence of resistance exercise timing, their population differed from the current study in studying people with type 1 diabetes where physiological responses will differ from healthy populations.

As mentioned previously, several limitations of the current study should be noted. The primary limitation is the relatively small sample size of six participants, which will have limited the ability to detect both the effects of exercise and the time of day at which it is performed. On top of this, the current study focused on healthy young adults which may limit the generalisability of the findings to other populations, although this remains a population of interest from the point of view of prevention of future metabolic disease. Furthermore, the current study measured insulin sensitivity 2 hours following a single bout

of exercise and it is possible that any differences that exist may have been missed as the acute effects of exercise can last up to 72 hours. Future research should consider these limitations and include larger sample size and consider the investigation of a time course of effects.

3.7 Conclusion:

In conclusion, the current study examined whether time of the day at which exercise is performed affects insulin sensitivity in response to a single bout of resistance exercise in healthy young adults. The findings indicate that a single session of resistance exercise had no effect on insulin sensitivity regardless of whether it was performed in the morning or evening. These results both align with and differ from previous research, despite its limitation, this study provides novel insight into the acute effect of resistance exercise timing on insulin sensitivity and highlights important methodological considerations for future research.

Chapter IV

4 The impact of the time of day on muscle and metabolic responses to resistance exercise in healthy adults: a randomised controlled trial

4.1 Abstract:

4.1.1 Background:

There are many health benefits associated with resistance exercise, including improved glucose control and enhanced muscular strength. Existing data remains unclear if the time of day resistance exercise is performed is related to the benefits gained.

4.1.2 Aim:

The aim of the current study, therefore, is to determine the effect of time of day on the muscle and metabolic responses to resistance exercise in young healthy adults.

4.1.3 Methods:

We recruited 38 participants (30±7 years old; and 28±4 kg/m^2) who were randomised into either a control, exercise in the morning (6:00-10am) or exercise in the evening (4:00-8:00pm) group. Those in the exercise groups performed 8 resistance exercises 3 times a week for 6 weeks, at their allocated time of day. At baseline and after the intervention we measured insulin sensitivity, interstitial glucose via flash glucose monitors, muscle strength and vastus lateralis muscle thickness.

4.1.4 Results:

Over the 6-week intervention period there were effects of time on insulin sensitivity ($p<0.001$), muscle thickness ($p=0.008$) and knee extensor maximal torque ($p<0.001$). But there were no significant time*group interactions. Post-hoc tests revealed increases in insulin sensitivity and knee extensor maximal torque in the morning group (+7.55 [3.33 to 11.77] mg l2 mmol−1 mU−1 min−1 p=0.003), with increases in muscle thickness (+1.17 [0.37 to 1.97] mm p=0.009) and knee extensor maximal torque in the evening group (+5.68

[2.36 to 8.99] Nm p=0.003). No time or time*group effects were noted for the mean and SD for interstitial glucose data.

4.1.5 Conclusion:

The current study highlights several of the benefits of resistance exercise and demonstrates that time of the day at which exercise is performed has little influence on these effects. Promotion of resistance exercise at times convenient to the individual is, therefore, recommended.

4.1.6 Registration:

ClinicalTrials.gov *ID: NCT05321914.*

4.1.7 Keywords:

Resistance exercise, Circadian rhythm, metabolic responses, time of day, exercise timing

4.2 Introduction:

Chronobiology is the study of the human internal body clock, and it regulates sleep cycles, body temperature, feeding and hormone secretion (Brown et al., 2002, Buhr et al., 2010). At a molecular level, circadian rhythms are controlled by transcriptional activators CLOCK and BMAL1 as well as their target genes period PER and cryptochrome (CRY) in mutant mice (Gerhart-Hines et al., 2015, Robinson and Reddy, 2014). This is approximately a 24 h transcription-translation feedback loop (TTFL) which drives the entire body's metabolism (Gabriel and Zierath, 2019). Changes in the circadian rhythm can increase the risk for chronic disease such as hypertension, diabetes, and cancer risk (Schernhammer et al., 2001, Forman et al., 2010). For example, metabolic disease has been associated with a disruption of mammals' circadian clocks (Panda, 2016). In humans, variations in glucose tolerance and insulin action throughout the day highlight that glucose

metabolism is influenced by circadian rhythms (Van Cauter et al., 1997, Gagliardino et al., 1984). It is possible that strategies to benefit metabolic health may interact with these circadian rhythms and alter their effects.

One such strategy is exercise which is an integral component of diabetes management with both aerobic and resistance exercise recommended (Diabetes Canada Clinical Practice Guidelines Expert et al., 2018). Both forms of exercise have broad health benefits (Sigal et al., 2004a, Diabetes Canada Clinical Practice Guidelines Expert et al., 2018, Yardley et al., 2013), with less research on resistance compared to aerobic exercise. Resistance exercise has the benefit of increasing muscle mass and strength, which are important for maintenance of physical function, blood pressure and glucose control, and morbidity/mortality risk (Celis-Morales et al., 2018, Kirwan et al., 2017, Colberg et al., 2010). Performance responses to exercise vary according to time of day, for example, power and strength peak in the early evening hours (Drust et al., 2005), and there has been suggestion that some of the benefits of exercise may be modulated by the time of day at which it is performed. For example, in people with type 1 diabetes, blood glucose responses to exercise vary depending on the time of day at which resistance exercise is performed (Toghi-Eshghi and Yardley, 2019) but data from people without diabetes is limited (Tanaka et al., 2021b). In chapter 2, based on a small number of studies, there was no clear effect of time of day on metabolic responses to exercise. There is also limited data on whether increases in muscle strength and mass vary depending on when resistance exercise is performed, although data tentatively indicates no such effect is present (Grgic et al., 2019), and further work is needed to confirm these findings.

The aim of the current study, therefore, is to determine the effect of time of day on the muscle and metabolic responses to resistance exercise in young healthy adults.

4.3 Methodology:

The current study was registered on April 11th, 2022 with ClinicalTrials.gov *ID: NCT05321914.*

4.3.1 Participants:

Participants were recruited through flyers and social media posts (Appendix 4-AI). Inclusion criteria were: age between 18-45 years old, body mass index (BMI) >23.0kg/m² - 40 kg/m² and self-reported participation in less than 1 hour of structured exercise training per week (Appendix 4-BJ) Exclusion criteria included: having undergone surgery for weight loss and a prior history of heart, lung, cancer, kidney, endocrine, or liver disease. The study was approved by the ethical review committee of the College of Medical Veterinary and Life Sciences at the University of Glasgow (No. 200210068) and all participants provided written informed consent, with the study adhering to the guidelines of the Declaration of Helsinki (Appendix 4-CK) & (Appendix 4-DL).

The current study is a pilot study, and no formal sample size calculation has been carried out. However, a target of 36 participants (12 per group) was set to detect a 1.15 SD difference in outcomes, and provide data for a future larger trial.

4.3.2 Study Design:

Following baseline assessment of Munich Chronotype Questionnaire (MCTQ) (Appendix 4-EM), insulin sensitivity via oral glucose tolerance test (OGTT), body composition, vastus lateralis muscle thickness, knee extensor maximal torque and grip strength, the 1-repetition maximum (1RM) was measured for resistance exercises. Participants were then randomised to either a control, exercise in the morning (6:00-10:00am) or exercise in the evening (4:00 – 8:00pm) group for the 6-week intervention period. The allocation sequence was generated by an independent researcher and participants assignment

contained within a sealed opaque envelope. Study investigators were blinded to the initial allocation sequence but not final group assignment. Following the baseline assessment, interstitial glucose levels were measured via a blinded flash glucose monitor (FGMs) for 14-days. This included the 7 days prior to beginning the intervention and the first 7 days of the intervention. Following the 6-week intervention a further assessment of insulin sensitivity, body composition, vastus lateralis muscle thickness, knee extensor maximal torque, grip strength and 1RM of training exercises was made at least 3 days after the final exercise session. Interstitial glucose levels were measured for the last 7 days of the intervention and 7 days after the end of the intervention. Participants were asked to fast overnight prior to the study visits and only consume water before coming to the laboratory. Insulin sensitivity was measured around 9:00am while the strength measurements were made between 12:00-1:00pm to ensure they were equidistant between the two training times. The study flow or participants, including recruitment, randomisation, and follow-up, is illustrated in (Figure 4-1).

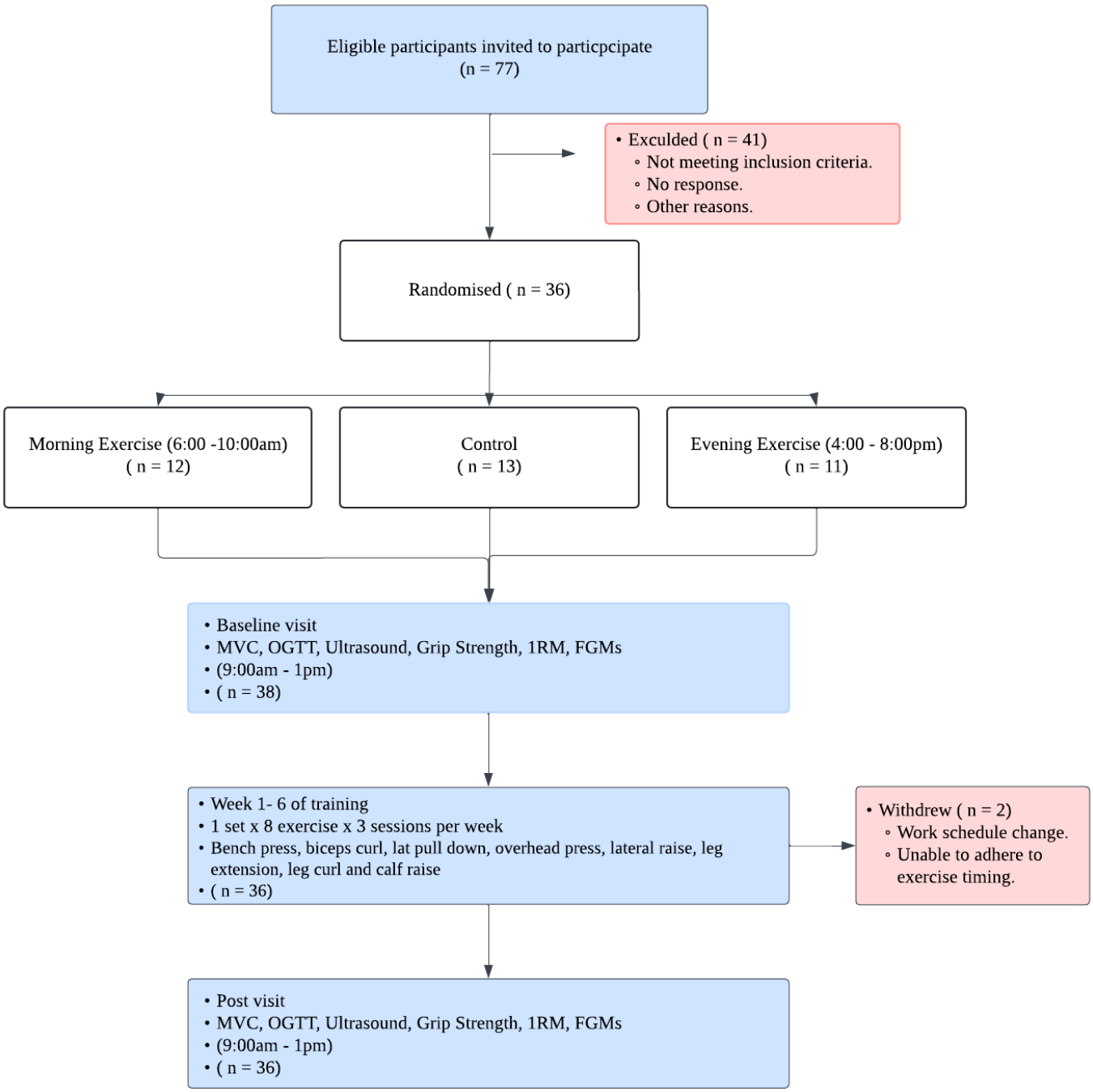


Figure 4-1: Flow diagram of participant recruitment, randomisation, and follow-up

4.4 Interventions:

4.4.1 Control:

The control group were asked to maintain their habitual physical activity levels.

4.4.2 Exercise:

Exercise consisted of 1 set x 8 exercises x 3 sessions per week for 6 weeks. The load was 80% of 1RM with each set performed to volitional failure. All sessions of training were supervised by a researcher and the following exercises were performed: Bench press, biceps curl, lat-pull down, overhead press, lateral raise, leg extension, leg curl and calf raise. Smith machine was used for bench press, overhead press and calf raises, while a pully machine was used for biceps curl, lat-pull down, leg extension and leg curl and dumbbells were used for lateral raises.

4.4.3 Outcome measurements:

Munich Chronotype Questionnaire (MCTQ): a self-reported sleep form that was given to all participants during the baseline and post intervention, to evaluate their sleep and chronotype (Ghotbi et al., 2020).

Insulin sensitivity (oral glucose tolerance test) - OGTT: A cannula was inserted into an antecubital vein and a baseline blood sample was collected. Participants consumed 75 g of glucose made up to 300 ml with water, and further blood samples were collected after 30-, 60-, 90- and 120-min. Blood samples were analysed for glucose and insulin levels in our clinical biochemistry laboratory.

Body composition: Bioelectrical impedance analysis (BIA) was used to measure lean and fat mass.

Vastus lateralis muscle thickness: Participants were asked to lie on an examination couch and an ultrasound device was used to measure the thickness of the vastus lateralis. Measurements were taken at 70% of the distance between the lateral condyle of the femur and greater trochanter as previously described (Ismail et al., 2019a).

Knee extensor maximal torque: Participants were strapped in a chair with their legs at a 90-degree angle and a strap was placed around the right ankle which was connected to a force transducer. Participants were asked to contract maximally for 5-10 s with the leg fixed in position and force was recorded.

Grip strength: Participants were asked to perform 3 maximal contractions, on each hand, with the hand grip dynamometer.

1-repetition maximum (1RM): All participants were asked to do 1RM for 8 exercises: Bench press, biceps curl, lat-pull down, overhead press, lateral raise, leg extension, leg curl and calf raise. Upper muscle exercises: bench press, biceps curl, lat-pull down, overhead press and lateral raises were combined as “upper body exercises 1RM” and lower muscle exercises: leg extension, leg curl and calf raises were combined as “lower body exercises 1RM” for data analysis.

Flash glucose monitoring (FGM): All participants were fitted, in the back of the upper arm, with a blinded FGM sensors for 14 days (FGMs; FreeStyle Libre Pro).

4.5 Data and statistical analysis:

Glucose and insulin area under the curve was calculated during the OGTT using the trapezoid rule. On top of this glucose and insulin data were also used to estimate insulin sensitivity via Matsuda index (Matsuda and DeFronzo, 1999) as follows:

$$Insulin\ sensitivity = \frac{10000}{\sqrt{(FPG * FPI) * (Mean\ OGTT\ glucose * mean\ OGTT\ insulin)}}$$

Using flash glucose monitoring (FGM) data mean and standard deviation of glucose were calculated using EasyGV (Hill et al., 2011) over four time periods.

The 6-hour period post exercise for both morning and evening exercise groups (week 1 and 6) named as "6-h post-exercise" for data presentation.

The 24-hour period on days of exercise for all three groups, with an average of all 24h periods used in the control group (week 1 and 6), named as "24-h exercise" for data presentation.

The 24-hour period on days following exercise for all three groups, with an average of all 24-hour periods used in the control group (week 1 and 6), named as "24-h post-exercise" for data presentation.

The 24-hour period averaged over all 7 days for all three groups (week 0 and 7), named as "24-h pre-post" for data presentation.

All data were tested for normality and skewness before selecting the appropriate test. A two-way (group*time point) repeated measures analysis of variance (ANOVA) was conducted to compare data, with a p value of < 0.05 being used to determine statistical significance. Data are presented as mean ± standard deviation (SD). This is an exploratory study; therefore no formal power calculation was performed. Statistical significance will be set at a $P=\leq 0.05$.

4.6 Results:

4.6.1 Participants recruitment and characteristics:

Out of 77 individuals screened for eligibility, 36 healthy adults (19 males, 17 females: age 30 ± 7 years old) met the inclusion criteria and were randomised into three groups: morning exercise, control and evening exercise (Figure 4-1). Additionally, all 36 participants completed the MCTQ at both times. Participant baseline characteristics are presented in (Table 7). All participants showed 100% adherence to exercise sessions.

Table 7: Baseline characteristics of the participants. Body Mass index (BMI). Data are mean ± SD

Study characteristics	
Variable (*n*=36)	Baseline data
Male/Female	19/17
Age (years)	30 ± 7
Height (cm)	169 ± 8
Weight (kg)	81 ± 15
BMI (kg/m^2)	28 ± 4

4.6.2 Muscle and metabolic data:

Sleep corrected mid sleep on free days (MSFsc), which is an indicator of chronotype was analysed during baseline (5:32 ± 2:00) and during the post visit (5:39 ± 1:57).

Muscle and metabolic data are presented in (Table 8). A two-way repeated measures ANOVA revealed a significant effect of time ($p<0.001$) with no significant time*group interaction ($p=0.206$) for the insulin sensitivity index. Post hoc paired t-tests showed an increase in the morning group (+7.55 [3.33 to 11.77] mg l2 mmol−1 mU−1 min−1 $p=0.003$) but not in the evening group (+6.82 [-0.49 to 14.13] mg l2 mmol−1 mU−1 min−1 $p=0.064$) or the control group (+0.70 [-3.18 to 4.58] mg l2 mmol−1 mU−1 min−1

p=0.693). No time or interaction effects were seen for body fat percentage (time: p=0.456. interaction: p=0.245) or fat mass (time: p=0.272. interaction: p=0.950). Analysis of vastus lateralis muscle thickness data showed an effect of time (p=0.008) but no time*group interactions (p=0.279). Post hoc paired t-test showed an increase in the evening (+1.17 [0.37 to 1.97] mm p=0.009), but not in the morning (+1.12 [-0.02 to 2.25] mm p =0.054) or control (+0.41[-0.08 to 0.90] mm p=0.091) groups.

Analysis of knee extensor maximal torque revealed an effect of time (p <0.001) but no time*group interactions (p = 0.151). Post hoc paired t-tests showed, a significant increase in the morning (+5.54 [1.87 to 9.21] Nm p=0.007), evening group (+5.68 [2.36 to 8.99] Nm p=0.003), and in the control group (+1.84 [0.26 to 3.41] Nm p=0.026). Analysis of grip strength did not reveal any time (p=0.851) or interaction (p=0.322) effects. Analysis of upper body 1RM revealed a significant effect of time (p<0.001) but no time*group interactions (p=0.107). Post hoc t-test showed, a significant increase in the morning (+11.50 [1.22 to 21.78] kg p=0.032) and evening group (+15.43 [6.50 to 24.36] kg p=0.003) with no effect in control (+0.800 [-4.39 to 5.99] kg p=0.743). Analysis of lower body exercise found no effect of time (p=0.618) and no time*group interactions (p=0.997).

Table 8: Muscle and metabolic data values are presented as mean ± standard deviation. AM: morning exercise group, BMI: body mass index, ISI: insulin sensitivity index, MVC: maximal voluntary contraction, 1RM: one repetition maximum.

	AM (n =12)		Change (95% CI)	PM (n=11)		Change (95% CI)	Control (n=13)		Change (95% CI)
	Pre	Post		Pre	Post		Pre	Post	
BMI (kg/m^2)	27.91 ± 4.54	27.60 ± 4.25	-0.31 (-0.97, 0.36)	28.06 ± 2.24	27.79 ± 2.36	-0.26 (-0.68, 0.15)	28.66 ± 3.57	27.15 ± 3.99	-0.92 (-1.32, -0.52)
Fat (%)	30.17 ± 9.16	32.86 ± 7.93	2.69 (-3.53, 8.91)	27.09 ± 6.07	29.02 ± 6.78	1.93 (-0.10, 3.96)	28.52 ± 6.55	26.45 ± 7.51	-2.08 (-4.17, 0.02)
Fat mass (kg)	23.97 ± 11.05	26.43 ± 10.89	2.46 (-2.30, 7.22)	21.56 ± 4.34	23.19 ± 5.51	1.63 (-0.28, 3.53)	23.95 ± 8.06	26.38 ± 14.31	2.44 (-6.34, 11.22)
ISI (mg l^2 $mmol^{-1}$ mU^{-1} min^{-1})	35.99 ± 21.62	43.54 ± 24.63	7.55 (3.33, 11.77)	42.97 ± 25.31	49.79 ± 28.73	6.82 (-0.49, 14.13)	36.60 ± 28.21	37.30 ± 27.58	0.70 (-3.18, 4.58)
MVC (Nm)	182.07 ± 26.58	187.61 ± 28.49	5.54 (1.87, 9.21)	195.73 ± 33.68	201 ± 33.34	5.68 (2.36, 8.99)	186.46 ± 64.51	188.29 ± 65.60	1.84 (0.26, 3.41)
Vastus lateralis muscle thickness (mm)	22.49 ± 3.03	23.60 ± 2.80	1.12 (-0.02, 2.25)	23.25 ± 3.73	24.41 ± 3.18	1.17 (0.37, 1.97)	22.20 ± 4.38	22.61 ± 1.60	0.41 (-0.08, 0.90)
Grip strength (kg)	35.75 ± 6.18	37.00 ± 6.35	1.25 (0.04, 2.47)	37.55 ± 6.15	39.27 ± 4.74	1.73 (-0.44, 3.90)	40.15 ± 11.69	39.62 ± 11.68	-0.54 (-1.84, 0.91)
Upper body exercises 1RM (kg)	118.00 ± 27.86	129.50 ± 24.20	11.50 (1.21, 21.78)	139.86 ± 19.29	155.29 ± 24.32	15.43 (6.50, 24.36)	114.40 ± 29.72	115.20 ± 32.06	0.80 (-4.39, 5.99)
Lower body exercises 1RM (kg)	118.54 ± 25.57	121.37 ± 18.64	2.83 (-11.24, 16.90)	116.43 ± 16.49	118.23 ± 25.37	1.80 (-19.23, 22.82)	107.44 ± 29.21	108.96 ± 28.89	1.52 (-7.54, 10.58)

4.6.3 Flash glucose monitoring (FGM):

Analysis of mean glucose data indicated no significant effects of time (p=0.721) or interaction time*group effects (p=0.554) during the 6-h post-exercise period. Similarly,

analysis of SD data revealed no significant effect of time (p=0.495) or interaction time*group effects (p=0.942) during the 6-h post-exercise period. Analysis of mean glucose data indicated no significant effects of time (p=0.372) or interaction time*group effects (p=0.140) during the 24-h exercise days. Similarly, analysis of SD data revealed no significant effect of time (p=0.805) or interaction time*group effects (p=0.238) during the 24-h exercise days. Analysis of mean glucose data over 24-h post exercise days indicated no significant effect of time (p=0.805) or interaction time*group effects (p=0.926) during the 24-h post exercise days. However, analysis of SD data 24-h post exercise days indicated a significant effect over time (p=0.041) but no interaction time*group (p=0.701). Post hoc paired t-tests, however, showed no change over time within the morning group (-0.063 [-0.166 to 0.040] p=0.202), evening group (-0.068 [-0.154 to 0.019] p=0.106) or the control group (-0.126 [-0.425 to 0.174] p=0.371) during the 24-h post exercise days. Furthermore, analysis of mean 24-h pre-post mean glucose data indicated no significant effects of time (p=0.118) or interaction time*group effects (p=0.647) during the 24-h pre-post comparison. Similarly, analysis of SD 24-h pre-post mean glucose data indicated no significant effects of time (p=0.251) or interaction time*group effects (p=0.807) during the 24-h pre-post comparison. All values for glucose monitoring measures are presented in (Table 9) & (Figure 4-2).

Table 9: Summary of Flash Glucose Monitoring (FGM) Data. Mean glucose levels and standard deviation (SD) at 6-h post-exercise, 24-h exercise, 24-h post-exercise, 24-h pre-post

	AM (n =12)		Change (95% CI)	PM (n=11)		Change (95% CI)	Control (n=13)		Change (95% CI)
	Pre	Post		Pre	Post		Pre	Post	
Mean 6-h post-exercise glucose	5.58 ± 0.57	5.42 ± 0.53	-0.16 (-0.48, 0.16)	5.68 ± 0.36	5.79 ± 0.66	0.11 (-0.34, 0.56)			
SD 6-h post-exercice glucose	0.69 ± 0.17	0.60 ± 0.15	-0.09 (-0.22, 0.03)	0.71 ± 0.16	0.68 ± 0.21	-0.03 (-0.20, 0.13)			
Mean 24-h exercise days glucose	5.42 ± 0.45	5.45 ± 0.53	0.02 (-0.27, 0.31)	5.42 ± 0.28	5.65 ± 0.43	0.24 (-0.06, 0.53)	5.53 ± 0.48	5.41 ± 0.39	-0.13 (-0.43, 0.17)
SD 24-h exercise days glucose	0.77 ± 0.15	0.70 ± 0.14	-0.07 (-0.20, 0.06)	0.68 ± 0.07	0.70 ± 0.13	0.02 (-0.10, 0.14)	0.82 ± 0.35	0.85 ± 0.10	0.02 (-0.19, 0.24)
Mean 24-h post-exercise days glucose	5.58 ± 0.48	5.54 ± 0.71	-0.04 (-0.49, 0.42)	5.61 ± 0.39	5.66 ± 0.59	0.05 (-0.18, 0.28)	5.53 ± 0.48	5.41 ± 0.39	-0.13 (-0.41, 0.15)
SD 24-h post-exercice glucose	0.74 ± 0.19	0.68 ± 0.22	-0.06 (-0.17, 0.04)	0.71 ± 0.12	0.65 ± 0.12	-0.07(-0.15, 0.02)	0.82 ± 0.35	0.85 ± 0.10	0.02 (-0.19, 0.24)
Mean 24-h pre-post glucose	5.51 ± 0.48	5.42 ± 0.62	-0.10 (-0.42, 0.22)	5.65 ± 0.64	5.47 ± 0.53	-0.17 (-0.73, 0.38)	5.58 ± 0.53	5.41 ± 0.40	-0.18 (-0.40, 0.04)
SD 24-h pre-post glucose	0.78 ± 0.17	0.69 ± 0.11	-0.09 (-0.21, 0.03)	0.73 ± 0.08	0.74 ± 0.14	0.004 (-0.21, 0.03)	0.85 ± 0.21	0.80 ± 0.15	-0.05 (-0.19, 0.09)

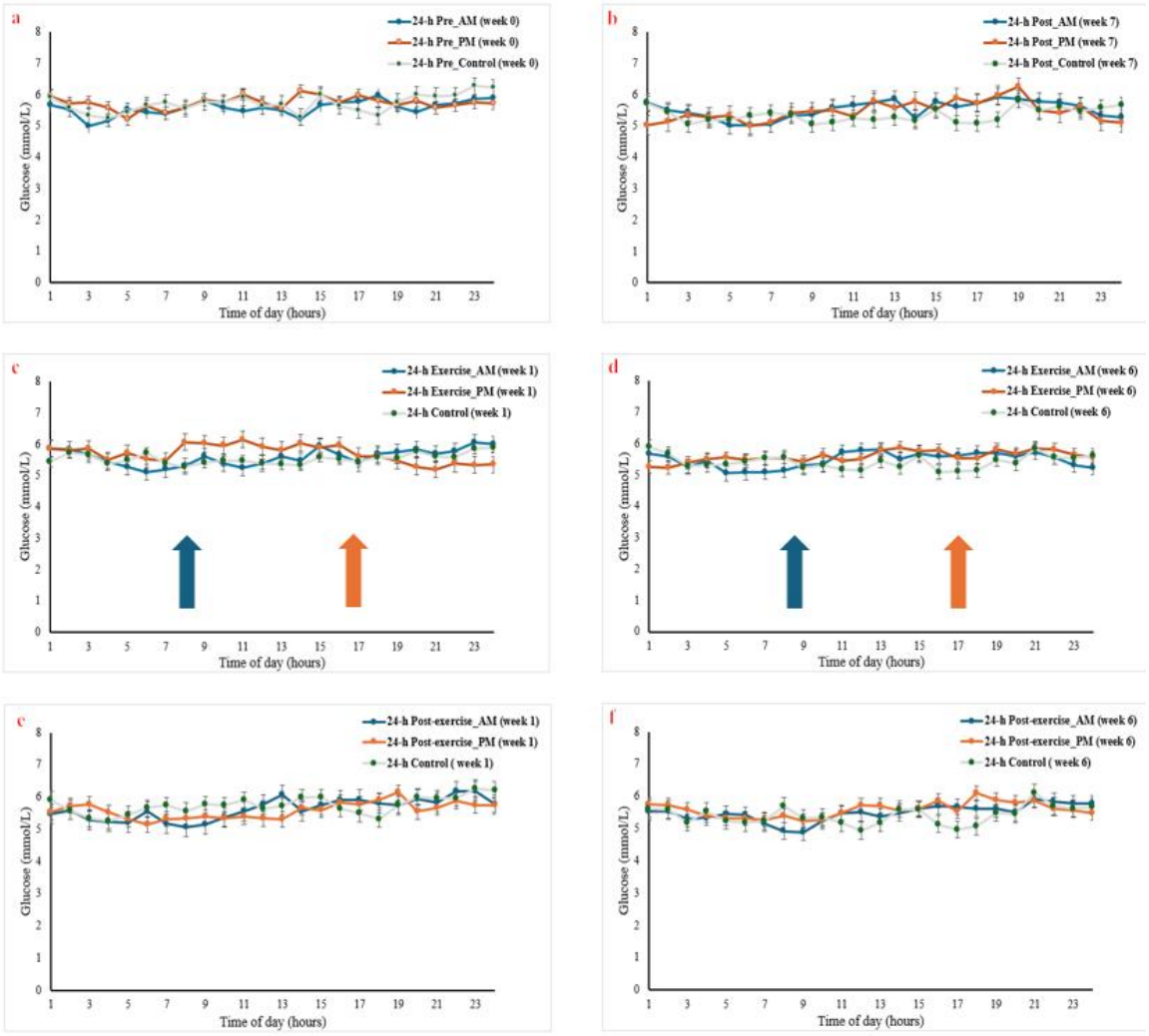


Figure 4-2: Flash glucose monitoring (FGM) based glucose levels in response to the intervention. (a) & (b). Comparison of 24-hour pre-post mean glucose levels from FGMs during the first (week 0) and last (week 7) weeks of the intervention. Data are presented for the AM exercise group (blue), PM exercise group (orange), and control group (grey). (c) & (d). Comparison of mean 24-h exercise glucose levels from FGMs during the first (week 1) and last (week 6) weeks of the intervention. Data are presented for the AM exercise group (blue), PM exercise group (orange), and control group (grey). Arrows indicate exercise timing (AM: 6-10 AM, PM: 4-8 PM). (e) & (f). Comparison of mean 24-h post exercise glucose levels from FGMs on rest days during the first (week 1) and last (week 6) weeks of the intervention. Data are presented for the AM exercise group (blue), PM exercise group (orange).

4.7 Discussion:

This study aimed to investigate the impact of the timing of resistance exercise on muscle and metabolic responses in young healthy adults. The findings demonstrated that six-weeks

of resistance exercise resulted in an improvement in muscle strength, muscle mass and insulin sensitivity, however, there was no clear effect of time of day. These results suggest that the benefits of resistance exercise may be achieved regardless of the time of day for healthy young adults and this should be the focus of public health strategies. Furthermore, these changes should be interpreted cautiously given the small effect sizes and potential measurement variability in body composition assessments.

The current study showed an improvement with insulin sensitivity over time with post hoc tests confirming this pre-post difference in the morning group, with a similar magnitude of effect in the evening group although this was not significant. This improvement in insulin sensitivity with 6 weeks of resistance exercise in healthy young people confirms the findings of Ismail et al (Ismail et al., 2019a), but has a stronger study design with the inclusion of a control group. In the Ismail et al paper, they used a pre-post design without a control group, which makes it challenging to distinguish training effects from other factors, such as day to day variation or a learning effect. However, the current research design allows a more confident attribution of changes to the resistance training intervention, due to the inclusion of a control group. This is the first study, to our knowledge, that has compared the effects of the time of day at which resistance exercise is performed on insulin sensitivity finding no effect, with a similar magnitude of improvement in the morning and evening groups. This goes against the previous hypothesis put forward that exercise in the evening would be more effective in improving insulin sensitivity compared to exercise in the morning (Heden and Kanaley, 2019).

On top of this insulin sensitivity data, the current study utilised FGM to monitor glucose responses and found no effect of exercise or time of day on either mean glucose or glucose variability. These findings are in conflict with previous studies investigating interactions between exercise and time of day on glucose responses. For example, Savikj reported that over a 2 week intervention period that afternoon high intensity interval training is more

effective in lowering glucose levels compared to morning training in people with type 2 diabetes (Savikj et al., 2019). On top of this, Yardley reported that, in people with type 1 diabetes, after an acute bout of morning (fasting) resistance exercise there was an increase in blood glucose, whilst it declined during afternoon resistance exercise, with higher glucose variability and more frequent hyperglycaemic events after morning exercise (Toghi-Eshghi and Yardley, 2019). However, it is important to notice that the type of population, with healthy people having tighter glycaemic control, and the type of exercise differed between the current study and the previous research. Primarily, the current study included participants free from diabetes, where interpretation of FGM data is not straightforward with no data to indicate any link between FGM-derived glucose data and any health outcomes (Guess, 2023). This is because FGM is relatively new technology.

The current study also investigated whether the time of day at which resistance exercise is performed influences adaptations in muscle strength and size. Previous research found that maximum strength peaks late afternoon with exercise compared to morning exercise (Drust et al., 2005) and this is often cited as a reason to hypothesise that muscular adaptations to resistance exercise will be superior in the afternoon/evening. The current data, however, found no clear effect of time of day on the adaptations to resistance exercise training. These effects were relatively modest given the short 6-week duration of the current intervention but this is in agreement with a previous systematic review and meta-analysis on the topic (Grgic et al., 2019). In this review it was shown, based on 11 studies, that increases in knee extensor maximal torque do not differ when comparing resistance training in the morning versus the evening ($p = 0.220$; SMD = 0.19, 95% CI = −0.11, 0.50; $I^2 = 0\%$). Similar results were found for muscle mass where, based on 5 studies, increases in muscle mass where similar when comparing resistance exercise training in the morning versus the evening ($p = 0.958$; SMD = 0.20, 95% CI: −0.40, 0.40; $I^2 = 0\%$). The current

study, therefore, supports these findings and, in our opinion, it is relatively clear that there is no effect of the timing of resistance exercise of adaptations in muscle strength and mass.

The current study is not without limitations, and it is prudent to consider these, alongside its strengths. A major strength of this study is that followed randomised controlled trial design. We employed blinded real time flash glucose monitoring to ensure that participants seeing this data did not result in behavioural changes. Moreover, the strict timing and the structure of the exercise sessions ensures study validity. A primary limitation is the study sample characteristics, particularly being healthy young adults, which limits the generalizability to all other populations. On top of this this study was a pilot study and not powered to detect differences in study outcomes, meaning real differences may exists that the current study was not able to detect. Furthermore, the study duration is 6 weeks which means adaptations to resistance exercise were relatively small, particularly for muscle strength and size, and so the potential for these to be influences by the time of day was relatively small. Moreover, the current study did not use the gold standard measure of muscle mass, although the use of ultrasound has been validated (Franchi et al., 2018). Insulin sensitivity was measure during an OGTT rather than the golden standard hyperinsulinemic euglycemic clamp (HEC).

In conclusion, with the lack of effect of the time of day at which exercise is performed then public health strategies should promote resistance exercise at times convenient to the individual to ensure its benefits (Ashton et al., 2020) reach the widest population possible.

CHAPTER V

5 GENERAL DISCUSSION

5.1 Summary and general discussion

The thesis comprised three studies examining the effect of the time of day on metabolic responses in adults. The systematic review and meta-analysis investigated the current literature on the impact of exercise timing on metabolic responses to exercise, considering both acute and more chronic studies. On top of that the second study investigated whether the time of the day has an effect on insulin sensitivity in response to a single resistance exercise session in adults in a cross over study. Further, the final study determined the effect of time of day on the muscle and metabolic responses to resistance exercises for six weeks in adults in a randomised control trail. Collectively, the main findings of the thesis indicate that any differences between morning and evening exercise timing on metabolic responses, muscle strength and muscle size in adults were not detectable with the statistical power available in these studies. However, power calculations suggest approximately 500 participants would be required to detect such small differences. Given the substantial resources required and modest effect sizes observed, pursuing such large studies may not be practically sensible for confirming these small timing effects.

While the interplay between circadian rhythms and physical activity is a complex area of research, while the interaction between the molecular clock within skeletal muscle and cellular physiology is established (Gabriel and Zierath, 2019), our findings suggest that the timing of exercise might be less important than previously suggested. This aligns with the recent meta-analysis who concluded that there is a little evidence about training at certain time of day might be more beneficial in terms of health and performance (Bruggisser et al., 2023). Additionally, Teo et al found no significant difference in fasting glucose and insulin when comparing morning exercise with evening exercise (Teo et al., 2020).

Regarding glucose regulation, our findings did not reveal a significant effect of the time of exercise on metabolic responses. Previous work had suggested that circadian rhythms and diurnal exercise

responses are influenced by the physiological regulation of glucose and triglycerides, which are controlled by the intrinsic clock (Gabriel et al., 2018). There have been several studies demonstrating time-of-day effects on glucose metabolism, including Savikj et al who reported that over a 2 week intervention period that afternoon high intensity interval training is more effective in lowering glucose levels compared to morning training in people with type 2 diabetes (Savikj et al., 2019). Additionally, Tanaka et al (2021) found that a single bout of exercise on a cycle ergometer, in the afternoon, decreased glucose levels over 24 h compared in the morning in healthy young adults (Tanaka et al., 2021b). However, our findings across the meta-analysis and after both a single session or six weeks of resistance exercise found no significant in both gluocse and insulin sensitivity.

In terms of muscle adaptations, the current data also investigated whether the time of day at which resistance exercise is performed influences adaptations in muscle strength and size. However, despite the short duration of six weeks, time of day did not appear to have a significant effect on resistance training adaptations, even though these adaptations were modest. This is in agreement with a previous systematic review and meta-analysis on the topic (Grgic et al., 2019). While some studies have reported superior strength gains with the afternoon exercise, for example previous research found that maximum strength peaks late afternoon with exercise compared to morning exercise (Drust et al., 2005). Additionally, research indicated that an improvement in 16 km cycling time at 17:30 h compared to 07:30 h (Atkinson et al., 2005). However, whilst these findings are encouraging, the result contrasted with current data, and it is important to notice that the type of population and the type of exercise differed between the current study and the previous research.

5.2 Limitations of the current thesis:

The current thesis has several limitations. A key limitation in this study is the relatively small sample size across our studies, which might have limited statistical power to detect any effect of the

time of the day. Furthermore, the focus on healthy adults limits the generalisability to our conclusions to other populations such as individuals with metabolic disorders.

Methodological consideration including the measurement techniques used for assessing metabolic response. Although the OGTT is a valid measure of metabolic response (Kim et al., 2016, Pintaudi et al., 2022), The use HEC technique might have detected more subtle timing effects. However, as all participants were healthy young adults with a normal blood gluocse levels, the OGTT was deemed appropriate for the current thesis aims.

Furthermore, the duration of the intervention study, particularly six-weeks in chapter 4 might have been insufficient to observe maximal training adaptation that could potentially be influenced by exercise timing. Previous research has demonstrated that adaptations to resistance exercise are generally observed after 8 to 12 weeks (Hakkinen et al., 1998, Folland and Williams, 2007, Hughes et al., 2018). Moreover, the current study did not use the gold standard measure of muscle mass, although the use of ultrasound has been validated (Franchi et al., 2018).

The heterogeneity in exercise modalities across the literature presents a challenge when synthesising the findings. While studies demonstrated 2 weeks of HIIT is more effective in the afternoon with blood gluocse in people with the type 2 diabetes (Savikj et al., 2019), there is limited research examining the timing effects of combined exercise modalities. This gap in the literature makes it difficult to draw conclusive recommendations about optimal timing for different exercise combinations.

5.3 Future work

Future work should address the limitations of the current thesis by extending the intervention durations to 8-12 weeks and by including a more diverse and larger sample of participants including people with metabolic disorders. However, these recommendations might face practical challenges,

such as increased the costs, participant recruitment difficulties and the need for medical supervision when including participants with metabolic disorders. Based on sample size calculations, detecting meaningful differences would require larger sample sizes, particularly for people with metabolic disorders as they show greater variability. While including participants with type 2 diabetes may increase the likelihood of detecting circadian effects due to their impaired glucose regulation, the required sample sizes could become prohibitively large. Future work should also employ more robust measurement techniques, for example the gold standard muscle mass assessment MRI and the hyperinsulinaemic clamp to measure insulin sensitivity. Moreover, future work should explore underlying chronobiological mechanisms of any effects noted, as currently our knowledge of these is lacking. These approaches would strengthen the evidence base for time-of-day exercise recommendations, if appropriate.

5.4 Conclusion

In summary, the current thesis provides an insight into the relationship between exercise timing and metabolic response in adults. These results suggest that the benefits of resistance exercise may be achieved regardless of the time of day for healthy young adults, and this should be the focus of public health strategies to improve population health.

6 Appendices

Appendix 2-A: Prospero registration for systematic and meta-analysis review (chapter 2)

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

A list of fields that can be edited in an update can be found here

1. * Review title.

Give the title of the review in English

The impact of the time of day on metabolic responses to exercise in adults: a systematic review

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/07/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/07/2022

Appendix 2-B: Prisma checklist (chapter 2)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix 2-C Search terms (chapter 2)

#1 Circadian OR Circadian rhythm OR Circadian system OR Circadian Clock OR Variation Rhythm OR Time-of-day OR Diurnal fluctuations OR Diurnal variation[MeSH Terms]
#2 Circadian*[Title/Abstract]
#3 (#1 OR #2)
#4 Exercise OR Physical activity OR Resistance exercise Physical exercise OR Isometric exercise OR muscle exercise OR Resistance training OR exercise training OR aerobic exercise OR acute exercise OR exercise OR Exercise OR Physical activity OR Resistance exercise OR Physical exercise OR Isometric exercise OR muscle exercise OR Resistance training OR exercise training OR aerobic exercise OR acute exercise [MeSH Terms]
#5 exercise*[Title/Abstract]
#6 (#4 OR #5)
#7 Blood sugar OR Blood Glucose OR Glucose OR PPG OR Postprandial glucose[MeSH Terms]
#8 Glucose*[Title/Abstract]
#9 (#7 OR #8)
#10 Insulin resistance OR Insulin sensitivity OR insulin [MeSH Terms]
#11 Insulin*[Title/Abstract]
#12 (#10 OR #11)
#13 BMI OR body mass index OR Body weight [MeSH Terms]
#14 weight*[Title/Abstract]
#15 (#13 OR #14)
#16 Total cholesterol OR Triacylglycerol OR Parathyroid hormone [MeSH Terms]
#17 cholesterol [Title/Abstract]
#18 (#16 OR #17)
#19 maximal oxygen consumption OR Vo2 OR Vo2max OR HR OR heart rate OR blood pressure [MeSH Terms]
#20 maximal oxygen consumption [Title/Abstract] OR Vo2[Title/Abstract] OR Vo2max[Title/Abstract] OR HR[Title/Abstract] OR heart rate[Title/Abstract] OR blood pressure[Title/Abstract]
#21 (#19 OR #20)
#22 Adult [MeSH Terms]

#23 adult [Title/Abstract]
#24 (#22 OR #23)

Appendix 2-D: Extraction form (chapter 2)

Data collection form

Intervention review – RCTs only

This form can be used as a guide for developing your own data extraction form. Sections can be expanded and added, and irrelevant sections can be removed. It is difficult to design a single form that meets the needs of all reviews, so it is important to consider carefully the information you need to collect, and design your form accordingly. Information included on this form should be comprehensive, and may be used in the text of your review, 'Characteristics of included studies' table, risk of bias assessment, and statistical analysis.

Notes on using a data extraction form:

- Be consistent in the order and style you use to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.

Review title or ID	Morning (Fasting) vs Afternoon Resistance Exercise in Individuals With Type 1 Diabetes: A Randomized Crossover Study
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	Toghi-Eshgi 2019
Report ID	10.1210/jc.2018-02384
Report ID of other reports of this study	
Notes	

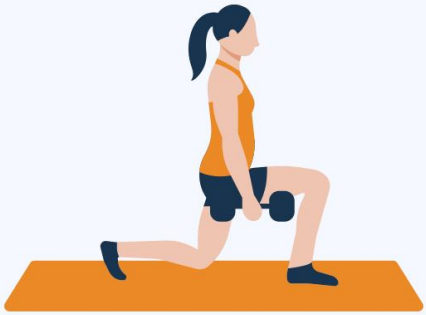
General Information

Date form completed *(dd/mm/yyyy)*	20/09/2021
Name/ID of person extracting data	Anas Dighriri
Reference citation	Toghi-Eshghi, S. R., & Yardley, J. E. (2019). Morning (fasting) vs afternoon resistance exercise in individuals with type 1 diabetes: A randomized crossover study. The Journal of Clinical Endocrinology and Metabolism, 104(11), 5214-5221. https://doi.org/10.1210/jc.2018-02384

Appendix 3-A : Flyer for the impact of the time of the day on insulin sensitivity in response to a single resistance exercise session in adults (chapter 3)

University of Glasgow

Volunteers Wanted



We are looking for volunteers of age 18-50; BMI> 20kg/m^2, free from injuries metabolic or cardiovascular disease.

Resistance training will involve 5 visits to the gym in both (morning and afternoon).

FURTHER INFORMATION

A.dighriri.1@research.gla.ac.uk

We will provide £50 upon on completion

Appendix 3-B : The physical activity Readiness Questionnaire (chapter 3)

2023 PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

The health benefits of regular physical activity are clear; more people should engage in physical activity every day of the week. Participating in physical activity is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

GENERAL HEALTH QUESTIONS

Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	**YES**	**NO**
1) Has your doctor ever said that you have a heart condition ☐ **OR** high blood pressure ☐?	☐	☐
2) Do you feel pain in your chest at rest, during your daily activities of living, **OR** when you do physical activity?	☐	☐
3) Do you lose balance because of dizziness **OR** have you lost consciousness in the last 12 months? Please answer **NO** if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4) Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)? **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
5) Are you currently taking prescribed medications for a chronic medical condition? **PLEASE LIST CONDITION(S) AND MEDICATIONS HERE:** _____	☐	☐
6) Do you currently have (or have had within the past 12 months) a bone, joint, or soft tissue (muscle, ligament, or tendon) problem that could be made worse by becoming more physically active? Please answer **NO** if you had a problem in the past, but it **does not limit your current ability** to be physically active. **PLEASE LIST CONDITION(S) HERE:** _____	☐	☐
7) Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.
Please sign the PARTICIPANT DECLARATION. You do not need to complete Pages 2 and 3.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow Global Physical Activity Guidelines for your age (https://www.who.int/publications/i/item/9789240015128).
- You may take part in a health and fitness appraisal.
- If you are over the age of 45 yr and NOT accustomed to regular vigorous to maximal effort exercise, consult a qualified exercise professional before engaging in this intensity of exercise.
- If you have any further questions, contact a qualified exercise professional.

PARTICIPANT DECLARATION

If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that the community/fitness center may retain a copy of this form for its records. In these instances, it will maintain the confidentiality of the same, complying with applicable law.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

If you answered YES to one or more of the questions above, COMPLETE PAGES 2 AND 3.

Delay becoming more active if:

- You have a temporary illness such as a cold or fever; it is best to wait until you feel better.
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the ePARmed-X+ at www.eparmedx.com before becoming more physically active.
- Your health changes - answer the questions on Pages 2 and 3 of this document and/or talk to your doctor or a qualified exercise professional before continuing with any physical activity program.

Appendix 3-C : Participant information sheet (chapter 3)

University of Glasgow | College of Medical, Veterinary & Life Sciences

PARTICIPANT INFORMATION SHEET

Study title:

The impact of the time of the day on insulin sensitivity in response to a single resistance exercise session in adults.

Invitation paragraph

We invite you to participate in an investigation which we believe to be of potential importance. In order to help you to understand what the investigation is about, please read the following information carefully. Be sure you understand it before you formally agree to participate. If there are any points that need further explanation, please ask a member of the research team. It is important that you understand what you are volunteering to do and are completely happy with all the information before you sign this form.

What is the purpose of the study?

It is known that resistance (weightlifting) exercise can have wide ranging health benefits, including control of blood sugar. There is some early data to suggest that the time of day at which the exercise is performed may influence its benefits. This study aims to determine whether the time of the day at which you perform resistance exercise affects the short-term improvements in control of blood sugar.

Why have I been invited to participate?

You have been selected as a possible participant in this investigation because you are healthy and aged between 18-50, with a BMI 20-40kg/m^2, who is healthy and safe to perform exercise.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and you will be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time and without giving a reason

What will happen to me if I take part?

If you choose to participant, you will be asked to attend 5 sessions in the laboratory. The initial visit can be at any time of day and 2 visits will be in the morning (8-10am) and 2 in the afternoon (2-4pm).

Initial visit (~1hour):

On your first visit you will be introduced to the laboratory personnel and familiarised with the study. You will be asked to complete a questionnaire to make sure you are safe to exercise. Then, an initial measurement of height, weight, and body composition (how much fat and muscle you have) will take place in our labs. Lastly, we will measure your one repetition maximum (1RM), which is the maximum weight you can lift once for the various exercises used in the exercise (details below).

Visits 2-5 (~3hours each):

Before these study visits, excluding the initial visit, we will ask you to fast for more than 6 hours. This means refraining from consuming any food or beverages, except water. Additionally, you will be asked to record your food intake for 24 hours prior to the first visit and replicate it prior to the other visits. The order of these visits will be random.

(a) Morning exercise:

Two hours following completion of the 8 resistance exercises (performed between 8-10am) then an oral glucose tolerance test (OGTT) will be done.

(b) Morning rest

An oral glucose tolerance test (OGTT) will be performed at the same time in a).

(c) Afternoon exercise:

Two hours following completion of the 8 resistance exercises (performed between 2-4pm) then an oral glucose tolerance test (OGTT) will be done.

(d) Afternoon rest:

An oral glucose tolerance test (OGTT) will be performed at the same time in c).

Exercise:

The exercise will consist of 5 sets of 8 exercises. The load to be used during training will be calculated as 80% of your 1RM, the maximum weight you could lift, and within each set you will perform the number of repetitions required until you can't manage to do any more. All sessions of training will be supervised by the researcher in our laboratory in the Sir James Black Building. The following exercises will be performed: Bench press, biceps curl, lat pull down, Leg press, squat, leg extension, leg curl and calf raise. These will be demonstrated to you.

Measurements:

Oral Glucose Tolerance Test (OGTT)

A small plastic tube (a cannula) will be inserted into an antecubital vein and a baseline blood sample collected. You will then consume 75 g of sugar made up to 300 ml with water, and further blood samples will be collected after 30-, 60-, 90- and 120-min. Blood samples will be analysed for blood sugar levels. A total of 50ml (10 teaspoons) of blood will be taken during the visit. Following completion of the OGTT we will provide you with a snack before completion.

Body composition

Bioelectrical impedance analysis scales will be used to measure muscle and fat mass.

1 repetition maximum

This involves increasing the weights applied during the exercise until you cannot perform a full single repetition of the exercise. We will ask you to warm up before each exercise and let you practice the technique.

What are the possible disadvantages and risks of taking part?

Exercise has a negligible risk in healthy adults, although maximal exercise does carry an extremely small risk of inducing myocardial ischaemia ("heart attack"). The screening procedures in place fo this study minimise this risk. The primary symptom of myocardial ischaemia is chest pain on exertion. If you experience any unusual sensations in your chest, feel unwell or do not want to continue for any other reason during exercise you should cease exercising immediately. If at any point you feel dizzy or unwell during exercise because of the fasting, then we will provide you wit food .

Blood sampling via the cannula may cause minor bruising, an inflammation of the vein or haematoma (a small accumulation of blood under the skin). Good practice, however, minimises this risk. Some people may feel faint when they give blood.

There is the chance that you will feel muscle soreness for a day or two after performing the exercises. This is a normal and short-lived feeling and we will minimise the chances of this with an appropriate warm up and cool down.

What are the possible benefits of taking part?

The information gained during the study will allow us to give you detailed feedback about what time day is best to perform resistance exercise.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the University will have your name and address removed so that you cannot be recognised from it. In addition, your records, samples and results will be identified by a number and not your name. The blood sample will be stored for a period of 10 years at University of Glasgow facility/facilities.

What will happen to my data?

All study data will be held in accordance with The General Data Protection Regulation (2018). The data will be stored in archiving facilities in line with the University of Glasgow retention policy of up to 10 years. After this period, further retention may be agreed or your data will be securely destroyed in accordance with the relevant standard procedures.

What will happen to the results of the research study?

The results from this study will be presented at scientific meetings and published in scientific journals. The results will also be used in the research project reports of the PhD student undertaking this research. A copy of the published results will be sent to you upon request. You will not be identifiable in any of the data presented or published from this study.

Who is organising and funding the research?

University of Glasgow.

Who has reviewed the study?

This study has been reviewed and approved by the Ethics committee of the College of Medical, Veterinary and Life Sciences at the University of Glasgow.

Contact for Further Information

Mr. Anas Dighriri

Institute of Cardiovascular and Medical Sciences

College of Medical, Veterinary and Life Sciences

University of Glasgow

Glasgow G12 8TA

Appendix 3-D : Participants consent form (chapter 3)

University of Glasgow | College of Medical, Veterinary & Life Sciences

Project Number:

Participant Identification Number for this trial:

Title of Project:

The impact of the time of the day on insulin sensitivity in response to a single resistance exercise session in adults.

Name of Researcher(s):

Mr. Anas Dighriri

Prof. Stuart Gray

Dr. James Boyle

Dr. Greig Logan

Miss. Lynsey Johnston

CONSENT FORM

Please initial box

I confirm that I have read and understood the Participant Information Sheet version 1 dated 25/04/2023. ☐

I confirm that I have read and understood the Privacy Notice version 1 dated 25/04/2023 ☐

I have had the opportunity to think about the information and ask questions and understand the answers I have been given. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I confirm that I agree to the way my data will be collected and processed and that data will be stored for up to 10 years in University archiving facilities in accordance with relevant Data Protection policies and regulations. ☐

I understand that all data and information I provide will be kept confidential and will be seen only by study researchers and regulators whose job it is to check the work of researchers. ☐

I agree that my name, contact details and data described in the information sheet will be kept for the purposes of this research project. ☐

I understand that if I withdraw from the study, my data collected up to that point will be retained and used for the remainder of the study. ☐

I agree to take part in the study. ☐

I understand and agree with how my collected samples will be processed and handled for purposes of this study. ☐

I agree to a sample of my blood being stored for a period of 10 years at University of Glasgow facility/facilities. ☐

_____ _____ _____

6.1.1.1 Name of participant **Date** **Signature**

_____ _____ _____

6.1.1.2 Name of Person taking consent **Date** **Signature**

(if different from researcher)

_____ _____ _____

6.1.1.3 Researcher **Date** **Signature**

(1 copy for participant; 1 copy for researcher)

Appendix 4-A : Flyer for Study the impact of the time of the day on muscle and metabolic response to resistance training (chapter 4)

University of Glasgow

VOLUNTEERS WANTED

Help us understand the impact of the time of day on muscle and metabolic responses to resistance exercise.

We are looking for volunteers of age 18 - 45 years; BMI >23.0kg/m², free from injury, metabolic or cardiovascular disease.

Resistance training exercise will involve 3 visits to the gym a week for 6 weeks (in either the morning or evening)

We will provide £50 upon completion to compensate you for your time

Further information please contact

A.dighriri.1@research.gla.ac.uk

Appendix 4-B : Health screen questionnaire (chapter 4)

HEALTH SCREEN FOR STUDY VOLUNTEERS Number .....

It is important that volunteers participating in research studies are currently in good health and have had no significant medical problems in the past. This is to ensure (i) their own continuing well-being and (ii) to avoid the possibility of individual health issues confounding study outcomes.

Please complete this brief questionnaire to confirm fitness to participate:

1. **At present,** do you have any health problem for which you are:
   - (a) on medication, prescribed or otherwise..... Yes ☐ No ☐
   - (b) attending your general practitioner..... Yes ☐ No ☐
   - (c) on a hospital waiting list..... Yes ☐ No ☐

2. **In the past two years,** have you had any illness which required you to:
   - (a) consult your GP ..... Yes ☐ No ☐
   - (b) attend a hospital outpatient department..... Yes ☐ No ☐
   - (c) be admitted to hospital ..... Yes ☐ No ☐

3. **Have you ever** had or been diagnosed with any of the following:
   - (a) Convulsions/epilepsy..... Yes ☐ No ☐
   - (b) Asthma/Respiratory disorders ..... Yes ☐ No ☐
   - (c) Eczema ..... Yes ☐ No ☐
   - (d) Diabetes..... Yes ☐ No ☐
   - (e) A blood disorder ..... Yes ☐ No ☐
   - (f) Head injury..... Yes ☐ No ☐
   - (g) Digestive problems..... Yes ☐ No ☐
   - (h) Heart problems ..... Yes ☐ No ☐
   - (i) Problems with bones or joints ..... Yes ☐ No ☐

(j) Disturbance of balance/coordination.....Yes ☐ No ☐

(k) Numbness in hands or feet .....Yes ☐ No ☐

(l) Disturbance of vision.....Yes ☐ No ☐

(m) Ear / hearing problems .....Yes ☐ No ☐

(n) Thyroid and adrenal problems.....Yes ☐ No ☐

(o) Kidney or liver problems.....Yes ☐ No ☐

(p) Allergies .....Yes ☐ No ☐

(q) High cholesterol ……. Yes ☐ No ☐

(r) High triacylglcyerol or any other form of dyslipidaemia…Yes ☐ No ☐

4. **Has any,** otherwise healthy, member of your family

died suddenly during or soon after exercise? .....Yes ☐ No ☐

5. **Are you**:

(a) dieting or taking dietary supplements ……Yes ☐ No ☐

(b) a smoker or have you ever smoked ……..Yes ☐ No ☐

6. **Have you** experienced significant weight loss/gain (greater than 10%) in the last 3 months?

……Yes ☐ No ☐

7. **How much** physical activity/exercise do you do on a weekly basis?…… (hours)

If you answered YES to any question, please describe briefly if you wish (eg to confirm problem was/is short-lived, insignificant or well controlled.)

……
……
……

Thank you for your cooperation!

University of Glasgow

Appendix 4-C : Participant information sheet (chapter 4)

University of Glasgow | College of Medical, Veterinary & Life Sciences

PARTICIPANT INFORMATION SHEET

1. **Study title**

The impact of the time of day on metabolic responses to resistance exercise in adults with a BMI greater than 23kg/m^2: a randomised controlled trial

2. **Invitation paragraph**

We invite you to participate in an investigation which we believe to be of potential importance. In order to help you to understand what the investigation is about, please read the following information carefully. Be sure you understand it before you formally agree to participate. If there a any points that need further explanation, please ask a member of the research team. It is important that you understand what you are volunteering to do and are completely happy with all the information before you sign this form.

3. **What is the purpose of the study?**

The aim of the current study is to determine the effect of time of day on the muscle and blood suga responses to resistance exercise training in adults with a BMI greater than 23 kg/m^2. To achieve th aim we have the following objectives: 1) Compare the effects of resistance exercise training performed in the morning vs the evening on the ability to control blood sugar levels. 2) Compare t effects of resistance exercise training performed in the morning vs the evening on gains in muscle mass and strength. 3) Compare the short-term blood sugar responses to resistance exercise performed in the morning vs the evening

4. **Why have I been invited to participate?**

You have been selected as a possible participant in this investigation because you are healthy and aged between 18-45 and not participating in any resistance exercise training or more than 1 hours per week of structured aerobic exercise.

5. **Do I have to take part?**

It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep and you will be asked to sign a consent form. If you do decide to take part, you are still free to withdraw at any time and without giving a reason.

6. What will happen to me if I take part?

You will be asked to visit the laboratory, at the University of Glasgow, at the beginning and the end of a 6-week period for various tests. We will randomly assign you to an exercise training or control group. If you are assigned to an exercise group, we will also ask you to attend 3 times per week for 6 weeks, either morning exercise (6:00-10:00am) or evening exercise (4:00-8:00pm). If you are assigned to the control group we will ask you to maintain your normal exercise habits. We ask all participants to maintain their normal diet during the study period.

Initial visit (~1hour)

On your first visit 1 week before you start the resistance training programme, you will be introduced to the laboratory personnel and familiarised with the study. You will be asked to complete a questionnaire to make sure you are safe to exercise. The Pittsburgh Sleep Quality Index (PSQI) and chronotype questionnaire will also be completed at baseline. Blood sugar responses will be measured using flash glucose monitors (FGMs) - a small sensor that sticks to your arm, the measurement will be worn for 14 days. This period will span 7-days prior to beginning the intervention and the first 7 days of the intervention.

Baseline visit (~3hours):

Prior to the baseline study visit we will ask you to record your food intake for 48 hours and replicate this prior to study visit on completion of the intervention. We will ask you to not eat anything overnight prior to the study visits and only consume water before coming to the laboratory. At baseline we will measure blood sugar control during an oral glucose tolerance test (OGTT), body composition (muscle and fat mass) and thigh muscle size via ultrasound, thigh muscle strength and grip strength. We will measure 1 repetition maximum (RM), which is the maximum weight you can lift once for the various exercises used in the exercise training. All participants will do the OGTT around (8:00-10:00am), while the strength measurements will be between (12:00 -1:00pm).

Intervention (6 weeks):

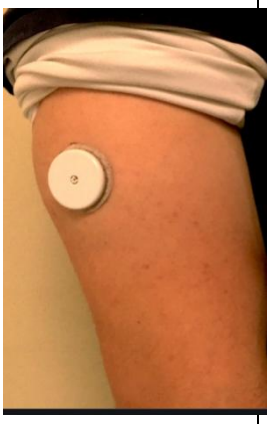
If you are randomized to exercise training then you will carry out exercise training for 6 weeks. Exercise will consist of 1 set of 8 exercises with 3 sessions per week for 6 weeks. The load to be used during training will be calculated as 80% of 1RM and within each set you will perform the number of repetitions required until you can't manage to do any more. Your 1RM will be re-tested on week 3, and the load adjusted accordingly. During the training period, all sessions of training will be supervised by the researcher in our laboratory in the Sir James Black Building. The following exercises will be performed: Bench press, biceps curl, lat pull down, overhead press, lateral raise, leg extension, leg curl and calf raise.

If you are randomized to the control group we will ask you to maintain your normal exercise habits for the 6 week period.

After 5 weeks of the intervention we will insert a flash glucose monitor again for a second 14 day period to cover the final 7 days of the intervention and 7 days following the end of the intervention period.

Post-intervention visit (~3hours):

The same measurements performed during the baseline visit will be repeated around 3 days after the completion of the exercise training.



Measurements:

Flash glucose monitors

The sensor sticks to your arm and continuously measures sugar levels in the fluid just under the skin (see picture to the right).

Oral Glucose Tolerance Test (OGTT)

A small plastic tube (a cannula) will be inserted into an antecubital vein and a baseline blood sample collected. You will then consume 75 g of sugar made up to 300 ml with water, and further blood samples will be collected after 30-, 60-, 90- and 120-min. Blood samples will be analysed for blood sugar levels. A total of 50ml (10 teaspoons) of blood will be taken during the visit. Following completion of the OGTT we will provide you with a snack before completion of the other measurements.

Thigh muscle size thickness

You will lie on an examination couch. We will then use a small handheld ultrasound device to measure the thickness of the thigh muscle.

Body composition

Bioelectrical impedance analysis scales will be used to measure muscle and fat mass.

1 repetition maximum

This involves increasing the weights applied during the exercise until you cannot perform a full single repetition of the exercise. We will ask you to warm up before each exercise and let you practice the technique.

Maximum voluntary contraction (MVC):

You will sit in a chair with your legs at a 90-degree angle. A strap will be placed around the right ankle which will be connected to a force sensor. We will ask you to contract maximally with the leg fixed in position and record force for 10 seconds. You will perform 3 contractions, with 1min rest between contractions.

Grip Strength:

We will ask you to perform 3 maximal contractions, on each hand, with the hand grip dynamometer.

7. What are the possible disadvantages and risks of taking part?

Exercise has a negligible risk in healthy adults, although maximal exercise does carry an extremely small risk of inducing myocardial ischaemia ("heart attack"). The screening procedures in place for this study minimise this risk. The primary symptom of myocardial ischaemia is chest pain on exertion. If you experience any unusual sensations in your chest, feel unwell or do not want to continue for any other reason during exercise you should cease exercising immediately.

Blood sampling via the cannula may cause minor bruising, an inflammation of the vein or haematoma (a small accumulation of blood under the skin). Good practice, however, minimises this risk. Some people may feel faint when they give blood.

There is the chance that you will feel muscle soreness for a day or two after performing the exercises. This is a normal and short-lived feeling and we will minimise the chances of this with an appropriate warm up and cool down.

8. What are the possible benefits of taking part?

The information gained during the study will allow us to give you detailed feedback about what time day is best to perform resistance exercise.

9. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the University will have your name and address removed so that you cannot be recognised from it. In addition, your records, samples and results will be identified by a number and not your name.

10. What will happen to my data?

All study data will be held in accordance with The General Data Protection Regulation (2018). The data will be stored in archiving facilities in line with the University of Glasgow retention policy of up to 10 years. After this period, further retention may be agreed or your data will be securely destroyed in accordance with the relevant standard procedures.

11. What will happen to the results of the research study?

The results from this study will be presented at scientific meetings and published in scientific journals. The results will also be used in the research project reports of the PhD student undertaking this research. A copy of the published results will be sent to you upon request. You will not be identifiable in any of the data presented or published from this study.

12. Who is organising and funding the research?

University of Glasgow.

13. Who has reviewed the study?

This study has been reviewed and approved by the Ethics committee of the College of Medical, Veterinary and Life Sciences at the University of Glasgow.

14. Contact for Further Information

Mr. Anas Dighriri

Institute of Cardiovascular and Medical Sciences

College of Medical, Veterinary and Life Sciences

University of Glasgow

Glasgow G12 8TA

Phone: 07984916774

E-mail: a.dighriri.1@research.gla.ac.uk

Appendix 4-D : Participants consent form (chapter 4)

University of Glasgow | College of Medical, Veterinary & Life Sciences

Project Number:

Participant Identification Number for this trial:

Title of Project: The impact of the time of day on metabolic responses to resistance exercise in adults who are obese or overweight: a randomised controlled trial

Name of Researcher(s):

Mr.Anas Dighriri

Dr. Stuart Gray

Dr. James Boyle

Dr. Hannah Lithgow

Dr. Brendan Gabriel

Miss. Lynsey Johnston

CONSENT FORM

Please initial box

I confirm that I have read and understood the Participant Information Sheet version 1 dated 11/11/2021. ☐

I confirm that I have read and understood the Privacy Notice version 1 dated 11/11/2021 ☐

I have had the opportunity to think about the information and ask questions and understand the answers I have been given. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I confirm that I agree to the way my data will be collected and processed and that data will be stored for up to 10 years in University archiving facilities in accordance with relevant Data Protection policies and regulations. ☐

I understand that all data and information I provide will be kept confidential and will be seen only by study researchers and regulators whose job it is to check the work of researchers. ☐

I agree that my name, contact details and data described in the information sheet will be kept for the purposes of this research project. ☐

I understand that if I withdraw from the study, my data collected up to that point will be retained and used for the remainder of the study. ☐

I agree to take part in the study. ☐

I understand and agree with how my collected samples will be processed and handled for purposes of this study. ☐

I agree to a sample of my blood being stored for a period of 10 years at University of Glasgow facility/facilities. ☐

_____ _____ _____

6.1.1.4 Name of participant **Date** **Signature**

_____ _____ _____

6.1.1.5 Name of Person taking consent **Date** **Signature**

(if different from researcher)

_____ _____ _____

6.1.1.6 Researcher **Date** **Signature**

(1 copy for participant; 1 copy for researcher)

Appendix 4-E : Munich Chronotype Questionnaire (MCTQ) (chapter 4)

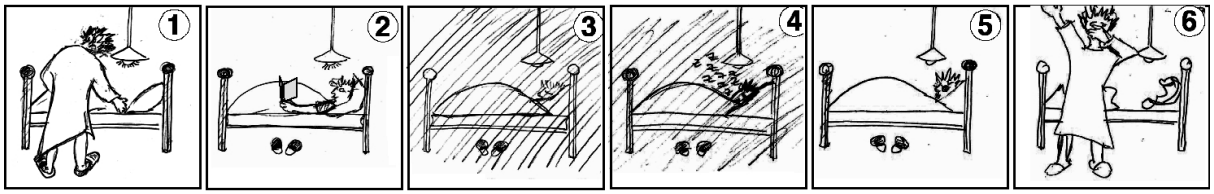
MCTQ

I have a regular work schedule (this includes being, for example, a housewife or househusband):

Yes ☐ I work on 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ day(s) per week.

No ☐

Is your answer "*Yes, on 7 days*" or "*No*", please consider if your sleep times may <u>nonetheless</u> differ between regular 'workdays' and 'weekend days' and fill out the MCTQ in this respect.



Please use 24-hour time scale (e.g. 23:00 instead of 11:00 pm)

Workdays

Image 1: I go to bed at_____ o'clock.

Image 2: Note that some people stay awake for some time when in bed!

Image 3: I actually get ready to fall asleep at _____ o'clock.

Image 4: I need _____ minutes to fall asleep.

Image 5: I wake up at _____ o'clock.

Image 6: minutes I get up

I use an alarm clock on workdays: Yes No

If "Yes": I regularly wake up BEFORE the alarm rings: Yes ☐ No ☐

Work Details

In the last 3 months, I worked as a shift worker.

No ☐ Yes ☐ (please continue with "*My work schedules are ...*").

My usual work schedule …

… starts at_____o´clock.

… ends at_____o´clock.

My work schedules are …

… very flexible ☐ … a little flexible ☐ … rather inflexible ☐ … very inflexible ☐

I travel to work …

… within an enclosed vehicle (e.g. car, bus, underground). ☐

… not within an enclosed vehicle (e.g. on foot, by bike). ☐

I work at home ☐

For the commute to work, I need____hours and____minutes.

For the commute from work, I need____hours and____minutes.

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