Exercise in Glycogen Storage Disease: Exploring Functional Decline, Physical Activity, and Nutrition

by

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Copyright Statement

Abstract

Glycogen storage diseases (GSDs) are a group of rare inherited metabolic Disorders (IMD) that remain broadly understudied due to their low prevalence. These diseases, often caused by single mutations in genes responsible for carbohydrate metabolism, manifest through significant physical limitations that impact patients from childhood through adulthood and typically affect the skeletal muscle and/or liver. A key characteristic of GSDs, particularly those affecting skeletal muscle, is severe exercise intolerance and muscle weakness, which leads to restricted physical activity, and impaired quality of life (QoL). The profound impact on exercise capacity not only contributes to the progressive nature of the disease, with increased morbidity and potential for severe disability, but also presents a chance to study GSDs from a new perspective. By investigating how these metabolic abnormalities directly impair exercise tolerance, we can gain valuable insights into disease mechanisms and explore therapeutic strategies specifically aimed at improving physical function.

Though the progressive decline in physical function is recognised, there is a paucity of data in which extensive clinical and functional outcomes, including exercise tolerance and muscle impairment, have yet to be fully quantified. This lack of comprehensive data is particularly evident in GSD 3a, a relatively common subtype involving significant muscle pathology, where the extent of exercise intolerance and related factors remains underexplored. Accurate benchmarking of these clinical outcomes is crucial to guide effective patient care and to understand the progression of the disease. Additionally, exercise intolerance, a hallmark feature across multiple GSD subtypes, underscores the need to investigate therapeutic strategies. These could include exercise training and dietary interventions, both of which have shown potential benefits but require further evaluation to determine their efficacy and optimal implementation in the GSD population.

Exercise training has shown benefits where it has been evaluated; however, a comprehensive review of its effects across all GSD subtypes is lacking. Consequently, key questions about the efficacy of exercise interventions, the specific subtypes that benefit, the optimal training modalities, and patient adherence remain unanswered. Furthermore, an understanding of physical activity behaviours and participation barriers across GSD populations is essential for designing effective, personalised interventions. Alongside exercise, dietary management also plays a critical role in addressing metabolic deficiencies. However current strategies are often confined to macronutrient manipulation, with the potential of novel dietary supplements, particularly in GSD 3a, requiring further exploration.

Given the significant burden that GSDs place on patients' daily lives and long-term health, there is a compelling need for research that not only quantifies the extent of physical impairment and disease progression but also explores effective treatment strategies to address critical knowledge gaps. Due to the rarity of these conditions, they are often under-researched, especially regarding monitoring the decline in physical function and overall well-being and exploring the potential of non-pharmacological treatments. This thesis aims to address these needs by investigating the natural progression of GSD 3a across a range of clinical, functional and psychological outcomes. It also reviews the role of exercise training across various GSDs, and assesses physical activity behaviours, and identifies barriers and facilitators to physical activity participation. Additionally, the research explores a novel dietary treatment specifically tailored for glycogenosis diseases like GSD 3a.

For the first time, the study in **Chapter 3** quantitatively assessed muscle strength and aerobic function limitations in GSD 3a, examining a group of 7 patients in a cross-sectional analysis. Exercise capacity was found to be profoundly limited, with aerobic capacity and muscle strength significantly lower than predicted. There was also a strong association between aerobic capacity and maximal leg strength. Furthermore, patients with a higher physical capacity had

superior muscle size and structural characteristics and a higher QoL. This was the first study to document the extent of the reduced physical capacity in GSD 3a and to examine the role of muscle size and quality on exercise impairment, ultimately highlighting the need for ongoing assessment.

Subsequently, a longitudinal follow up of three GSD 3a patients in **Chapter 4** documented, for the first time, the significant and variable progression of exercise limitation using robust and validated methodologies. This case series revealed substantial reductions in aerobic capacity and muscle strength, along with pronounced reductions in muscle volume and physiological cross-sectional area. Additionally, undesirable changes in body composition were observed, with increased body fat and reductions in lean mass. The rate of decline in skeletal muscle structural and functional characteristics varied among cases, underscoring the potential role of physical activity in attenuating this decline and its promise as an intervention.

This research, along with others', has identified a significant reduction in exercise capacity and muscle function in GSD 3a and various other GSD subtypes. This decline in function impacts well-being and may be amenable to change through physical activity interventions, offering a valuable opportunity for therapeutic intervention, where exercise training could be beneficial. Although existing exercise training studies have shown promise, they are limited by small sample sizes, varying GSD types, and diverse interventions, underscoring the need for more comprehensive evaluations. In **Chapter 5**, a systematic review was conducted to evaluate the effectiveness of exercise as a therapeutic intervention across all GSDs. The findings indicate that supervised aerobic and/or resistance training is safe and effective for adults with GSD 2 and GSD 5, leading to improvements in aerobic capacity, muscle strength, functional capacity, disease severity, and overall well-being. However, the impact of exercise training on other GSD types, particularly GSD 3a, has not been studied and warrants investigation.

While the previous chapter indicated the benefits of exercise for specific GSD subtypes, the extent of exercise engagement among individuals with GSD is still not well understood. Therefore **Chapter 6** explored physical activity levels, behaviours, barriers, facilitators and activity preferences across the GSD population through an online survey. As expected, physical activity was low across the cohort, with fatigue and motivation associated to these reduced levels along with multiple barriers reported, such as the severity of symptoms, concerns that physical activity might worsen their condition, and a lack of motivation. Despite the barriers, the majority (86%) of respondents showed a strong interest in participating in physical activity programs, especially outdoor or home-based light to moderate strengthening and cardiovascular activities, administered with professional support.

Building on these insights, **Chapter 7** conducted a more detailed investigation into the barriers and facilitators to physical activity in individuals with GSDs through semi-structured interviews and focus groups. The qualitative analysis uncovered a wide range of factors influencing physical activity. Notably, individuals' physical health, particularly disease-specific symptoms, emerged as a significant barrier, often affecting their motivation to engage in physical activity. Additionally, access to exercise facilities and support from friends, family and professionals could serve as either barriers or facilitators, depending on their presence or lack of. Given the diversity of challenges, it was evident that tailored interventions that address individual barriers with professional support may be beneficial.

In addition to exercise training, **Chapter 8** explored oral lactate supplementation as a potential novel treatment strategy. A proof-of-concept study assessed the feasibility, safety, and efficacy of oral calcium lactate in healthy participants who became glycogen-depleted during prolonged exercise, mimicking conditions similar to those with glycogenolytic/glycolytic deficiencies like GSD 3a, GSD 5, and GSD 7. The study found that oral lactate supplementation induced positive changes in acid-base balance and Ratings of Perceived

Exertion (RPE), though these benefits did not improve exercise performance. While the supplementation appears safe, further research is needed to determine the optimal and efficacious dosing, especially before considering application in the GSD population.

Overall, the findings within this thesis detail the profound physical limitation and exercise intolerance in those with GSD 3a, with progressive decline in aerobic capacity and muscle strength throughout adulthood. This exists alongside existing evidence of a general decline in physical performance found across other forms of GSDs and presents a unique opportunity to implement physical activity interventions to improve outcomes. Our systematic review suggests that exercise training may be effective in improving aerobic capacity and muscle function, but research is limited to GSD 2 and GSD 5. Despite the beneficial effects of exercise being acknowledged, physical activity levels are low compared to the general population, with the severity of symptoms (including myopathy, hypoglycaemia, fatigue), a lack of accessibility and a lack of support from others presenting as key challenges. These specific barriers, along with the facilitators to physical activity discovered would need to be carefully considered to implement effective exercise programmes within this clinical population. Furthermore, lactate supplementation has the potential to circumvent the metabolic block in glycogenolytic/glycolytic diseases such as GSD 3a, offering a promising treatment approach. This could complement the established benefits of glucose and sucrose supplementation, which are well-documented in GSD 5. While lactate has demonstrated notable effects on acid-base balance and perceived exertion in a healthy population, further research is necessary to determine optimal dosing strategies that could maximise metabolic and physiological benefits before its application in the GSD population.

List of Key Abbreviations

BMI: Body mass index

CPET: Cardio Pulmonary Exercise Test

CV: Coefficient of variation

GET: Gas Exchange Threshold

GLUT1: Glucose transporter type 1

GLUT2: Glucose transporter type 2

GLUT4: Glucose transporter type 4

GSD: Glycogen Storage Disease

HR: Heart Rate

ICC: Intraclass correlation coefficient

IMD: Inherited Metabolic Disorders

MVC: Maximum voluntary contraction

RTD: Rate of Torque Development

$\dot{V}O_{2max}$: Maximal oxygen uptake

$\dot{V}O_{2peak}$: Peak oxygen uptake

$\dot{V}O_2$: Oxygen uptake

QoL: Quality of life

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Preface

Unless otherwise indicated by reference to published resources, the work in this thesis is that of the author and has not been previously submitted for another degree to this or any other University. While the data for Chapter 3 had been previously collected, the author conducted data analysis and manuscript preparation.

Some of the work within this thesis has been published in peer-reviewed journals and/or presented at conferences:

Published Original Investigations

Hennis, P. J., Murphy, E., Meijer, R. I., Lachmann, R. H., Ramachandran, R., Bordoli, C., Rayat, G., & Tomlinson, D. J. (2022) Aerobic capacity and skeletal muscle characteristics in glycogen storage disease IIIa: an observational study. *Orphanet Journal of Rare Diseases*, 17(1). https://doi.org/10.1186/s13023-022-02184-1.

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Chapter 1 – General Introduction

Glycogen storage diseases (GSDs) or glycogenosis represent a rare heterogeneous group of inherited metabolic disorders (IMD) with an estimated prevalence of 1 case in 20,000 to 40,000 live births, though prevalence can vary by type (Ozen, 2007). These diseases are caused by single gene mutations that encode enzymes involved in carbohydrate metabolism (Hicks et al., 2011), leading to defective glycogenosis, glycolysis or glycogen synthesis (Smit et al., 2006). The specific enzyme deficiency and tissue involvement are used to classify people to one of at least 16 well-recognised types, though further subtypes and mutations have been described (Heller et al., 2008; Ross et al., 2020). These typically affect the skeletal muscle and/or the liver (Heller et al., 2008) although the heart, kidney and brain may also be affected (Gumus & Ozen, 2023). Physical manifestations are highly variable between different GSD types and individuals (Bhengu et al., 2014; Chien et al., 2013; Schoser et al., 2017) in which some cases are asymptomatic, while others have serious pathophysiological implications, significantly impacting physical health, QoL, and life expectancy (Kanungo et al., 2018). Liver involvement may lead to hypoglycaemia, hepatomegaly, and liver disease (Tarnopolsky, 2018), and skeletal muscle involvement often results in skeletal myopathy, muscle weakness, and cramps (Heller et al., 2008; Tarnopolsky, 2018). These manifestations contribute to compromised habitual functioning, increased morbidity, and in some cases, premature death
(Mate-Munoz et al., 2007; Preisler et al., 2013; Vissing, 2016).

The extent of exercise intolerance and muscle impairment is not well quantified across all GSD subtypes and this is particularly true in GSD 3a, one of the more prevalent types of GSD with muscle involvement. While a decline in exercise tolerance and muscle function is commonly observed in GSD 3a, particularly with increasing age, the available evidence on clinical and functional outcomes remain limited, especially regarding genetic diagnosis, treatment, and

assessment of muscle size, strength, bone mineral density, physical activity, and QoL. Retrospective reviews of medical records are available (Hijazi et al., 2021; Sentner et al., 2016), however, data is largely descriptive, and the progression of exercise intolerance and muscle impairment across the lifespan and associated factors has not been established. Obtaining comprehensive data across a range of clinical and functional outcomes within a prospective longitudinal natural history study, is therefore required to improve our understanding of the mechanisms underpinning the progression of GSD 3a. This data will also provide valuable information for patients and health care professionals to evaluate the effectiveness of current and future treatments, including relevant endpoints and comparator normative data, which are key requirements for any future clinical trials and drug discovery efforts.

More broadly, the prevalence of exercise intolerance and known progression is not just limited to GSD 3a but exists in the broader context of GSDs and as such presents a distinct opportunity for therapeutic intervention; particularly as at present no curative treatment options are available (Stone et al., 2021). Supervised exercise training programs have been recommended as therapeutic in consensus guidelines for GSDs (Cupler et al. 2011; Kishnani et al., 2006; Kishnani et al., 2010; Lucia et al., 2021; Wicker et al., 2023) with exercise programmes including aerobic, resistance, and respiratory muscle training championed by researchers and clinicians for their potential therapeutic benefits. Indeed, research suggests that these interventions are safe and effective in reducing symptoms, enhancing QoL, and improving general health and fitness, without adverse effects (Preisler et al., 2014; Quinlivan et al., 2011). The available evidence base includes studies with relatively small sample sizes and heterogenous methodologies, which complicates drawing generalisable conclusions. Therefore, in order to fully understand this heterogenous body of literature, a robust and comprehensive review of the existing evidence is required. Furthermore, despite the advocacy for physical activity in GSD management (Cupler et al., 2011; Kishnani et al., 2006; Lucia et al., 2021), it

is not known whether individuals with GSDs engage in physical activity and what specific barriers or facilitators they encounter. Furthermore, investigation into the optimal design and implementation of exercise interventions that meet the specific needs and preferences of those with different GSD types has not been identified. Exercise is likely beneficial for individuals with GSDs, though the variable onset and progression of symptoms may present unique challenges compared to individuals without GSDs, warranting further investigation into the specific barriers faced. Knowledge of physical activity levels and awareness of factors that influence exercise participation is crucial, particularly for researchers and health professionals to effectively tailor their support and develop effective interventions to meet the needs and lifestyles of their patients, ultimately aiming to improve health outcomes long term.

In addition to exercise training, dietary treatment has proved an effective therapeutic strategy over the last 50 years, with variations in dietary treatment depending on the underlying enzyme defect and metabolic pathway involved (Bhengu et al., 2014; Heller et al., 2008). In hepatic GSDs, therapeutic strategies focus particularly on preventing hypoglycaemia, improving metabolic disturbances, and supporting normal blood glucose levels (Ross et al., 2020). However, despite decades of research there is a lack of general consensus on the optimal dietary treatment, which is largely limited to the manipulation of macronutrients (Bhengu et al., 2014; Heller et al., 2008). Moreover, other therapeutic options include Enzyme replacement therapy (ERT) which is clinically efficacious in GSD 2, however despite ongoing research, is not available for other GSDs (van der Ploeg et al., 2010) and supportive measures such as non-invasive ventilation (NIV) and cough assistive devices are only of benefit in GSD 2 (Chien et al., 2013; Gaeta, et al., 2015). Despite these therapeutic options shown to be of benefit, impairments in functional capacity and QoL still persist (Heller et al., 2008; Ross et al., 2020), thus there is a need to explore further novel dietary treatments to enhance treatment efficacy in GSD patients.

As an adjunct therapy to exercise training and macronutrient manipulation, novel treatments such as oral lactate supplementation may potentially improve exercise tolerance within GSDs. Lactate is no longer deemed a harmful waste product, but an important energy intermediate (Brooks, 2018). Lactate has gained attention as a potential energy substrate and pH balance mediator, and emerging research has investigated its effects on exercise performance, including in healthy human populations (Morris et al., 2012). However, more recent research suggests lactate supplementation could be beneficial in those with complete glycogenolytic/glycolytic deficiencies (Ørngreen et al. 2015). Research has shown that, despite a block in glycogenolysis, lactate is still released from active muscles in individuals with GSD 5, similar to what occurs in healthy controls, although the overall metabolic response may differ (Ørngreen et al. 2015). In GSD 5 however, lactate uptake exceeds this release, resulting in a net lactate uptake and oxidation. Lactate supplementation could potentially serve as an ergogenic aid in GSD patients, particularly in those with complete glycogenolytic/glycolytic deficiencies, such as GSD types 5 and 7, though further research is needed to confirm its efficacy (Ørngreen et al. 2015). It remains unexplored if lactate supplementation, could be tolerated and if such supplementation would indeed be of benefit to performance. This highlights the need for targeted research to assess both the tolerability and the potential performance outcomes of lactate supplementation.

The rarity of GSDs has resulted in a significant lack of comprehensive literature, which underpins many of the challenges in advancing research and improving patient outcomes. This scarcity of data is particularly evident in GSD 3a, where gaps in knowledge persist regarding normative fitness, disease progression, and the mechanisms driving exercise intolerance. Despite well-documented physical limitations and a progressive decline in muscle function, studies investigating the natural history of GSD 3a and associated clinical and functional outcomes remain limited. Existing research is mostly descriptive and fails to provide extensive, longitudinal insights necessary to guide effective treatment strategies.

Furthermore, while exercise intolerance is widespread across various GSD types, and exercise training has shown potential as a therapeutic intervention, the available evidence is fragmented, derived from small studies with heterogeneous methodologies and outcomes. There is also limited understanding of the current physical activity levels and exercise behaviors among individuals with GSDs, as well as the barriers and facilitators they face. Additionally, few novel therapeutic options have been explored to address exercise intolerance specifically.

Given these gaps, there is an urgent need for comprehensive, long-term studies to establish the natural history of GSD 3a, quantify exercise limitation, and identify risk factors contributing to disease progression. This research will generate crucial benchmarking data to improve patient care and support drug discovery through well-defined clinical endpoints and robust external comparator data. Since exercise intolerance offers a unique opportunity for therapeutic intervention, systematic reviews and studies exploring the effectiveness of exercise training, as well as the factors influencing exercise participation, are essential. Moreover, the exploration of adjunct therapies like lactate supplementation is necessary to expand the limited treatment options available for glycogenolysis disorders such as GSD 3a. Together, these efforts will deepen our understanding and ultimately improve clinical care for those affected by these rare metabolic conditions.

Chapter 2 - Literature Review

2.1 Inherited Metabolic Diseases

Inherited metabolic disorders (IMD) are genetic disorders that may occur as a result of enzymatic deficiency and cause disruption of metabolic pathways (Ferreira, & van Karnebeek, 2019). This can lead to disease through several mechanisms including as a result of the toxic accumulation of substrates proximal to the metabolic block, deficiencies of substrates distal of the metabolic block or via the diversion of substrates along alternative pathways (Ferreira & van Karnebeek, 2019). Inherited metabolic disorders are therefore highly variable in clinical and biochemical phenotype, presentation and treatment and there appears to be a wide spectrum of metabolic tolerance even within the same disorder. As a result of the heterogeneity in clinical presentation, which can overlap with many other diseases, the diagnosis and classification of IMDs can prove particularly challenging (Ferreira & van Karnebeek, 2019; Waters et al., 2018). At present, the International Classification of Inherited Metabolic Disorders (ICIMD) includes 1,462 disorders (ICIMD, 2025). The vast majority of these have been classified by Ferreira et al. (2021) into 24 categories, comprising of 124 groups, with the initial 13 categories encompassing disorders of intermediary metabolism involving the metabolism of protein, lipids or carbohydrate. Although individually rare, these disorders are considered collectively common. Reported prevalence ranges from greater than 1 in 800 individuals (Wilcox, 2018) to an estimated global birth prevalence of 50.9 per 100,000 live births (Waters et al., 2018). These figures however should be interpreted with caution, as estimates vary by population and screening methods, and are susceptible to underestimation due to missed diagnosis and incomplete coverage (Waters et al., 2018). The implementation of newborn screening, along with advancements in screening, diagnosis, and treatment, has led to increased awareness of IMDs and a growing population of affected individuals, particularly as they transition into adulthood. Recent European estimates suggest that approximately 50% of IMD patients are

adults, although this proportion varies depending on the specific disorder, healthcare access, and regional differences (Gariani et al., 2020; Schwarz & Wendel, 2005; Sirrs et al., 2015).

2.2 Glycogen Storage Diseases

Glycogen storage diseases (GSDs) are a rare heterogeneous group of IMDs characterised by abnormalities in carbohydrate metabolism, most often arising from single pathogenic variants but sometimes from multiple variants or compound heterozygosity in genes that encode enzymes specifically involved in glycogen metabolism (**Appendix A**; Hicks et al., 2011; Kanungo et al, 2018). This results in enzyme deficiencies and subsequent defects in glycogen metabolism, affecting glycogenolysis or glycogenesis and, in some types, glycolysis (Hicks et al., 2011; Smit et al., 2006). As such, the inability to effectively synthesise or utilise glycogen is central to the development of GSDs (Hicks et al., 2011), warranting further consideration of the role of glycogen in human metabolism and the impact of these enzymatic disruptions.

Glycogen is a branched polymer of glucose, consisting of chains of alpha (1-4) glycosyl bonds and alpha 1-6 glycosyl branch points, with each molecule unique in structure and of no fixed size (Haller, 2015; Kishnani, 2014). Although glycogen is present in all tissues, it is predominantly stored within glycogen granules in the cytoplasm of hepatocytes and myocytes (Kanungo et al, 2018). By weight, the liver contains the highest percentage of glycogen (up to approximately 10%) with muscle storing approximately 2% by weight. However, since total muscle mass exceeds that of the liver, total glycogen within the skeletal muscle is approximately double that of liver (Stone et al., 2021). Liver glycogen contributes to the maintenance of normoglycemia, with glucagon released in response to hypoglycaemia during short periods of fasting, stimulating glycogenolysis or in the case of excess post prandial circulatory glucose, insulin is released stimulating glycogen storage (Kanungo et al., 2018). In contrast to the liver, skeletal muscle utilises glycogen as a key substrate in moderate-intensity

exercise, prolonged endurance activity and particularly during high-intensity exertion (Smit et al., 2006). As a consequence, symptoms associated with GSDs typically manifest in the liver and skeletal muscle (Di Mauro et al., 2004; Laforet et al., 2012) with hepatic GSDs typically presenting with hypoglycaemia ± hepatomegaly (Tarnopolsky, 2016), whereas skeletal muscle GSDs typically present as exercise intolerance and rhabdomyolysis or fixed muscle weakness without rhabdomyolysis (Tarnopolsky, 2016). In some cases, the kidneys, heart and the brain can also be affected (Aoun et al., 2020; Kanungo et al., 2018). The disruption in normal glycogen synthesis or breakdown due to genetic variations underpins the pathophysiology of GSDs, in which the specific enzyme deficiency and relative tissue involvement are used to classify people to one of at least 19 GSD types currently ranging from Type 0 to Type XV (Stone et al., 2025) and the majority inherited in an autosomal recessive manner (Walter et al., 2016). GSD types are commonly classified by the order of their discovery in roman numerals, by the deficient enzyme or the author who first described them. However, these naming conventions are not applied consistently, with GSD IX being a notable exception since it includes multiple subtypes of phosphorylase kinase deficiency classified by the affected gene rather than a single numerical designation (Derks et al., 2018).

2.2.1 Prevalence and Epidemiology

The prevalence of all GSD subtypes is estimated to be between 1 in 20,000 to 1 in 43, 000 live births (Ozen, 2007), however, this is likely to be an underestimation due to significantly mild forms going undiagnosed and others resulting in early foetal or neonatal death without a diagnosis (Hannah et al, 2023; Stone et al., 2025). Additionally, as with other rare diseases, GSDs suffer from a lack of well-developed and regularly updated registries, further complicating accurate prevalence estimates. Current data indicates that the most prevalent GSD types are GSD 1, GSD 2, GSD 3, GSD 5, GSD 8 and GSD 9 (Molares-Vila et al., 2021), however epidemiological data is lacking, particularly in GSD 0a, GSD 0b, GSD 7, GSD 10,

GSD 11, GSD 12, GSD 13, GSD 15, PGMI-CDG, FBS and PGK deficiency (Hannah et al, 2023). No sex differences in prevalence or incidence have been observed for most autosomal recessive GSDs. However, in X-linked GSDs (e.g., GSD 9A1, GSD 9A2, PGK deficiency) the prevalence is higher in males (Hannah et al, 2023). Furthermore, despite substantial allelic heterogeneity between GSDs, the presence of founder variants have been discovered, which, may in part, explain the differences in prevalence and/or incidence and physical manifestations between those of different ethnicities (Hannah et al, 2023). For instance, GSD 3 is more commonly observed in individuals of North African and Jewish descent, while GSD 6 is more prevalent among the Old Order Mennonite population (Stone et al., 2025). The low prevalence of these disorders poses significant challenges for research, often leading to gaps in our understanding and slower progress in developing effective treatments.

2.2.2 Metabolic Pathways involved in GSDs

To understand the clinical manifestations of GSDs, it is crucial to first explore the underlying mechanisms of glycogen metabolism and the specific enzymatic defects characteristic of each GSD type, as illustrated in **Figure 2.1**. The interconversion of glucose through glycogen synthesis and degradation is central to glycogen metabolism and may influence glucose homeostasis, depending on the tissue involved, with defects in these processes forming the basis of GSD aetiology. Since glycogen is largely stored in the liver and muscle tissues, this discussion focuses on glucose metabolism primarily within these tissues in response to the contrasting physiological states of fed and fasted which govern glucose utilisation and storage. Additionally, the storage and degradation of glycogen in the lysosomes will be discussed, in which metabolic defects within these pathways give rise to lysosomal GSDs such as GSD 2.

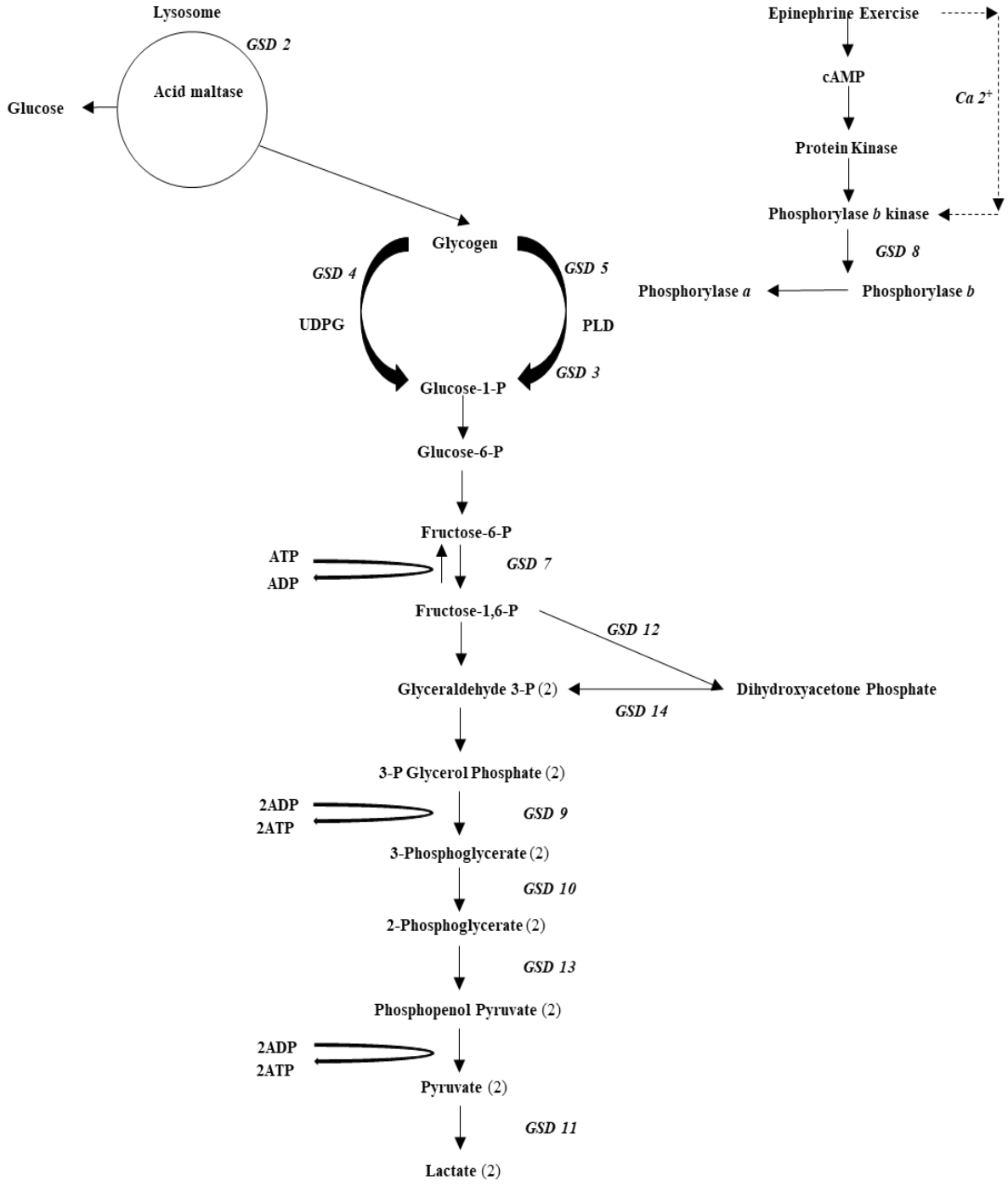


Figure 2.1 Glycogen metabolism pathways and designated GSDs affecting muscle (Adapted from Di Mauro, 2007).

The GSDs include defects in the following enzymes: GSD 2, acid maltase; GSD 3, debrancher. GSD 4, brancher; GSD 5, myophosphorylase; GSD 7, phosphofructokinase (PFK); GSD 8, phosphorylase *b* kinase (PHK); GSD 9, phosphoglycerate kinase (PGK); GSD 10, phosphoglycerate mutase (PGAM); GSD 11, lactate dehydrogenase (LDH); GSD 12, aldolase A; GSD 13, β-enolase. Abbreviations: c-AMP, cyclic adenosine monophosphate; ADP, adenosine diphosphate; ATP, adenosine triphosphate; PLD, phosphorylase-limit dextrin; UDPG, uridine-diphosphate glucose.

2.2.2.1 Skeletal muscle glucose utilisation

Glucose is transported into skeletal muscle via two glucose transporters known as GLUT4 and GLUT1 (Thorell et al., 1999). GLUT4 is located both in the sarcolemma and in intracellular vesicles and can relocate to the sarcolemma in response to insulin release or muscle contraction, thereby increasing glucose uptake. In contrast, GLUT1 is unresponsive to insulin or muscle contraction (Hayashi et al., 1997). Once inside skeletal muscle, glucose is phosphorylated by hexokinase II to form glucose-6-phosphate. Depending on the physiological state, glucose-6-phosphate is either directed towards glycogen synthesis for storage or enters the glycolytic pathway (Tarnopolsky, 2018).

In the fed state, insulin levels are high and glycogenesis occurs, beginning with the conversion of glucose-6-phosphate to glucose-1-phosphate by the enzyme phosphoglucomutase-1. Glucose-1-phosphate is then converted to UDP-glucose by UDP-glucose pyrophosphorylase. These UDP-glucose molecules are sequentially attached in a 1,4-configuration to the glycogenin-1 protein backbone, a crucial priming step. Insulin activates glycogen synthase, which further extends the glycogen chain through α-,4 linkages. The glycogen branching enzyme then introduces α-1,6 linkages, creating a branched glycogen structure. This glycogen is stored in granule-like structures beneath the sarcolemma (subsarcolemmal) and between actin-myosin contractile elements (intermyofibrillar) (Tarnopolsky, 2018). Skeletal muscle typically contains 200-400 mmol/kg dry muscle weight of glycogen, a level that can increase by up to two-fold in athletes and individuals with GSDs (Costill et al., 1981; Tarnopolsky, 2018).

In the fasted state or during periods of heightened metabolic demand glycogenolysis occurs, driven by elevated levels of epinephrine. This triggers the phosphorylation of phosphorylase b kinase, which in turn activates myophosphorylase. Myophosphorylase hydrolyses the α-1,4-glycosidic bonds in glycogen, initiating glycogenolysis. The glycogen debranching enzyme

(GDE) further hydrolyses the α-,6-glycosidic bonds, yielding glucose-1-phosphate. Glucose-1-phosphate is subsequently converted to glucose-6-phosphate by phosphoglucomutase-1 and then to fructose-6-phosphate by G-6-P-isomerase, marking the entry into glycolysis. Glycolysis begins when fructose-6-phosphate is converted to fructose 1,6-bisphosphate by the rate-limiting enzyme phosphofructokinase (PFK), which is activated by inorganic phosphate and possibly creatine (Storey & Hochachka, 1974). The six-carbon fructose 1,6-bisphosphate is then cleaved by aldolase into two three-carbon molecules: glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (Tarnopolsky, 2018). When energy demand is particularly high, dihydroxyacetone phosphate is converted back to glyceraldehyde 3-phosphate by triosephosphate isomerase. Glyceraldehyde 3-phosphate is then transformed into 1,3-bisphosphoglycerate through the action of phosphoglycerate kinase (PGK), which is subsequently converted to 2-phosphoglycerate by phosphoglycerate mutase 2 (PGAM-2). Next, 2-phosphoglycerate is converted to phosphoenolpyruvate (PEP) by β-enolase, and PEP is finally converted to pyruvate by pyruvate kinase (PK) (Tarnopolsky, 2018). During the transition from rest to exercise and/or under anaerobic conditions and even under aerobic conditions, pyruvate is converted to lactate by lactate dehydrogenase. This regenerates NAD^+, allowing glycolysis to proceed at the glyceraldehyde-3-phosphate dehydrogenase step. If oxygen is available and metabolic demand persists, pyruvate can instead enter aerobic metabolism. In this case, it undergoes dehydrogenation and decarboxylation by the pyruvate dehydrogenase (PDH) complex, enabling its entry into the TCA cycle for oxidation (Tarnopolsky, 2018).

2.2.2.2 Liver glucose utilisation

While skeletal muscle primarily uses glucose for energy, the liver plays a crucial role in maintaining glucose homeostasis (Kanungo et al., 2018). Glucose is transported into hepatocytes by GLUT2, a high-capacity, low affinity transporter facilitating glucose entry down a concentration gradient (Adeva-Andany et al., 2016). Once inside the liver, glucose is phosphorylated by glucokinase to form glucose-6-phospate (Chen & Weinstein, 2016). As with skeletal muscle, glucose-6-phosphase can enter a number of metabolic pathways depending on the physiological state (Adeva-Andany et al., 2016).

In the fed state, when circulating glucose levels are elevated, glycogen synthesis represents a major route for glucose storage in hepatocytes, alongside glucose oxidation via glycolysis and the TCA cycle (Adeva-Andany et al., 2016). As within skeletal muscle, glucose-6-phosphate is converted to glucose-1-phosphate and then to UDP-glucose. UDP-glucose then attaches to glycogenin, serving as a priming step. Further elongation of the glycogen chain by the addition of glucose units via glycogen synthase and the creation of branch points by branching enzyme forms the highly branched glycogen structure (Chen & Weinstein, 2016).

Alternatively, if immediate energy is required, glucose-6-phosphate enters the glycolytic pathway as previously described to form pyruvate. Pyruvate can then be converted to acetyl-CoA and enter the TCA cycle for ATP production or, where glucose is in excess and glycogen stores are saturated, acetyl-CoA is diverted towards lipogenesis contributing to the synthesis of fatty acids and triglycerides (Adeva-Andany et al., 2016). Additionally, a portion of glucose-6-phosphate can be shunted into the pentose phosphate pathway (PPP) to provide NADPH for the synthesis of fatty acids and ribose-5-phosphate, a nucleotide precursor (Adeva-Andany et al., 2016).

During fasting, glycogenolysis is initiated in response to glucagon or epinephrine to maintain glucose homeostasis (Chen & Weinstein, 2016). Glycogen phosphorylase is activated via phosphorylation by phosphorylase b kinase, and cleaves the α-1,4, glycosidic bonds to release glucose-1-phosphate from glycogen. The debranching enzyme removes glucose residues from branch points by cleaving α-1,6-linkages. Glucose-1-phosphate is converted to glucose-6-phosphate by phosphoglucomutase. In contrast to muscle cells, the liver possesses glucose-6-phosphatase, which catalyses the final step of glycogenolysis. This enzyme hydrolyses the phosphate group from glycose-6-phosphate, creating free glucose to be released into the bloodstream (Chen & Weinstein., 2016; Ellingwood & Cheng, 2018).

During prolonged fasting, when glycogen stores are exhausted, glucose can be generated in the liver via gluconeogenesis from non-carbohydrate precursors (Chen & Weinstein., 2016) such as lactate (via the Cori cycle), glycerol, pyruvate, and glucogenic amino acids (Adeva-Andany et al., 2016). Together, glycogenolysis and gluconeogenesis ensure a continuous supply of glucose during fasting states.

2.2.2.3 Lysosomal glycogen degradation

Lysosomal glycogen degradation, also known as glycogen autophagy or glycophagy, occurs alongside cytosolic glycogenolysis as one of two main pathways of glycogen breakdown (Ellingwood & Cheng, 2018). In this pathway, glycogen is delivered to lysosomes via autophagic vacuoles for degradation. This process relies on the enzyme α-glucosidase (GAA), which is initially synthesised in the endoplasmic reticulum and subsequently transported to the lysosomes via the golgi apparatus, where it hydrolyses lysosomal glycogen (Adeva-Andany et al., 2016; Ellingwood & Cheng, 2018). The cytosolic and lysosomal glycogen degradation pathways serve distinct physiological roles. Cytosolic glycogenolysis (via glycogen phosphorylase) provides a rapid source of glucose-1-phosphate for energy production and blood glucose maintenance, whereas lysosomal glycogen degradation (via acid α-glucosidase,

GAA) contributes to long-term glycogen turnover and prevents pathological glycogen accumulation, particularly in muscle tissue. Together, these complementary pathways are essential for maintaining normal glycogen balance and preventing disease (Patino & Orrick, 2024).

These metabolic processes discussed are tightly regulated by numerous enzymes, each playing a specific role in the control of glycogen synthesis and breakdown. Given the complexity of these pathways and the critical functions of these regulatory enzymes, it is unsurprising that mutations or enzymatic deficiencies observed in GSDs can result in profound alterations in glycogen storage and utilisation. These biochemical disruptions form the basis of the pathophysiology of GSDs, leading to diverse physical manifestations that vary depending on the specific enzyme affected and the tissues involved (Kanungo et al., 2018).

2.2.3 Clinical findings and Diagnosis

Despite GSDs being originally identified as childhood diseases, it is now known that initial presentation can occur in adulthood, therefore diagnosis and management should involve both paediatric and adult clinicians (Gumus & Ozen, 2023). Early diagnosis and subsequent treatment are crucial towards reducing the pathological effects of glycogen accumulation, improving QoL and extending lifespan (Hicks et al., 2011). Clinical diagnostic and practical clinical guidelines have been formulated for a variety of GSDs including GSD 1, GSD 2, GSD 3, GSD 4, GSD 5, GSD 6, GSD 7, hepatic GSD 9 and PGM1-CDG (Altassan et al., 2021; Kishani et al., 2006; Kishnani et al., 2010; Kishnani et al., 2014; Kishnani et al., 2019a; Koch et al., 2023; Lucia et al., 2021; Rake et al., 2002; Visser et al., 2002). Due to the variability in phenotypic presentation, diagnosis can prove challenging, particularly in mild phenotypes and in those with skeletal and/or cardiac presentation (Gumus & Ozen, 2023). Diagnostic work up includes a full assessment of a patient's phenotype including medical history, physical examination, blood tests and imaging such as an abdominal ultrasonography, CT or MRI to

detail organ involvement (Hannah et al., 2023). Commonly, those with a suspected GSD, present with a wide range of symptoms of differing severity. The presentation of hypoglycaemia, hepatomegaly, failure to thrive, hyperlipidaemia, elevated liver enzymes and/or hepatic adenomas, lead towards GSDs with hepatic involvement to be considered. In contrast, limb/trunk muscle weakness (for example GSD 2, GSD 3a, GSD 4, GSD 5, GSD 15) and/or fatigue, exercise intolerance, pain, myoglobinuria and rhabdomyolysis may point towards a GSD with muscle involvement (Hannah et al., 2023). Genetic testing can be used as a confirmatory step where there is suspicion of GSD in neonates, infants, children and adults (Hicks et al., 2011). Furthermore, prenatal testing on foetal tissue from chorionic villus sampling or amniocentesis can be used in the diagnosis of GSDs where parents are known genetic carriers or have a family history (Chen et al., 2002).

2.2.4 Physical manifestations

GSDs manifest along a broad disease spectrum, ranging from asymptomatic cases to severe complications that can impact physical health, QoL, and life expectancy (Chen et al., 2021; Derks et al., 2021; Kanungo et al., 2018; Gungor et al., 2015). The onset and severity of symptoms vary widely, appearing anywhere from early childhood to late adulthood, and can differ significantly both between GSD types (Bhengu et al., 2014; Chien et al., 2013; Schoser et al., 2017) and within the same type (Kishnani et al., 2014). Notably, some GSDs, such as GSD 2 and GSD 4, illustrate this spectrum clearly: early-onset forms are typically more severe, while later-onset forms present milder symptoms. This variability, often linked to differences in genetic mutations and residual enzyme activity levels, underscores the complexity of these diseases and highlights the need for individualised approaches to diagnosis and management (Kishnani et al., 2014).

Overall, GSDs are broadly categorised into those with hepatic involvement, those with skeletal muscle involvement and those with both hepatic and skeletal muscle involvement (**Figure 2.2**;

Hannah et al., 2023). Those with hepatic involvement commonly present with fasting hypoglycaemia (Tarnopolsky, 2018) (including GSD 0a, 1, 3, 6, 9 and 11) which can result in seizures, cognitive impairment and if severe, comas and/or death (Hannah, et al., 2023). Additionally, organomegaly, including hepatomegaly and renomegaly, as well as organ impairment like liver disease and glomerulopathy, may occur due to glycogen deposition. These complications are observed in specific GSD subtypes, such as hepatomegaly in types 1, 3, and 6, and glomerulopathy primarily in type 1 (Hannah et al., 2023; Tarnopolsky, 2018).

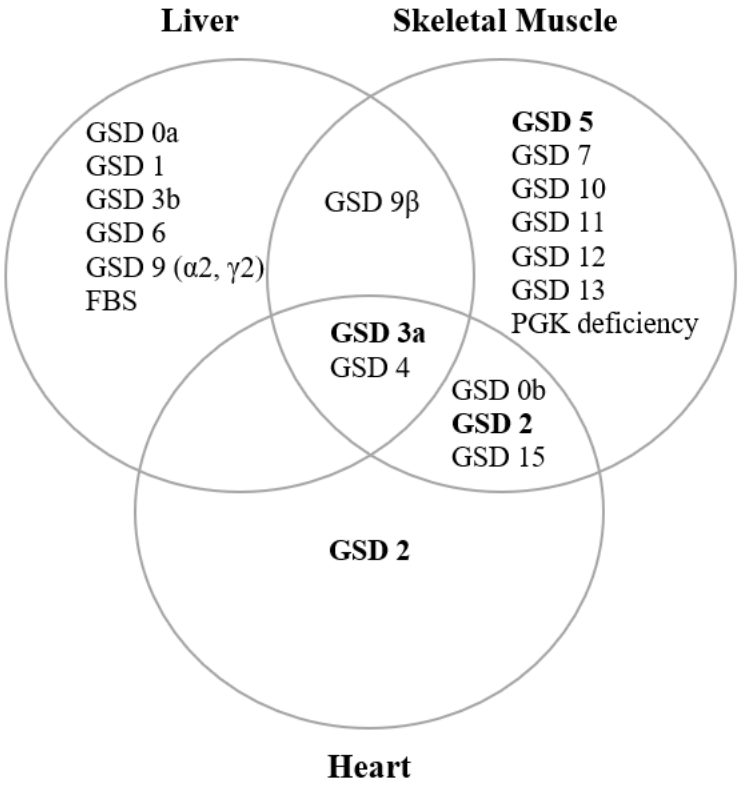


Figure 2.2 Predominant tissue involvement in different GSD types (Adapted from Hannah et al., 2023).
FBS, Fanconi-Bickel Syndrome; LDHA, Lactate dehydrogenase; Phosphoglycerate kinase.

Furthermore, defective metabolic pathways and the subsequent accumulation of metabolites can impact alternative metabolic pathways and lead to disease (Hannah et al., 2023). For example, in GSD 1, lactic acidosis, hyperlipidaemia and increased uric acid resulting from

inability to convert G6P into glucose may cause gout, fatty liver and pancreatitis (Hannah et al., 2023). Furthermore, exercise tolerance may also be implicated in those with hepatic involvement due to the direct effects of liver glycogen content on exercise capacity as detailed in rodents (Lopez-Soldado et al., 2021) and the indirect effect of glycogen via its role in the maintenance of blood glucose homeostasis (Gonzalez et al., 2016).

In contrast, where there is skeletal muscle involvement, skeletal myopathy is a prominent feature (Tarnopolsky, 2018). Those with skeletal muscle involvement can typically be divided into those showing static symptoms with loss of muscle mass and strength (GSD 2, GSD 3) and those with dynamic exercise-related symptoms of fatigue, muscle pain and contractures, often associated with exercise-induced muscle damage (GSD 5, GSD 7, GSD 9D, GSD 10, GSD 14) (Preisler et al., 2014). However, clinically these phenotypes can overlap, and precise classification can be challenging (Preisler et al., 2014). In the GSDs with muscle involvement, exercise intolerance can lead to compromised habitual functioning, with increased morbidity and even premature death in some (Haller & Lewis, 1991; Mate-Munoz et al., 2007; Preisler, et al., 2013; Vissing, 2016). In addition, as a likely consequence of exercise intolerance, many people with GSDs lead a sedentary lifestyle, which in itself is associated with unwanted metabolic adaptations and further health issues (Stein & Wade, 2005). This highlights the critical need for tailored management strategies to mitigate the systemic impact of glycogen accumulation and improve overall QoL in individuals with GSDs.

2.2.5 Management

Given that GSDs are multisystemic, effective management requires a team of medical specialists. This multidisciplinary strategy is crucial for enhancing metabolic regulation, improving QoL and reducing morbidity and mortality (Burda & Hochuli, 2015). Specific management guidelines are available for a range of GSDs including GSD 1 (Kishnani et al., 2014; Rake et al., 2002; Visser et al., 2002), GSD 2 (Kishnani et al., 2006), GSD 3 (Kishnani

et al., 2010), GSD 4 (Koch et al., 2023), GSD 5 (Lucia et al., 2021), GSD 6 (Kishnani et al., 2019a), GSD 7 (Lucia et al., 2021), Hepatic GSD 9 (Kishnani et al., 2019a) and PGM1-CDG (Altassan et al., 2021). Broadly speaking, as there are currently no curative treatments, the goal of medical, pharmacological and therapeutic interventions including nutrition and exercise is to alleviate disease manifestation and reduce long term complications (Gumus & Ozen, 2023).

2.2.5.1 Medical Management

Patients with GSDs should undergo life-long surveillance in order for clinicians to monitor disease progression and the appearance of new manifestations across the broad phenotype (Hannah et al., 2023). Laboratory monitoring in those with hepatic GSDs focusses upon monitoring blood sugars in which continuous glucose monitoring may be particularly useful and can be used to inform dietary treatment towards maintaining tight blood sugar control (Herbert et al., 2018; Peeks et al., 2021; Rossi et al., 2022). Furthermore, liver function can be assessed via blood alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels and coagulation studies (Hannah et al., 2023). Where there is muscle involvement, laboratory assessment additionally includes obtaining serum Creatine Kinase (CK) to monitor disease progression and treatment responses (Hannah, et al., 2023). Supplementary tests may be of use within specific GSDs, including obtaining HbA1C, lipid levels and uric acid in GSD 5 and Urine GLc4 in GSD 2 and hepatic GSDs. Furthermore, imaging may be used in the evaluation of specific features, in which the specific method such as ultrasonography, CT, MRI and frequency of measurements, is determined by the individual patient, GSD type and previous results. Echocardiography is used where there is risk of cardiomyopathy and arrhythmias (including in GSD 2 and GSD 4) and additionally indicated where there is risk of pulmonary hypertension (GSD 1). Furthermore, where there is a risk of low bone mineral density, Dual X-ray Absorptiometry (DEXA) may be warranted and specific renal imaging in GSD 1 (Hannah et al., 2023).

Pharmacological management is commonly required for the treatment of elevated metabolites within hepatic GSDs. Lipid lowering medications may be used to treat hyperlipidaemia, allopurinol in cases of gout (Kishnani et al., 2014) and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) with progressive renal disease (Hannah et al., 2023). Furthermore, sodium-glucose cotransporter 2 (SGLT2) inhibitors can be used to improve neutropenia and neutrophil dysfunction (Veiga-da-Cunha et al., 2023) in GSD 1b and D-Galactose has been shown to have multiple symptomatic benefits in GSD 14 (Altassan et al., 2021).

Enzyme replacement therapy (ERT) was introduced in 2006 as an approved and continually evolving treatment for GSD 2, though it is not yet available for other GSD types (Angelini et al., 2013; Wisselaar et al., 1993). ERT has significantly altered the natural course of both infantile and late-onset forms of GSD 2, leading to measurable improvements in walking distance, lung function, and overall QoL (Feeney et al., 2014; Savarese et al., 2023; Taverna et al., 2020; Whitaker et al., 2004). Despite these advancements, challenges remain. The response to therapy is highly variable among patients (Angelini et al., 2012; Hahn et al., 2018; Harlaar et al., 2019; Kuperus et al., 2017; Massimiliano et al., 2019; Stepien et al., 2016; Strothotte et al., 2009; van der Ploeg et al., 2012) and even where improvements are observed, they often plateau or decline after 2-3 years of treatment (Angelini et al., 2012; Stepien et al., 2016; Strothotte et al., 2009). This highlights the need for ongoing research to better understand the natural history of GSDs. In particular, there is a critical need to identify novel and clinically relevant biomarkers that can more accurately track disease progression, guide the timing of therapeutic interventions, and evaluate the long-term effectiveness of ERT (Labella et al., 2023). Additionally, adenovirus vectors have shown promise within early phase clinical trials in GSD 2 and GSD 1a (Kishnani et al., 2019b). Liver transplantation may be necessary in some patients or combined liver and kidney transplantation in GSD 1 or combined liver and heart

transplantation in GSD 3 and GSD 4 (Hannah et al., 2023). Organ transplantation can provide significant benefits and enhance the QoL of those with GSD and their families; However, opting for liver transplantation requires a meticulous evaluation of its potential risks and advantages for individual patients and should be carefully considered along with other available options (Hannah et al., 2023).

2.2.5.2 Therapeutic Management

Diet along with exercise constitute the fundamental basis of therapeutic measures, aimed at improving the QoL by alleviating signs and symptoms (Stone et al., 2025). Dietary treatment varies across GSDs depending on the specific enzyme defect and pathophysiology (Ross et al., 2020). Dietary interventions have significantly enhanced disease prognosis, transforming what was once considered a fatal condition into a manageable illness, enabling individuals to experience a decent QoL (Ross et al., 2020). The overarching aims of treatment in the hepatic GSDs such as types 0, 1, 3, 6, 9 and 11 is to avoid hypoglycaemia and further associated metabolic dysfunction (Heller et al., 2008). Glycaemic control is particularly important in the severe hepatic forms such as GSD 1, where there is impaired glucose-6-phosphatase activity and subsequent inhibition of both glycogenolysis and gluconeogenesis. Whereas, in less severe forms known as ketotic GSDs, which include types 0, 3, 6, and 9, substrates such as amino acids, glycerol (produced through fatty acid oxidation), and lactate can be used for gluconeogenesis, thus providing an alternative energy source to maintain blood glucose levels, with hypoglycaemia therefore less prevalent during fasting or periods of increased energy demand (Ross et al., 2020).

Cornstarch is commonly used and considered essential to prevent severe hypoglycaemia and fasting intolerance that can be seen in many hepatic GSDs. It is typically consumed in small amounts every 3-4 hours as a slow-release source of complex carbohydrate, thereby supporting the maintenance of euglycemia. Compared with continuous nocturnal feeding, cornstarch

therapy has been associated with lower insulin responses while still providing sustained glucose availability (Crigler & Folkman, 1977; Weinstein & Wolfsdorf, 2002). To extend euglycemia, particularly during the night, a new starch with a slower rate of absorption has been approved and utilised since 2009 (Ross et al., 2020). The maize starch (Glycoside) can effectively be used to lengthen the time of euglycemia between nocturnal feeds and concurrently improve sleep quality (Rake et al., 2002). There is some evidence that it can be effective for daytime use (Heller et al., 2008; Ross et al., 2015), however it may not be suitable in circumstances where energy is suddenly required such as during physical activity (Ross et al., 2020).

Considering the diet as a whole, carbohydrate including cornstarch and other dietary carbohydrate need to be carefully balanced as excess, can result in hyperinsulemia, hepatomegaly and rebound hypoglycaemia and ultimately weight gain and additional metabolic complications. Overall complex carbohydrates are recommended over simple carbohydrates (Ross et al., 2020). Simple sugars including fructose, sucrose and galactose are to be specifically restricted in GSD 1 as these cannot be metabolised due to defective Glucose-6-phosphate leading to hyperlactatemia and acidosis (Fernandes, 1974). Furthermore, in GSDs where gluconeogenesis is intact, a diet rich in protein can be adopted, to supply an alternative glucose source via glucogenic amino acids. This approach helps reduce glycogen accumulation while encouraging muscle synthesis (Kishnani et al., 2010; Kishnani et al., 2019a). Overall, there is a lack of general consensus on the optimal diet therapy across the broad spectrum of GSDs, thus it is necessary for dietary treatment to be individualised and regularly assessed (Heller et al., 2008; Ross et al., 2020).

For many years, researchers and clinicians have promoted the potential therapeutic benefits of exercise training for individuals with GSDs, leading to the incorporation of physical activity recommendations in multiple clinical guidelines (Cupler et al., 2011; Kishnani et al., 2006;

Kishnani et al., 2010; Lucia et al., 2021; Wicker et al., 2023). Regular physical activity has been shown to provide numerous benefits, with increasing evidence highlighting its role not only in alleviating symptoms but also in improving overall QoL, rather than potentially exacerbating the condition (Preisler et al., 2014). Moreover, physical activity plays a crucial role in combating sedentary behaviour, which has been closely linked to skeletal muscle atrophy and unfavourable metabolic alterations (Wicker et al., 2023). The efficacy of exercise interventions will be explored in detail elsewhere, with a particular focus on the research supporting the utility of exercise training within different GSD subtypes.

2.3 Glycogen Storage Diseases 2, 3 and 5

Given the breadth and complexity of GSDs, a comprehensive overview of all of the GSD subtypes is beyond the scope of this thesis. Instead, this work focuses on three of the most prevalent GSD subtypes, which are GSD 2, GSD 3 and GSD 5. Glycogen storage disease 2 is distinct from other disorders, as it involves lysosomal glycogen accumulation, which does not directly contribute to energy metabolism within skeletal muscle but can lead to progressive muscle myopathy (Gumus & Ozen, 2023). Glycogen storage disease 3 includes subtypes that either affect the liver exclusively or involve both the liver and skeletal muscle, leading to a wide clinical presentation with both hepatic and myopathic symptoms (Shen et al., 1996). In contrast, GSD 5, which is the most common of these disorders, affects skeletal muscle exclusively and is subsequently characterised by symptoms such as exercise intolerance, muscle contractures, atrophy, and weakness (Hannah et al., 2023). This thesis, therefore, explores a spectrum of GSD-related muscle myopathies, providing a focused analysis of their pathophysiology, clinical manifestations, and potential therapeutic strategies.

2.3.1 Glycogen Storage Disease 2

2.3.1.1 Genetics and Epidemiology

GSD 2 is also known as Pompe disease or acid maltase deficiency and has a prevalence of between 1 per 4447 to 1 per 37,094, which is found to differ between countries due to variations in ethnicities and screening tools (Labella et al., 2023). It is an autosomal recessive disorder caused by pathogenic mutations of the GAA gene located on chromosome 17q25.3 (Kanungo et al., 2018), in which at least 500 pathogenic variants have been recognised (Gutschmidt et al., 2021). In contrast to other GSDs, in which the majority of genes encode cytosolic proteins, the impaired acid-alpha glucosidase (GAA) is localised within the lysosomes and is therefore regarded as a lysosomal GSD (Kanungo et al., 2018). As a result, the 1,4 and 1,6 glycosidic bonds within lysosomal glycogen cannot be hydrolysed, leading to an accumulation of

glycogen within the lysosomes and ultimately lysosomal dysfunction, enlargement and rupture (Moreland et al., 2004; Raben et al., 2007; Raben et al., 2012; Selvan et al., 2021). All tissues can be affected, particularly skeletal, respiratory and cardiac muscles (Kanungo et al., 2018; Smit et al., 2006). GSD 2 can manifest from early infancy into adulthood, classified into two distinct clinical phenotypes: Infantile Pompe disease (IOPD) and Late onset Pompe disease (LOPD) including childhood, juvenile and adult-onset disease (Leslie & Bailey, 2023) with physical manifestations varying depending on age of onset, organ involvement, disease severity and rate of progression (Meena & Raben, 2020; Reuser et al., 1995). The classical infantile form is known as the most severe, with almost a complete absence of lysosomal acid-alpha glucosidase (GAA) (<1% of enzyme activity compared to normal controls) (Hirschhorn & Reuser, 2002; Kishnani, 2014). Symptoms usually present in the first days or weeks of life and progress rapidly (Kishnani, 2014), often resulting in fatality within the first two years of life if not treated with ERT (Kishnani et al., 2006; Slonim et al., 2000). The thesis focuses on LOPD, a form of GSD 2 that encompasses a spectrum of clinical presentations, including childhood, juvenile, and adult forms.

2.3.1.2 Clinical Findings and Diagnosis

The diagnosis of LOPD can be challenging due to its similarity to other neuromuscular disorders, requiring a high level of clinical suspicion for accurate identification (Labella et al., 2023). LOPD is typically suspected in infants, children, and adults with proximal muscle weakness and respiratory difficulties without significant cardiac involvement (Leslie & Bailey, 2023). Enzyme activity testing, often via dried blood spots (DBS) using tandem mass spectrometry or fluorometry, serves as a quick first-line diagnostic tool (Lukacs et al., 2020; Vissing et al., 2013) before confirmation through genetic testing (Taverna et al., 2020). Increasingly, muscle weakness cases are diagnosed directly through gene panels including the

GAA gene, and newborn screening is now implemented in countries like Taiwan, Austria, Japan, and parts of the USA (Hopkins et al., 2015; Mechtler et al., 2012; Oda et al., 2011).

Clinical assessments following suspicion of LOPD include blood tests, electromyography (EMG), muscle MRI, and muscle biopsy (Labella et al., 2023). While blood tests may reveal elevated biomarkers such as creatine kinase (CK), cardiac troponin T, ALT, and AST, these are non-specific (Gutiérrez-Rivas et al., 2015; Hoeksma et al., 2007; Kishnani et al., 2006; Musumeci et al., 2015; Spada et al., 2013; Wagner et al., 2013; Wens et al., 2016). Electromyography (EMG) can show myopathic patterns, including spontaneous activity and electrical myotonia (Kassardjian et al., 2015; Müller-Felber et al., 2007), and muscle MRI often detects abnormalities in axial muscles, especially trunk extensors, even before symptoms manifest (Carlier et al., 2011). Even where pulmonary tests appear normal, diaphragmatic dysfunction can be detected (Harlaar et al., 2021; Harlaar et al., 2022; Wens et al., 2015). Muscle biopsies, analysed via histological techniques such as periodic acid-Schiff (PAS) staining, often reveal vacuolar myopathy with glycogen accumulation, though a normal biopsy does not exclude LOPD (AANEM, 2009; Montagnese et al., 2015; Werneck et al., 2013). These clinical assessments provide valuable but non-specific insights and ultimately a definitive diagnosis should be confirmed through molecular genetic testing (e.g., single gene or multigene panels) or by measuring GAA enzyme activity in tissues such as lymphocytes or mixed leukocytes (Amartino et al., 2005; Winchester et al., 2008).

2.3.1.3 Physical manifestations

Late Onset Pompe Disease is a subtype of GSD 2 that manifests across childhood, juvenile, and adult forms, differing mainly in age of onset and symptom severity. Onset ranges from infancy to the sixth decade (Kishnani, 2014; Labella, et al., 2023), with residual enzyme activity between 2% and 40% of normal levels (Hirschhorn & Reuser, 2002; Leslie & Bailey, 2023). Despite variability in presentation, all forms are marked by progressive muscle

weakness and respiratory complications influenced by residual enzyme activity and disease progression.

The juvenile form typically begins after the first year of life with impaired motor skills, hypotonia, and profound muscular weakness, particularly in the proximal, truncal, and respiratory muscles (Güngör & Reuser, 2013; Smit et al., 2006), but without significant cardiac involvement. The adult form usually appears in the third or fourth decade with progressive weakness, starting in truncal and respiratory muscles and later affecting pelvic and paraspinal muscles, leading to limb-girdle muscular dystrophy or polymyositis. This progression often results in mobility and respiratory difficulties (Smit et al., 2006). The progression of muscular myopathy in LOPD gradually leads to severe respiratory complications and, ultimately, respiratory failure, which is the primary cause of mortality (Smit et al., 2006). Muscle weakness typically begins in the pelvis, paraspinal muscles, and diaphragm, causing symptoms resembling limb-girdle muscular dystrophy or polymyositis, which significantly impacts mobility and respiratory function. As the disease advances, patients experience increasing difficulty walking and often require mobility aids. Additionally, profound diaphragmatic weakness results in a substantial need for ventilatory support, with many patients eventually relying on assisted ventilation (Bolano-Diaz & Diaz-Manera, 2022).

Longitudinal studies in individuals not receiving ERT have documented this progressive decline, with muscle strength decreasing by 1.3% per year (manual muscle testing) and 2.6% per year (hand-held dynamometry; both $p<0.001$) and forced vital capacity declining by 1.3% annually ($p = 0.02$). Furthermore, a longer disease duration (>15 years) and significant pulmonary involvement (forced vital capacity in the sitting position <80%) are associated with a more rapid decline (van der Beek et al., 2012). This decline in muscle strength and pulmonary function has profound clinical consequences, with 50% of patients becoming wheelchair-bound and 19% requiring ventilatory support (van der Beek et al., 2009). However, the majority of

longitudinal data available includes individuals receiving ERT (Papadimas et al, 2021; Vanherpe et al., 2020) and thus do not provide an accurate picture of the natural history of the disease for the many people that do not have access to ERT.

The skeletal muscle weakness and wasting described, is thought to result from the ineffective breakdown of glycogen and its accumulation in the lysosomes within muscle fibres (Preisler et al., 2012a). However, the exact pathogenesis remains unclear and may also be as a result of myogenic and neurogenic involvement (Martin et al., 1973). This muscular dysfunction contributes to prominent exercise intolerance, a hallmark of GSD 2. Beyond these muscle and respiratory issues, patients with LOPD may also suffer from life-threatening complications such as aneurysms of cerebral arteries, which have been documented as fatal in some cases (Smit et al., 2006). Furthermore, advanced osteoporosis, likely due to decreased mobility, has become more frequently recognised, further complicating the disease's impact on patients' QoL (Case et al., 2007; Leslie & Bailey, 2023; Oktenli, 2000).

2.3.1.5 Management

In order to assess the extent of the disease and guide the treatment of the primary physical manifestations, specific guidelines have been published for LOPD (Cupler et al, 2011). Within these guidelines a multidisciplinary approach is essential in providing individualised care for cardiomyopathy, physical therapy for muscle weakness, respiratory support including inspiratory/expiratory muscle training, CPAP, BiPAP and/or tracheostomy, nutrition support and surgery where needed (Cupler et al. 2011; Leslie & Bailey, 2023). The overall clinical management and rehabilitation strategies for LOPD patients encompass preserving or enhancing motor function, minimising the risk of secondary complications, capitalising on the advantages of ERT and emerging therapies, maintaining overall well-being while addressing disease-related symptoms, and enhancing the overall QoL (Cupler, et al., 2011).

Since 2006, ERT, with intravenous recombinant human acid α-glucosidase (rhGAA) has been the only approved treatment for LOPD in the U.S. and Europe (Labella et al., 2023). The European Consensus recommends starting ERT in all symptomatic LOPD patients with a confirmed diagnosis and residual skeletal or respiratory function. Some patients, however, are diagnosed before symptoms arise and at present there is no evidence to support the efficacy of ERT in asymptomatic patients (van der Ploeg et al., 2017). The beneficial effects of ERT are most pronounced when initiated promptly after a diagnosis (Bolano-Diaz & Diaz-Manera, 2022) in which it primarily helps stabilise the progressive loss of respiratory and motor functions through degrading accumulated lysosomal glycogen (Kanungo et al., 2018; Leslie & Bailey, 2023).

The first clear evidence of the beneficial effect of ERT in LOPD came from the first randomised, double blind, placebo-controlled study (LOTS) conducted by van der Ploeg et al (2010) which showed improvements in 6-Minute Walk Test (6MWT) (28 ± 13.1 m) and Forced Vital Capacity (FVC) (3.4 ± 1.2%), with the greatest improvements occurring within the first 26 weeks, which were found to be maintained for 78 weeks. Further studies have confirmed the early onset of beneficial effects of ERT, within the first few months of treatment, in which a meta-analysis of LOPD patients (n=438) found a mean improvement of 43 meters in 6MWTs following 12 months of treatment compared to untreated patients. Furthermore, rapid improvements of 1.4% in forced vital capacity (FVC) were found during the first 2 months of treatment compared to untreated. Overall, these improvements lead to beneficial effects on mortality, in which mortality rates were 5 times lower compared to those untreated (Schoser et al., 2017).

However, despite the initial benefits observed with ERT, particularly within the first few months, long-term studies of LOPD patients treated for 5 to 10 years reveal a plateau in effect. This plateau can persist for several years, after which patients often begin to experience a

decline (Gutschmidt et al., 2021; Harlaar et al. 2019; Kuperus et al., 2017). A meta-analysis by Harlaar et al. (2019) found that 93% of patients showed improvements in 6MWT and FVC after starting ERT. However, over time, 76% experienced a subsequent decline, and at final assessment, only 52% maintained or improved their 6MWT and/or FVC compared to baseline, while 48% had outcomes below baseline. Furthermore, the response to ERT is highly variable between individuals, with factors such as phenotype and genotype likely influencing efficacy, though the exact mechanisms remain unclear (Sarah et al., 2021).

Given the variable ability of ERT to alter the natural course of LOPD and its diminishing effectiveness over time, there is a pressing need for further research to establish valuable clinical outcomes and benchmarking measures for monitoring disease progression. Prospective natural history studies are particularly well-suited for this purpose, as they provide a robust framework for evaluating the impact of existing pharmacological treatments, such as ERT, as well as emerging therapies. By offering deeper insights into both disease progression and treatment efficacy, these studies can help refine and optimise therapeutic approaches over the long term, ultimately improving patient outcomes (Liu et al., 2022).

For patients with LOPD, the primary management goals are to address the progressive accumulation of glycogen and the increased utilisation of amino acids (Slonim et al., 1983; Slonim et al., 2000). A high-protein, low-carbohydrate diet combined with aerobic exercise has shown potential benefits in reducing glycogen deposition, enhancing fatty acid oxidation, and compensating for increased protein oxidation (Slonim et al., 1990; Slonim et al., 2006b). However, others have not demonstrated improvements with high-protein diets, highlighting the need for further research (Bodamer et al., 2000). Furthermore, feeding and swallowing difficulties may arise from facial and oral muscle impairments, potentially leading to some individuals to require a soft diet or enteral feeding (Cupler et al. 2011; Leslie & Bailey, 2023). Overall, maintaining adequate nutrition is crucial, with a particular emphasis on increased

protein intake (20–25%) as well as ensuring sufficient vitamins and minerals (Cupler et al., 2011).

Research on the effects and therapeutic roles of physical activity and nutrition in LOPD is limited, due to uncontrolled studies of variable duration and small sample sizes (Case & Kishnani, 2006; Slonim et al., 2006a, 2006b). Although more data is required, existing studies suggest that submaximal aerobic exercise may enhance muscle strength and function by improving glycogen clearance in the muscle cytosol (Bembi et al., 2003). However, there appears insufficient evidence supporting resistance training, with concerns that excessive muscle contraction could cause glycogen leakage from lysosomes or even lysosomal rupture, potentially accelerating muscle damage (Griffin., 1984). Current recommendations advocate for a cautious approach, starting therapeutic exercise gradually, with rest periods, and progressing to moderate aerobic activity at 60–70% of maximal effort, three to five times weekly (Abresch et al., 2009; Kishnani et al., 2006; Slonim et al., 2006b). Strengthening exercise guidelines for other degenerative muscle diseases should also apply to LOPD (Eagle, 2002; Fowler., 2002). Ideally, therapists should design an individualised program incorporating submaximal aerobic exercises (e.g., walking, cycling, swimming) and preventive stretching to prevent contractures and deformities. Programs should avoid overwork, strenuous exercises and excessive fatigue (Cupler et al., 2011; Kishnani et al., 2006). In practice, safe exercise limits can be gauged by monitoring for clinical indicators such as disproportionate muscle pain or cramps, persistent fatigue, or declining functional capacity (for example, a shorter walking distance or new difficulties with daily activities). For individuals with GSD 5, international clinical practice guidelines emphasise recognising early fatigue or muscle pain, typically occurring before the onset of the “second wind” phenomenon, and adjusting or stopping activity if these symptoms are severe (Lucia et al., 2021). Additional concerning features include muscle cramps, dark urine suggestive of myoglobinuria, or marked exertional

symptoms such as disproportionate breathlessness or an inappropriately rapid heart rate, which may indicate that exercise intensity or duration has exceeded safe limits (CDC, 2023; IAMGSD, 2022). Overall, consensus recommendations highlight that exercise should be individualised, titrated to tolerance, and ideally supervised to maximise benefit and minimise risk (Cupler et al., 2011; Tarnopolsky, 2012).

2.3.2 Glycogen Storage Disease 3

2.3.2.1 Genetics and Epidemiology

Glycogen storage disease 3 (GSD 3) accounts for approximately 24% of all GSDs, with approximately 1 case per 83,000 live births in Europe (Parvari et al., 1997). It was first described by Illingsworth & Cori (1952) in which excessive amounts of abnormally structured glycogen in the liver and muscle of a patient was identified and subsequently confirmed to be as a result of a deficiency of glycogen debranching enzyme (GDE) (Illingworth et al., 1956). This GSD is an autosomal recessive disorder (Smit et al., 2006) caused by biallelic pathogenic variants in the AGL gene which spans 85 kb of DNA on chromosome 1p21.2 and is composed of 35 exons (Bao et al., 1996). Pathogenic homozygous or compound heterozygous mutations of the AGL (amylo-α-1,6-glucosidase/4-α-glucanotransferase) gene result in glycogen debrancher enzyme deficiency (GDE) which impedes glycogenolysis and results in excessive glycogen storage with an abnormally compact structure known as phosphorylase limit dextrin (Smit et al., 2006). Complete glycogenolysis requires the action of glycogen phosphorylase and glycogen debrancher enzyme (GDE) (Kishnani, 2014). Glycogen is composed of linear chains of six-carbon glucose with 1,4 linkages and irregular 1,6 linkages forming outer branch points (Kishnani, 2014). Glycogen phosphorylase shortens peripheral chains of glycogen by cleaving the alpha 1-4 glycosyl bonds in the linear chains to within 4 residues of a branch point (Haller, 2015). Glycogen debrancher enzyme (amylo-1,6-glucosidase,4-alpha-glucanotransferase (AGL) (Haller, 2015) has two independent catalytic activities that occur at

different sites on the same polypeptide chain (Sentner et al., 2016), namely amylo-alpha-1, 6-glucosidase activity and 4-alpha-glucanotransferase activity (Berling et al., 2021). Initially 3 of the final 4 residues at branch points are transferred and attached in an alpha 1-4 linkage for phosphorylase breakdown, then the alpha 1-6 bond is split by the debrancher to release the final glycosyl residue as free glucose (Haller, 2015). Deficiency of GDE therefore, results in incomplete glycogenolysis and an accumulation of glycogen with short outer branch points, forming an abnormally compact structure known as limit dextrin (Smit et al., 2006).

At present, a high degree of genetic heterogeneity has been shown, with at least 110 disease causing variants reported (Ko et al., 2013). Overall GSD 3 consists of four subtypes due to differences in tissue expression of the deficient GDE, in which the majority (85%) have enzyme deficiency within the liver, muscle, heart, leukocytes and cultured fibroblasts thus displaying both hepatic, myopathic and cardiomyopathy (GSD 3a). In contrast, those with GSD 3b (approximately 15%) only present with liver manifestations. Further subgroups display a selective deficiency in one of the two activities of the debranching enzyme GDE, with loss of either glucosidase (GSD 3c) or transferase (GSD 3d), although these are particularly rare (Ding et al., 1990; van Hoof & Hers, 1967; Sugie et al., 2001).

2.3.2.2 Clinical findings and diagnosis

GSD 3 should be suspected in individuals with any of the following clinical findings: hepatomegaly, short stature/failure to thrive, hepatic cirrhosis and hepatic adenomas, weakness/myopathy, exercise intolerance or hypertrophic cardiomyopathy. Furthermore, laboratory findings including ketotic hypoglycaemia or ketotic normoglycaemia, increased creatine kinase, increased transaminase, hyperlipidaemia with elevated triglycerides, and/or cholesterol (Schreuder et al., 1993). A definitive diagnosis should be established by identification of biallelic AGL pathogenic variants by molecular genetic testing (Schreuder et al., 1993) including gene targeted testing (single-gene testing, multigene panel) or

comprehensive genomic testing (exome sequencing, genome sequencing) depending on the phenotype. If the diagnosis cannot be established via molecular genetic testing, deficiency of the debranching enzyme in circulating blood cells (leukocytes or erythrocytes), cultured skin fibroblasts or liver or muscle biopsy tissue is necessary (Schreuder et al., 1993). A muscle biopsy may be considered to distinguish between GSD 3a with liver and muscle involvement from GSD 3b with just liver involvement (Kishnani et al., 2010).

2.3.2.3 Physical Manifestations

Physical manifestations in GSD 3 are complex and heterogenous, likely due to the diverse mutations having a variable effect on glucosidase and transferase function in muscle and other tissues (Shen & Chen, 2002). The age of onset, rate of disease progression and severity is highly variable (Kishnani et al., 2010) with there being no clear genotype: phenotype correlation (Lucchiari et al., 2002). Hepatic symptoms are predominantly observed during childhood, with hepatomegaly, ketotic hypoglycaemia without hyperlacticaemia, hyperlipidemia (secondary to lipolysis) and short stature/failure to thrive (Berling et al., 2021; Smit et al., 2006). These symptoms largely improve with age and can even disappear after puberty (Bernier et al., 2008; Coleman et al., 1992), partly thought to be attributable to a reduction in relative glucose requirements (Kishnani et al., 2010). However, in some, hepatic symptoms can progress, with severe hepatic complications including hepatic cirrhosis, adenomas and/or carcinomas occurring in 11% of patients (Sentner et al., 2016). Skeletal muscle manifestations may not be evident in infants or children, although hypotonia and delayed motor milestones can present in some (Smit et al., 2006). A cohort study of 28 children with GSD 3 showed 10% displayed delayed sitting, 25% delayed standing and 64% delayed onset of walking. Furthermore, 21% displayed mild muscle weakness and 18 of the 28 children displayed exercise intolerance (Mogahed et al., 2015). Similar patterns of decreased motor function, muscle weakness and exercise intolerance has been found by others (Ben Chehida et al., 2019; Kishnani et al., 2010).

Furthermore, cardiomyopathy in childhood has been reported, with rare cases even presenting within the first year of life. Most are asymptomatic, however there have been reports of severe cardiac dysfunction, congestive heart failure and sudden death (Austin et al., 2012; Clearly et al., 2002; Focardi et al., 2020). Additionally facial signs including deep set eyes, bow shaped lips and depressed nasal bridge with an upturned nasal tip may present in younger patients (Cleary et al., 2002).

Myopathy becomes increasingly apparent with age and is the primary clinical feature in adulthood, typically emerging during the third or fourth decade of life (Berling et al., 2021; Kishnani et al., 2010). This muscular involvement generally follows the resolution of earlier liver-related symptoms, such as hepatomegaly (Kishnani et al., 2010; Smit et al., 2006). However, in some adult patients, muscle symptoms may manifest independently, without any prior history of liver dysfunction (Gumus & Ozen, 2023). Exercise intolerance including muscle fatigue, cramps and pain remain a common complaint, reported by over 50% of patients (Ben Chehida et al., 2019; Mogahed et al., 2015; Sentner et al., 2016). Traditionally, the exercise intolerance was thought to primarily result from the condition's association with static symptoms such as fixed muscular weakness and muscle atrophy, which vary in severity and distribution (Kishnani et al., 2010). Muscle weakness is typically symmetrical and can involve proximal, distal, or more generalised muscle groups. Patients with distal myopathy often exhibit weakness in the proximal muscles of the upper and lower extremities as well as in the small distal muscles of the hands and feet, sometimes accompanied by foot deformities (Ben Chehida et al., 2019; Kishnani et al., 2010). The underlying mechanisms of weakness are not fully understood but have been attributed to the accumulation of glycogen, which disrupts the contractile function of muscle fibres (Preisler et al., 2014). Furthermore, muscle imaging studies have detailed fat infiltration correlating to disease severity with or without muscle wasting (Tobaly et al., 2019; Wary et al., 2010). Distal myopathy and muscle atrophy may also

suggest an underlying peripheral neuropathy, which can become more pronounced with age and may involve the median nerve (Kishnani et al., 2010). Electromyography (EMG) studies have further identified abnormal nerve conduction and neuropathic features in affected individuals (Kishnani et al., 2010).

More recently however, dynamic exercise-related symptoms, unrelated to weakness, have been recognised (Preisler et al., 2013). The presence and severity of exercise intolerance variable among patients, likely in part to mutational differences having varying impact on glucosidase and transferase function (Shen & Chen, 2002). The significantly reduced exercise capacity observed within those with GSD 3a, has been linked to impaired muscle glycogenosis, leading to insufficient energy production and an acute energy crisis during sub maximal exercise (70% $\dot{V}O_{2peak}$) (Preisler et al., 2013). The key manifestations of exercise intolerance observed during sustained, submaximal exercise, is high and rapidly increasing levels of perceived exertion, premature fatigue and muscle pain (Preisler et al., 2013; Preisler et al., 2014). These dynamic-exercise related symptoms often precede the occurrence of permanent muscle weakness and wasting, and are most likely underdiagnosed, as moderate muscle symptoms during childhood are often overshadowed by the more prominent liver manifestations (Preisler et al., 2013). In contrast to other muscular glycogenosis, such as GSD 5, individuals with GSD 3a experience milder dynamic-exercise related symptoms, in which myoglobinuria and rhabdomyolysis are particularly rare (Di Mauro et al., 2004; Kishnani et al., 2010). This is thought to be due the partial metabolism of glycogen's outer branches by myophosphorylase, which allows a small amount of glucose to be available at the onset of exercise, until the glycogen-debranching enzyme reaches a branching site along the glycogen molecule (Preisler et al., 2014). Due to the small amount of glucose available, the main energy crisis is not therefore at the onset of exercise and no second wind phenomenon is observed (Berling et al., 2021). Furthermore, in contrast to GSD 5, blood glucose levels can drop during exercise leading to symptomatic

hypoglycaemia. This is due to an increase in the uptake and utilisation of glucose (of which up to 40% of glucose utilised is liver-derived) or a reduced hepatic glucose output or a combination of these factors (Preisler et al., 2013; Preisler et al., 2015; Stojkovic et al., 2009; Tegtmeyer et al., 2014). Due to the incomplete block in muscle glycogenolysis, in which some glucose residues are available for metabolism, there is a small increase in lactate observed on forearm testing (Preisler et al., 2013). However, on maximal exercise testing, despite not being as severe as GSD 5, $\dot{V}O_{2peak}$ and W_{peak} is still significantly lower compared to age and gender matched controls ($\dot{V}O_{2peak}$: 25.4 ± 5.1 mL/kg/min vs 46.4± 7.2 mL/kg/min; W_{peak} 108±27 versus 209 ± 55) (Preisler et al., 2013). The reduced oxidative capacity is due to the restriction in carbohydrate availability, in which during peak exercise, carbohydrate only accounted for 40% of oxygen utilisation, as opposed to 100% in a healthy population (Jensen & Richter, 2012).

Along with muscular symptoms, GSD 3a is characterised by variable cardiac involvement, affecting 58-91% of individuals (Ben Chehida et al., 2018; Sentner et al., 2016; Vertilus et al., 2010). It often begins within the first decade of life (Ben Chehida et al., 2018; Sentner et al., 2016) and is caused by the accumulation of glycogen in the heart tissue (Akazawa et al., 1997; Austin et al., 2012; Di Mauro et al., 1979; Miller et al., 1972; Olson et al., 1984; Tada et al., 1995). Cardiomyopathy can be asymptomatic or symptomatic, with electrocardiographic and/or echocardiographic signs of ventricular hypertrophy frequently identified (Schreuder et al., 1993). Cardiac involvement appears progressive, but this is highly variable among patients (Carvalho et al., 1993; Chong-Nguyen et al., 2018; Vertilus et al., 2010) and has no correlation with the extent of hepatic, cardiac and muscle involvement (Kishnani, 2014). Despite most patients being asymptomatic, severe cardiac dysfunction, heart failure and sudden death have been documented (Austin et al., 2012; Focardi et al., 2020).

Beyond cardiac involvement, GSD 3a also impacts other systems, notably skeletal health and cognitive function. Patients face an increased risk of osteoporosis and osteopenia, particularly those with myopathy (Cabrera-Abreu et al., 2004). The aetiology appears multifactorial, involving myopathy, poor nutrition, and metabolic disturbances such as reduced insulin-like growth factor 1, insulin, osteocalcin, and chronic hyperlipidaemia (Melis et al., 2016). Additionally, impaired global cognitive efficiency has been documented, with deficits in executive functions and emotional regulation linked to orbito-frontal dysfunction resulting from abnormal glycogen metabolism (Michon et al., 2014).

With advancing age, the physical manifestations described often become more severe, progressively impairing physical function; which in many cases leads to significant disability, with some patients eventually requiring mobility aids to maintain independence (Hijazi, et al., 2021; Hobson-Webb, et al., 2010). Despite the recognised decline in physical function associated with GSD 3a, there is a notable lack of natural history data. This stands in stark contrast to the extensive international registries available of patients with GSD 2 and GSD 5 (Byrne et al., 2011; Pinós et al., 2020) which have significantly advanced understanding and management of these diseases.

The current literature available on the progression of GSD 3a, is largely derived from cross-sectional studies (Decostre, et al., 2016; Hoogeveen, et al., 2021; Preisler et al., 2013; Preisler et al., 2015). These cross-sectional studies highlight that cardiovascular fitness is greatly reduced, particularly when compared to healthy individuals (Preisler et al., 2015) and thought to be attributable to muscle weakness, impaired energy metabolism and exercise limitation (Hoogeveen, et al., 2021; Preisler et al., 2013; Preisler et al., 2015). Indeed, progressive muscle weakness in GSD 3a has been shown (Decostre, et al., 2016; Verbeek et al., 2016) with annual losses of 0.70% of predicted values for muscle strength (Decostre, et al., 2016). Furthermore, peripheral neuropathy was found to be more common with age (Hobson-Webb, et al., 2010).

However, these findings are from small cross-sectional studies, where data was collected at a single point in time and may have been affected by generational differences and additional confounding factors. Furthermore, many of these studies relied on retrospective data from medical visits, which often lacked standardised assessment protocols and had variations in treatments (Decostre, et al., 2016; Hobson-Webb, et al., 2010). Additionally, due to their cross-sectional design, these studies do not allow for the observation of changes over time, limiting the ability to track trends, disease progression, or establish cause-and-effect relationships. As a result, it is difficult to determine individual disease trajectories from this data.

At present, very few longitudinal studies have been conducted investigating the progression of GSD 3a, largely due to the rarity of the disease and challenges in data collection. These studies document the vast heterogeneity in diagnosis, genotype, management, clinical course and outcomes in GSD 3 patients (Hijazi et al., 2021; Sentner et al., 2016) and specifically GSD 3a (Decostre et al., 2017). These indicate, that while early therapeutic interventions such as dietary adjustments can help control symptoms, many patients with GSD 3a develop progressive muscle weakness and cardiomyopathy with age. However, the existing longitudinal data are primarily based on retrospective studies, which lack original data and are largely descriptive, in which detailed analysis of the progression of exercise intolerance and muscle impairment across the lifespan and associated factors has not been established. The retrospective nature of the data may have introduced biases and inconsistencies in how patients' outcomes were recorded and monitored over time. Moreover, these studies exhibit high variability in follow up duration (0-61 years) (Decostre, et al., 2017; Hijazi, et al., 2021) with some not extending into adulthood. This variability may have led to an underrepresentation of long-term complications and failed to truly capture the disease's progression. Additionally, much of the data collection commenced more than a decade ago and given the advances in diagnosis and treatment may not be reflective of the current progression of the disease.

The lack of longitudinal data presents a significant barrier to understanding the dynamic nature of disease progression and establishing more robust cause-and-effect relationships. Robust longitudinal studies are essential to understand the natural history of the disease and assessing its long-term implications. By following the same individuals over time, these studies can reveal changes, trends and developments in behaviours, health and disease can be observed and as such cause-and-effects relationships between variables can more accurately be inferred. Additionally, by repeatedly measuring the same individuals, longitudinal studies better account for confounding variables that might influence outcomes, whilst also minimising the risk of cohort effects, all issues that often confound cross-sectional studies.

2.3.2.5 Management

As with other GSDs, GSD 3 affects multiple systems and thus requires a multidisciplinary team including cardiologists, gastroenterologists, neuromuscular specialists, physical therapists, occupational therapists, metabolic dietitians and genetic counsellors with specialist knowledge of the disease (Kishnani et al., 2010). Management guidelines include the medical management of cardiac and liver manifestations and further metabolic dysregulation (Kishnani et al., 2010). Liver transplantation may be indicated with severe liver dysfunction, cirrhosis and/or hepatocellular carcinoma (Gumus & Ozen, 2023). Gene therapy and gene-based therapeutic approaches are currently under development (Gumus & Ozen, 2023).

Dietary treatment remains the primary treatment for GSD 3 and is individualised, based upon the subtype, age of diagnosis and clinical manifestations (Kishnani et al., 2010). Treatment within infancy/childhood with either GSD 3a or GSD 3b, primarily focusses upon the prevention of hypoglycaemia with small frequent meals (every 3-4 hours) encouraged to avoid fasting (Kishnani et al., 2010; Schreuder et al., 1993). Higher protein is recommended (approx. 3g/kg or 255 of total energy) (Schreuder et al., 1993), particularly in GSD 3a where myopathy and growth failure present (Slomin et al., 1982; Slonim et al., 2006). Increased protein may be

of particular benefit due to several reasons; during fasting protein derived alanine can be used as a source of glucose via gluconeogenesis, muscle protein synthesis may increase and subsequently improve muscle function and with protein intake replacing some carbohydrates less abnormal glycogen would ultimately be stored (Kishnani et al., 2010; Schreuder et al., 1993). Unlike GSD 1, in GSD 3 sucrose, fructose and lactose are not restricted as gluconeogenesis is intact (Kishnani et al., 2010), although complex carbohydrates and protein are recommended over simple sugars to reduce glycogen storage (Kishnani et al., 2010). Recommendations for fat are in line with usual recommendations, with the use of MCTs as an alternative fuel requiring further research (Kishnani et al., 2010). Vitamins and minerals are prescribed where needed following overall nutritional assessment, with vitamin D and/or calcium recommended to augment bone mineralisation (Schreuder et al., 1993). Cornstarch can be gradually introduced as early as the first year of life and used early to maintain blood sugars, with potentially several doses necessary (approx. starting at approx. 1g/kg) depending on glucose and ketone levels/monitoring (Schreuder et al., 1993). In certain cases where blood sugars cannot be maintained within normal ranges, continuous overnight feeding may be necessary (Kishnani et al., 2010) and Glycosidase extended-release corn-starch utilised, particularly where there are risks of nocturnal hypoglycaemia (Ross et al., 2015). Care must be taken to avoid overtreatment with cornstarch or carbohydrates which can result in glycogen accumulation in the liver and weight gain (Gumus & Ozen, 2023) and undertreatment may potentially lead to hyper ketosis (Kishnani et al., 2010).

Treatment in adulthood, involves the management of hypoglycaemia but also focusses upon the importance of protein, specifically in those with myopathy (Kishnani et al., 2010), in order to prevent muscle breakdown and preserve skeletal and cardiac muscle (Kishnani et al., 2010). Nutritional recommendations range from 20 to 30% protein, 35 to 55% carbohydrates and 20 to 35% fat (Kishnani et al., 2010). A high protein diet of up to 30% of total calories and

moderate cornstarch to maintain euglycemia has been shown to significantly improve cardiomyopathy (Dagli et al., 2009). With regards to carbohydrates, complex carbohydrates are generally recommended over simple sugars which can lead to sudden fluctuations in blood sugars (Kishnani et al., 2010). Ketogenic diets have been shown to be of benefit in GSD 3, with significant reductions in cardiomyopathy found following a ketogenic diet or a ketogenic diet with increased protein and ketone bodies (Francini-Pesenti et al., 2019; Valayannopoulos et al., 2011). Similarly, a Modified Atkins diet has reported both improvements in cardiac function and exercise tolerance (Mayorandan et al., 2014). Furthermore, a high fat, low calorie and high protein diet has been shown to improve cardiomyopathy (Kumru et al., 2022; Sentner et al., 2011) which may be explained by a reduction in glycogen storage and the utilisation of fats, ketone bodies and protein as fuels, however the long-term benefits warrant further investigation (Derks & Smit, 2014).

Currently, limited information is available in order to provide firm recommendations for regular exercise in individuals with GSD 3. However, insights from GSD 5 suggest that aerobic conditioning may offer similar benefits for those with GSD 3 (Haller et al., 2006; Kishnani et al., 2010). The role of resistance or strength training remains unclear due to the lack of specific studies, and caution is advised when engaging in maximal effort exercises, given the risk of injury seen in other muscle glycogenolysis and glycolysis disorders (Kishnani et al., 2010). Aerobic exercises tailored to the patient's strength and endurance can be proposed during consultations and incorporated as regular physical activity, following a cardiological evaluation, to stimulate the fatty acid oxidation pathway (Wicker et al., 2023). Exercise may be particularly beneficial for individuals with GSD 3a, as it may help manage manifestations such as myopathy, low bone mineral density, and hypoglycaemia (Kishnani et al., 2010). On the whole, no exercise restrictions are advised for individuals with GSD 3 unless significant cardiac

abnormalities develop, in which case exercise should be modified accordingly (Kishnani et al., 2010).

2.3.3 Glycogen Storage Disease 5

2.3.3.1 Genetics and Epidemiology

GSD 5 was first described in 1951 by Brian McArdle (McArdle, 1951) and is one of the most common GSDs with a prevalence of 1 in 100,000 to 1 in 167,000 (Kanungo, et al., 2018). It is an autosomal recessive disorder, caused by pathogenic mutations of the gene encoding the skeletal muscle isoform of phosphorylase (PYGM) resulting in deficient myophosphorylase activity (Smit et al., 2006). Myophosphorylase is required to catalyse the initial step of glycogenosis within muscle fibres by removing alpha-1,4, glucosyl units from the outer glycogen branches and releasing glucose-1-phosphate (G1P) (Dubowitz & Oldfors). As a consequence, G1P cannot enter glycolysis and thus energy production from muscle glycogen stores is impaired, ultimately leading to physical implications of muscle weakness and cramping (Kishnani, 2014). As the PYGM isoform of glycogen phosphorylase is only expressed in skeletal muscle this differs from other GSDs such as GSD 2 where multiple tissues and organs are severely affected and can prove potentially fatal (Nogales-Gadea et al., 2016). In GSD 5, a total of 147 pathogenic mutations and 39 polymorphisms have been identified, in which the p.R50X or R50X mutation is the most common and represents approximately 40% to 50% of the alleles in Caucasian GSD 5 patients (Nogales-Gadea et al., 2015). Despite many mutations having been identified, no genotype: phenotype correlation exists, thus patients with the same genotype can have differing physical manifestations, which cannot fully be explained by differences in lifestyle (Santalla et al., 2017; Smit et al., 2006).

2.3.3.2 Clinical findings and diagnosis

Despite symptoms commonly presenting in childhood, diagnosis is rare before adulthood, with a median diagnosis age of 33 years, as prior symptoms are commonly dismissed and overlooked (Santalla et al., 2017; Scalco et al., 2017). A diagnosis may be suspected in those with consistently elevated CK (Smit et al., 2006) and recurrent episodes of rhabdomyolysis which can lead to myoglobinuria, renal dysfunction and often high urate (Kanungo et al., 2018; Lucia et al., 2012). Less common signs may include difficulty with mastication, dysphagia and poor oral motor function, spontaneous compartment syndrome (Triplet et al., 2017) or posterior neck muscle contractures (Scalco et al, 2016). The forearm ischemic exercise test (FIE) involving the measurement of lactate and ammonia from the antecubital vein before and after repetitive exercise with cuff induced ischemia was considered informative to identify suspected GSD 5 patients, in which the failure of a normal lactate rise and an increased rise in ammonia can be shown (McArdle, 1951; Smit et al., 2006; Tarnopolsky et al., 2003). This method, however, is now largely abandoned due to it being painful and not proven to be reliable, reproducible, or specific (Smit et al., 2006). Alternatively, a non-ischemic version of the FIE can be used which has a high sensitivity and specificity for GSD 5 and similar to the FIE, there is a failure of a normal lactate rise (less than 2 fold, with most displaying less than a 50% increase) and an elevated rise in ammonia (greater than 2.5 fold) (Tarnopolsky, 2018). Furthermore, alternatively, a cycle-based test can be used, in which a decrease in heart rate between the 7^{th} and 15^{th} minute of moderate intensity exercise signifies the second wind phenomenon (Vissing & Haller, 2003a). The forearm tests and incremental cycling tests are used in addition to medical history and physical assessments/clinical assessments and used to assist the interpretation of other results. A normal lactate and ammonia response following exercise, could potentially eliminate consideration of nearly all metabolic GSDs (Tarnopolsky, 2018). Where a muscle biopsy is obtained, muscle histochemistry shows subsarcolemmal lakes

of PAS positive material that is diastase positive (Kishnani, 2014). Specific myophosphorylase enzyme activity can be assayed in muscle tissue and demonstrated by histochemical stains on frozen sections from muscle biopsy (Kishnani, 2014) and in most cases can be diagnostic, except where the specimen is obtained too soon after an episode of myoglobinuria (Smit et al., 2006). Where taken too soon following acute rhabdomyolysis, nonspecific necrosis, neutrophils and macrophages can be visible, masking clinical features and as such be misleading (Tarnopolsky, 2018).

Genetic testing is available and best to confirm diagnosis (Kishnani, 2014), particularly in Caucasian patients with the R49X mutation, where its presence even in one allele indicates diagnosis (Smit et al., 2006). Targeted mutation panel analysis for common pathogenic gene mutations has traditionally been used; however, as there are a broad range of pathogenic mutations reported, Sanger sequencing of all coding regions of the PYGM gene can be effectively utilised (Tarnopolsky, 2018). Many companies now provide next-generation sequencing-based myopathy panels that include a large number of the structural genes that can results in exercise intolerance and all of the GSD-associated genes. It has been found that 90% of those with GSD 5 have experienced initial misdiagnosis therefore the use of appropriate clinical assessment and diagnostic tests is paramount for clinicians to recognise and distinguish features of GSD 5 (Scalco et al., 2017).

2.3.3.3 Physical manifestations

The clinical presentation often begins in childhood, with 58% of individuals experiencing symptoms within the first decade of life, though onset can vary, with 28% developing symptoms in the second decade and 14% in the third or fourth (Lucia et al., 2012). Exercise intolerance is the main manifestation, typically with the occurrence of early fatigue, myalgia, muscle stiffness and contractures, particularly in the first few minutes of exercise. This is due to the deficiency in myophosphorylase, resulting in a complete blockage of muscle

glycogenolysis (Smit et al., 2006), while liver phosphorylase is spared, preserving the liver's ability to mobilise glycogen for systemic glucose homeostasis (Haller & Vissing, 2002; Smit et al., 2006). As a consequence, the physical symptoms are more likely to become apparent on sudden intense isometric exercises such as pushing a static vehicle or carrying weights; or sustained vigorous lower intensity exercise such as stair climbing or walking in the snow (Santalla et al., 2017; Smit et al., 2006). High intensity exercise can lead to painful cramps and contractures, resulting in significant muscle damage and rhabdomyolysis, with a sudden flux of intramuscular proteins including creatine kinase (CK) and myoglobin into the blood stream and myoglobinuria, known to occur in around 50% of patients (Kanungo et al., 2018; Lucia et al., 2012). As a consequence of the severe muscle damage that can accompany symptoms ranging from exercise intolerance to rhabdomyolysis, renal failure presents a significant, yet often non-fatal, complication in these patients (Lucia et al., 2012). The progression to such serious complications underscores the critical need for ongoing management to mitigate these risks.

A unique characteristic often demonstrated across those with GSD 5 is patients developing a "second wind" phenomenon, which is observed as a marked improvement in exercise tolerance after approximately 8-10 minutes of dynamic exercise (Pearson et al., 1961). During the first few minutes of aerobic exercise of moderate intensity such as brisk walking or cycling, heart rate and rate of perceived exertion (RPE) gradually and continuously increase beyond what would be expected at that work rate, with maximal levels observed at 6-8 minutes of exercise. Heart rate and RPE then begin to decline, and there is a marked improvement in exercise tolerance (Haller & Vissing, 2002). This is attributable to vasodilation and enhanced-uptake and utilisation of blood-borne glucose from the liver which can subsequently be utilised via glycolysis, downstream of the metabolic block and an increase, by approximately 25% in the oxidation of circulating free fatty acids (Haller & Vissing, 2002; Lucia et al., 2021; Orngeen et

al., 2009; Riley et al., 1993; Vissing et al., 1992). More recently, a third wind has even been recognised, with improvements in exercise tolerance reported after 2 hours, thought to be attributable to a gradual increase in the use of carbohydrate from gluconeogenesis compared to healthy individuals (Godfrey et al., 2019).

In addition to the dynamic-exercise intolerance described, ongoing muscle damage, indicated by elevated baseline serum creatine kinase (CK) activity, even in the absence of strenuous exercise, is also a dominant feature (Lucia et al., 2008; Lucia et al., 2012). As a consequence, fixed muscle weakness with muscle wasting occurs in around 25% of patients, particularly affecting proximal upper limb and axial muscles (Lucia et al., 2012; Nogales-Gadea et al., 2016; Quinlivan et al., 2010). This weakness and exercise intolerance, as with GSD 2 and GSD 3, not only limits physical function but may also lead to difficulties with activities of daily living and reduced QoL, especially as the disease advances, often resulting in a gradual loss of independence (Lucia et al., 2021)

Longitudinal data, detailing the progression of the disease is particularly limited. Where available, existing data documents the worsening of symptoms with age in 28% of individuals. Muscle weakness, a critical factor affecting daily functioning, is notably more prevalent in individuals aged 40 years or older (34%) compared to younger patients (16%), highlighting a significant age-related disparity. Furthermore, cardiorespiratory fitness declines with age (-0.20 mL O_2/kg/min per year, $p<0.001$), with 42% of individuals aged 40 or older having a $\dot{V}O_{2peak}$ below the threshold required for independent living (13 mL O_2/kg/min), compared to 15% of younger participants (Lucia et al., 2012). These findings underscore the need for larger longitudinal studies including comprehensive outcomes, to better understand the natural history of GSD 5, with a particular focus on identifying age-related changes and developing targeted interventions to preserve muscle strength and cardiorespiratory fitness, particularly in older populations.

2.3.3.5 Management

There is no known cure for GSD 5, and it appears unlikely that an effective enzyme replacement therapy will be developed in the near future. Various treatments have been explored, such as stop codon-based therapies (Schroers et al., 2006); induced expression of brain and liver isoforms of glycogen phosphorylase in muscle (Howell et al., 2008a) and gene therapy (Howell et al., 2008b). Despite these treatments demonstrating encouraging results in animal studies, their efficacy in humans has not yet been established. Therefore, at present the most effective treatment strategies focus upon healthy lifestyle interventions, in which exercise and nutrition play a vital role (Kanungo et al., 2018).

Nutrition has been shown to be an important therapeutic strategy, particularly in conjunction with exercise for the improvement of exercise tolerance and protecting the muscle from rhabdomyolysis. The goal of nutritional interventions is to ensure a consistent supply of blood glucose to active muscles. One such strategy to ensure increased hepatic glycogen stores and thus sufficient blood glucose is through consuming a diet high in complex carbohydrates (65%) and reduced fat (20%) (Andersen & Vissing, 2008; Lucia et al., 2021). A further strategy to ensure adequate blood glucose supply is the ingestion of simple carbohydrates prior to engaging in exercise, particularly within the first few minutes of exercise, where circulating levels of fuels are low (Lucia et al., 2021). Research has shown that the ingestion of seventy-five grams of sucrose, 30-40 minutes prior to exercise provides a source of exogenous glucose and fructose which can circumvent the metabolic block in glycogenosis and subsequently improve exercise tolerance (Bangsbo et al., 1992). Furthermore, reduced doses of 30-40g of glucose, fructose or sucrose, translating to 400-500ml of most commercially available sports drinks within 5 mins of commencing exercise (Andersen et al., 2008b) can be used. The provision of pre-exercise fuel therefore eliminates the second wind phenomenon (Haller & Vissing, 2002; Vissing & Haller, 2003b).

Despite traditional guidance advising against exercise, careful supervision of exercise training by professionals presents a promising option for these individuals. The possibility that myophosphorylase deficiency could potentially impact brain or cardiac tissue lends additional support to the implementation of exercise interventions due to the wide-ranging multi-organ benefits including enhanced neurogenesis and cognitive function, which no single medication is likely to surpass (Fiuza-Luces et al., 2013). Moderate exercise is recommended for at least 20 minutes, up to a maximum of 1.5 hours, 2-4 times per week including activities such as brisk walking, cycling, and swimming (Lucia et al., 2021; Quinlivan et al., 2011). Due to the risk of rhabdomyolysis, exercise should always take place under supervision and should be preceded by a 5-10 minute warm up in order for individuals to get into the "second wind" and improve their exercise tolerance (Haller et al., 2006; Maté-Muñoz et al., 2007; Porcelli et al., 2016; Vissing & Haller, 2003b). Light dynamic stretching and adequate hydration post-exercise is also recommended (Lucia et al., 2021). Furthermore, strength training is advised 2-3 non-consecutive days per week to promote favourable adaptions included increased muscle mass, reduction in disease severity, lower baseline CK levels, and prevention of fixed muscle weakness (García-Benítez et al., 2012; Pietrusz et al., 2018; Santalla et al., 2014). Since the ATP-phosphocreatine system, which supports high-intensity efforts of up to 10 seconds, remains unimpaired in GSD 5 (Baker et al., 2010; Bogdanis et al., 1996; Lucia et al., 2021; Santalla et al., 2014), resistance training sets should consist of efforts lasting no longer than 6 seconds (Baker et al., 2010; Bogdanis et al., 1996; Lucia et al., 2021; Santalla et al., 2014). The optimal session should include consuming 20-30g of simple carbohydrates (e.g. 330ml isotonic drink) to enhance glucose delivery to the muscle (Nogales-Gadea et al., 2016; Vissing & Haller, 2003b), then 10–15-minute warm-up, targeting both upper and lower body, such as walking, cycling, arm-crank ergometer. Strength exercises should include large muscle groups, structured as a circuit with sets of up to 6 repetitions, followed by a 3-minute rest between

exercises to allow phosphagen synthesis (García-Benítez et al., 2012; Santalla et al., 2014). During rest, 10–30 seconds of stretching is recommended to prevent muscle stiffness (García-Benítez et al., 2012; Pietrusz et al., 2018; Santalla et al., 2014). The session should conclude with a cool-down, incorporating low-intensity dynamic exercises (e.g., walking, cycling) and passive stretching, followed by hydration (Santalla et al., 2014).

2.4 Exercise Intolerance across Glycogen Storage Diseases

Exercise intolerance is not only a hallmark of GSD 2, GSD 3a, and GSD 5 but also occurs across the spectrum of glycogen storage diseases, which primarily affect the liver and skeletal muscle (Kanungo et al., 2018). Individuals with hepatic involvement often experience fasting hypoglycaemia, which can impact exercise tolerance due to both the direct effect of liver glycogen levels on exercise capacity, and the indirect role of glycogen in maintaining blood glucose homeostasis (Gozalez et al., 2016; López-Soldado et al., 2021; Tarnopolsky, 2018). Within, GSDs with muscle involvement, they can generally be divided into two main clinical phenotypes; those with static (fixed) symptoms, including muscle atrophy and weakness (Di Mauro & Lamperti, 2001; Vissing, 2016) and those with exercise-related (dynamic) symptoms, that are due to a deficiency in ATP (Preisler et al., 2014; Vissing, 2016). In patients with static symptoms, muscle wasting and persistent weakness result from the loss of muscle tissue caused by structural damage. This damage is partly linked to the abnormal accumulation of glycogen or lipids within the cells, which disrupts normal contractile function (Vissing, 2016). In contrast, in those with exercise-related (dynamic) symptoms, impairment in exercise tolerance is due to a reduced carbohydrate supply, inhibiting skeletal muscle ATP production (Preisler et al., 2014). However, clinically, these phenotypes may overlap, making it challenging to distinguish between static and dynamic symptoms in some patients (Preisler et al., 2014; Vissing, 2016). Exercise intolerance across the broad range of GSDs is highly variable, even presenting differently among those with the same GSD type (Echaniz-Laguna, et al., 2010; Ørngreen, et

al., 2008; Preisler, et al., 2012). As a consequence of the widespread exercise intolerance described, many patients adopt sedentary lifestyles, which further contribute to skeletal muscle atrophy and an unfavourable metabolic shift towards reduced glycogen utilisation and increased fat storage, ultimately exacerbating exercise intolerance (Stein & Wade, 2005).

2.5 Exercise as a Therapeutic Intervention

The significant exercise intolerance across the breadth of GSDs is known to progress over time. Despite this progression, no curative treatments are currently available and as such therapeutic approaches primarily focus on symptom management and improving QoL (Stone et al., 2025). Dietary interventions have demonstrated improvements in exercise tolerance in GSDs affecting both the liver and skeletal muscle (Ross et al., 2020), and ERT has been shown to be of benefit to those with GSD 2, although it has not been developed for use in other GSD types (van der Ploeg et al., 2010). However, even with these current treatments, impairments in QoL persist (Heller et al., 2008; Ross et al., 2020). Given this ongoing challenge, additional therapies, such as exercise training, should therefore be explored as potential strategies to further improve patient outcomes.

Exercise as a therapeutic intervention may initially appear counterintuitive to both patients and clinicians, especially considering the widespread exercise intolerance across GSDs (Vissing, 2016). However, growing evidence, particularly over the last decade indicates that exercise can help alleviate symptoms and improve QoL, rather than exacerbating the condition (Preisler et al., 2014). Exercise may be crucial in metabolic myopathies for several reasons. First, the exercise intolerance experienced by most individuals with metabolic myopathies is partly due to a sedentary lifestyle. Inactivity not only leads to skeletal muscle atrophy but also causes metabolic changes that increase reliance on glycogen and reduce the capacity for fatty acid oxidation (Stein & Wade, 2005). Second, exercise acts as a powerful adaptive mechanism for metabolic changes in skeletal muscle, modifying skeletal muscle substrate metabolism towards

the utilisation of fatty acid oxidation (Lucia et al., 2012; Lucia et al., 2013; Perez et al., 2007). Furthermore, muscle vasodilation, increases the delivery of blood-borne substrates including free-fatty acids and glucose to contracting muscle (Haller et al., 2006). Lastly, as with healthy individuals, a properly implemented regular exercise program has the potential to enhance overall health and fitness, as well as improve QoL (Blair et al., 1995; Pedersen & Saltin, 2006). In light of this, the potential therapeutic benefits of exercise training for individuals have been advocated by researchers and clinicians for many years, with supervised exercise training programmes incorporated in therapeutic guidelines (Cupler et al. 2011; Kishnani et al., 2006; Kishnani et al., 2010; Lucia et al., 2021; Wicker et al., 2023).

2.5.1 The Effect of Exercise Training in GSDs

Research has assessed the benefits of aerobic exercise for those with GSD 5, with light (60-70% maximal heart rate) aerobic exercise (cycling or walking) completed 3, 4 or 5 times per week for either 8 weeks (Olivier et al., 2005), 14 weeks (Haller et al., 2006) or 8 months (Mate-Munoz et al., 2007). Haller et al. (2006) observed a 36% improvement in average work rate and a 14% increase in average oxygen uptake during exercise, along with a 15% rise in cardiac output. Additionally, increased enzyme activity following training was noted, which may have contributed to enhanced oxidative phosphorylation rates. Similarly, Mate-Munoz et al. (2007) reported significant improvements, including a 44% increase in $\dot{V}O_{2peak}$ and a 38% increase in peak power output. In contrast, with lower training volumes, no significant improvements were found (Olivier et al., 2005). Most importantly, all training protocols were well tolerated, with no adverse events reported. Moreover, supervised low-load strength training in GSD 5 has been found to reverse muscle weakness and atrophy, helping to mitigate disease severity (Santalla et al., 2014). Within GSD 2, combined strength and aerobic training, completed 3 times per week for 12 weeks (n=23) has shown promising results with improvements in endurance, muscle strength, muscle function and core stability (van den Berg et al., 2015). Smaller studies

(*n*=5) have also shown beneficial effects of combined training, with improvements in 6-minute walking distance and strength (Terzi et al., 2011). Despite the existing literature detailing the beneficial effects of exercise training within GSDs, the current research is sparse and highly heterogenous. Studies are a mixture of controlled and uncontrolled trials, with small sample sizes, of differing GSD subtypes and the inclusion of a diverse range of interventions with variable follow up and outcomes.

Considering the limited and highly varied nature of the research, it is difficult for researchers and healthcare professionals to determine the feasibility and utility of using exercise training as a therapeutic option across the broad range of GSDs. The research has been previously reviewed systematically by Quinlivan et al. (2011), however despite this review concluding that aerobic exercise promoted physiological improvements without adverse events, it was limited to only three studies in GSD 5. The narrow focus of this review highlights a significant gap in our understanding of how exercise impacts other GSD subtypes. Since this review was published, numerous studies, including randomised controlled trials (Jones et al., 2020), have emerged, but no comprehensive review has been conducted to synthesise these findings. A more extensive review is urgently needed to assess the broader effects of exercise across all GSD subtypes. Such a review could help determine whether exercise interventions are beneficial, including which exercise modalities and in which specific GSD subtypes. Furthermore, a robust review could assess overall adherence and any potential adverse effects. This information would be valuable to guide future clinical guidelines and research.

2.5.2 Factors Influencing Physical Activity Participation in Glycogen Storage Diseases

As outlined, physical activity is recommended as a therapeutic strategy for individuals with GSD, as it has been shown to alleviate symptoms and improve QoL rather than worsen the condition (Preisler et al., 2014). Consequently, researchers and clinicians have long advocated for the benefits of exercise training, with a growing number of therapeutic guidelines now

incorporating supervised exercise programs (Kishnani et al., 2006; Kishnani et al., 2010; Cupler et al., 2011; Lucia et al., 2021; Wicker et al., 2023). However, the manifestations of GSDs present several challenges towards engaging in physical activity. GSDs with liver involvement, as described previously have been shown to present with symptoms of hypoglycaemia (Gozalez et al., 2016; López-Soldado et al., 2021; Tarnopolsky, 2018), whereas GSDs with muscular involvement may incur fixed muscle wasting and weakness (Di Mauro & Lamperti, 2001; Vissing, 2016) and exercise-related symptoms due to a deficiency in ATP (Preisler et al., 2014; Vissing, 2016). Moreover, these physical symptoms are highly variable in their onset and progression, presenting differently even within the same GSD type (Echaniz-Laguna et al., 2010; Ørngreen et al., 2008; Preisler et al., 2012b). Furthermore, alongside the physical impairments, individuals with GSDs often report psychological implications, including fatigue and low motivation, which can further compound their condition (Slipsager et al., 2024). The combination of physical and psychological factors experienced by this population are likely to create unique and additional barriers, that hinder physical activity participation, presenting challenges beyond those faced by the general population.

Physical activity offers numerous potential benefits for individuals with GSDs, with growing evidence underscoring its role in alleviating symptoms and enhancing QoL, rather than exacerbating the condition (Preisler et al., 2014). As outlined earlier, research has demonstrated the benefits of exercise in managing GSD 2 and GSD 5 (Terzis et al.,2011; van den Berg et al., 2015; Quinlivan et al., 2011). Aerobic exercise, in particular, has been found to act as a natural driver of metabolic change by promoting increased substrate delivery and enhanced fatty acid utilisation (Preisler et al., 2014). Additionally, resistance exercise has been found to reverse muscle weakness and atrophy, thereby reducing disease severity (Santalla et al., 2014); with these benefits collectively contributing to improved exercise tolerance (Haller et al., 2006; Maté-Muñoz et al., 2007; Olivier et al., 2005; Santalla et al., 2014). Furthermore, physical

activity has been proposed as a means to combat physical inactivity commonly observed across the GSD spectrum, potentially improving overall health, fitness, and QoL (Blair et al., 1995; Ding et al., 2020; Pedersen & Saltin, 2006). Recognising these therapeutic benefits, researchers, clinicians, and even patients themselves have increasingly advocated for adopting an active lifestyle (Karazi et al., 2024; Kishnani et al., 2006). As a result, recommendations for physical activity have been incorporated into multiple guidelines (Cupler et al., 2011; Kishnani et al., 2006; Kishnani et al., 2010; Lucia et al., 2021; Wicker et al., 2023). These guidelines specifically promote regular mild to moderate aerobic exercise, within GSD types 2, 3, 5, and 7 (Cupler et al., 2011; Kishnani et al., 2006; Kishnani et al., 2010; Lucia et al., 2021), along with the inclusion of resistance exercise for GSD 5 (Lucia et al., 2021) which should be tailored to individuals exercise capacity and regularly monitored.

Despite physical activity being widely recommended, the manifestations of GSDs, which vary in onset and progression (Echaniz-Laguna et al., 2010; Ørngreen et al., 2008; Preisler et al., 2014), pose significant challenges to physical activity engagement. These manifestations include hypoglycaemia, particularly in individuals with liver involvement (Gozalez et al., 2016; Lopez-Soldado et al., 2021; Tarnopolsky, 2018), as well as fixed muscle weakness and wasting (Di Mauro & Lamperti, 2001; Preisler, Haller & Vissing 2014; Vissing, 2016) and/or dynamic exercise-related symptoms, such as muscle pain and fatigue in those with muscle involvement (Preisler et al., 2014; Vissing, 2016). These physical impairments negatively affect functional capacity and daily activities, thereby reducing QoL (Chen et al., 2021; Derks et al., 2021; Güngör et al., 2015). Research in GSD 5 specifically, has highlighted these impacts, showing significant reductions in QoL, particularly in the physical health domain. Furthermore, moderate to severe fatigue, including physical, general, and mental fatigue, is prevalent and strongly associated with symptom severity. Unsurprisingly, low levels of physical activity have been observed in this GSD type (Karazi et al., 2023; Karazi et al., 2024; Slipsager et al., 2024).

Certainly, Karazi et al. (2024), using the International Physical Activity Questionnaire (IPAQ) as part of an online survey, found that nearly half (47%) of participants did not engage in vigorous physical activity (e.g., heavy lifting), 29% avoided moderate activity (e.g., cycling), and 13% reported not walking for at least 10 minutes in the previous 7 days. These findings ultimately classify individuals with GSD 5 as more sedentary than the general population (Munguia-Izquierdo et al., 2015; Scalco et al., 2020). Collectively, this initial research suggests that both physical and psychological factors uniquely influence physical activity engagement in GSD patients, which may be similar or extend beyond what is observed in the general and other clinical populations.

Within the general population a wide range of factors are known to impact participation in physical activity programs, including time constraints, language barriers, financial limitations, inadequate social support, access and underlying health conditions (Mbabazi et al., 2022). Many of these barriers, such as lack of time, social support, motivation, and access to facilities, are also prevalent in clinical populations, such as individuals living with chronic pain (Vadar et al., 2019). However, research has identified that clinical populations often face additional and unique challenges to physical activity participation. For instance, individuals with chronic pain encounter specific barriers such as escalating pain levels, fatigue, unpredictable pain fluctuations, and perceived risks such as heightened pain and potential injury (Karlsson et al., 2018; Vadar et al., 2019). Similarly, those with musculoskeletal disorders report a fear of increased pain with physical activity, along with time constraints and limited support (McPhail et al., 2014). In conditions such as Charcot-Marie-Tooth disease (CMT) and arthritis; pain, fatigue, and restricted mobility further hinder exercise participation (Anens et al., 2015; Wilcox et al., 2006). Moreover, these physical symptoms, including pain and fatigue, have been shown to negatively impact motivation and reduce the likelihood of future exercise participation (Karlsson et al., 2018; Wilcox et al., 2006). Conversely, several factors have been identified as

facilitators of physical activity in clinical populations. These include improvements in health and symptom management, social support, access to appropriate exercise facilities and equipment, and the availability of time and opportunities to engage in physical activity (McPhail et al., 2014; Wilcox et al., 2006).

Despite the benefits of physical activity being well-recognised within GSDs, as yet no studies have thoroughly explored physical activity engagement, behaviours or perceived barriers and facilitators of physical activity across this population. Consequently, it remains unclear whether individuals with GSDs, despite recommendations, engage in regular physical activity and the specific challenges they encounter. While multiple factors are known to impact physical activity participation in the general population (Mbabazi et al., 2022) and in other clinical populations (Anens et al., 2015; Karlsson et al., 2018; McPhail et al., 2014; Vadar et al., 2019; Wilcox et al., 2006); the variable onset and progression of symptoms in individuals with GSD is likely to create additional and unique challenges that warrant further investigation. Furthermore, given that physical activity is promoted, with specific activity programmes incorporated in therapeutic guidelines (Cupler et al., 2011; Kishnani et al., 2006; Kishnani et al., 2010; Lucia et al., 2021; Wicker et al., 2023), exploring optimal approaches for designing and implementing exercise interventions that address the specific needs and preferences of individuals with different GSD subtypes is crucial but currently unexplored.

To address this gap in the literature, further research is necessary to comprehensively quantify current physical activity levels, behaviours, barriers and facilitators and physical activity preferences in those with GSDs. Moreover, contributing factors that influence physical activity such as psychological factors including fatigue and motivation should be explored. In addition, due to the variability in individual onset and progression within and between GSD subtypes, future research should focus on qualitative exploration of individual-level facilitators and barriers, offering in-depth, context-specific insights. This research would provide extensive and

valuable information, which could serve as a foundation for the development and implementation of effective physical activity programmes, tailored to this population, ultimately aiming to encourage long-term adherence, improve QoL, and enhance overall health outcomes.

2.6 Lactate Supplementation: A Novel Dietary Treatment

Alongside the therapeutic benefit of exercise, dietary treatment has proven to be an effective therapeutic strategy in GSDs over the last 50 years; with specific dietary treatments adapted to the underlying enzyme defect and metabolic pathway involved (Bhengu et al., 2014; Heller et al., 2008). In those with hepatic involvement, a particular focus is placed upon preventing hypoglycaemia and improvement of metabolic disturbances (Heller et al., 2008; Ross et al., 2020). Complex carbohydrates are favoured over simple sugars (Ross et al., 2020) and cornstarch is commonly used to avoid severe hypoglycaemia and fasting intolerance (Ross et al., 2020; Weinstein & Wolfsdorf, 2002). In GSDs with intact gluconeogenesis and particularly in those with muscular involvement, a higher protein diet may be utilised to supply an alternative source of glucose via glucogenic amino acids, helping to reduce glycogen accumulation, while also preventing muscle breakdown and encouraging muscle synthesis (Kishnani et al., 2010; Kishnani et al., 2019a). Moreover, specific ketogenic diets (Francini-Pesenti et al., 2019; Valayannopoulos et al., 2011) and modified Atkins diets have been reported as beneficial (Mayorandan et al., 2014) in specific GSD types such as GSD 3. Overall, however, there is a lack of general consensus on the optimal dietary treatment, which remains largely limited to the manipulation of macronutrients (Bhengu et al., 2014; Heller et al., 2008). Despite the benefits of current dietary therapy, impairments in functional capacity and QoL remain prevalent (Heller et al., 2008; Ross et al., 2020). Consequently, there is a need to explore novel dietary treatments which would enhance outcomes in individuals with GSD. One such potential

adjunct to consider, alongside exercise training and traditional macronutrient manipulation, is lactate supplementation.

2.6.1 Lactate

The terms lactate and lactic acid are often used interchangeably but are known to be two different molecules (Powers & Howley, 2012). The lactic acid produced following glycolysis is more than 99% dissociated into lactate anions (La^-) and protons (H^+) within the physiological pH range of skeletal muscle and blood (Ferguson et al., 2018; Gladden, 2004; Robergs et al., 2004; Robergs et al., 2005; Sahlin, 1986; Lindinger et al., 2005). The production, metabolism and functional role of lactate has been studied for nearly two centuries and is still a subject of controversy (Hall, 2010).

Traditionally, lactate was largely viewed as a harmful waste product of anaerobic metabolism, formed following the metabolism of glucose-6-phosphate via glycolysis during high intensity exercise (Gladden, 2004; Morris et al., 2012). Its production was thought to be the primary contributor to muscular acidosis and fatigue (Fitts, 1994; Rabinowitz & Enerbäck., 2020). During muscle contraction, phosphocreatine levels, required to supply ATP to actin-myosin and myosin filament cross-bridges begin to decline, and glycogenolysis is activated to produce pyruvate and ATP (Cairns, 2006). As pyruvate production exceeds the mitochondria's capacity for oxidation, excess pyruvate is converted to lactate in the myoplasm (Gladden, 2004). This increase in lactate concentration is accompanied by an increase in H^+ ions, leading to decreased intramuscular pH and acidosis (Spriet et al., 1987a). The resultant acidosis disrupts metabolic processes and excitation-contraction coupling, thereby contributing to muscle fatigue (Juel, 1997). However, the “lactic acid hypothesis” which views the formation of lactate directly with hydrogen ion production and fatigue was based upon correlation-type studies (Dawson et al., 1978; Spriet et al., 1987a; Spriet et al., 1987b; Troup et al., 1986) which although suggestive, does not prove cause and effect (Cairns, 2006). These studies also correlate fatigue with factors

such as ATP reduction (Fitts & Holloszy., 1976), increases in inorganic phosphate (Pi) (Dawson et al., 1978), elevated adenosine diphosphate (ADP), and phosphocreatine (PCr) depletion, amongst others, suggesting multiple contributors of fatigue and the exact cause remains elusive (Gladden, 2004). Moreover, this theory has been contested, with Robergs et al. (2004) arguing that the accumulation of H^+ is not from the production of lactate but from ATP hydrolysis within glycolysis. Others propose, based on physicochemical principles, that the strong acid anions such as lactate ions, produced with increased glycolysis require an increase in net positive charge to maintain electroneutrality, leading to H^+ formation from water dissociation (Lindinger et al., 2005).

Over the past 30 years, perspectives have therefore begun to shift, with growing evidence pointing to lactate's role as more than just a waste product (Cairns, 2006). Research now indicates that lactate acts as a valuable energy substrate, metabolic buffer and signalling molecule (Brooks et al., 2021; Morris, 2012) which as part of the lactate shuttle theory can be actively transported within and between cells, serving as an important energy intermediary (Brooks et al., 2021).

2.6.2 The Lactate Shuttle Theory

The lactate shuttle theory, first introduced by Brooks et al. (1986), describes the movement of lactate between producer (driver) cells and consumer (recipient) cells under both anaerobic and aerobic conditions. This process relies on mono carboxylate transporters (MCTs), bi-directional cell membrane proteins that facilitate lactate transport based on lactate and hydrogen ion gradients (Garcia et al., 1994; Garcia et al., 1995; Roth & Brooks, 1990). Lactate shuttling occurs between the muscle, heart, liver, and kidneys, with muscle serving as the predominant site (Brooks, 2023).

2.6.2.1 The Intracellular Lactate Shuttle

The intracellular lactate shuttle theory describes the glycolytic production and oxidation of lactate within the cell of its origin (Ferguson et al., 2018; Gladden, 2004). Once lactate is produced following glycolysis in the cytosol, it is transported into the mitochondria via MCT1 (Gladden, 2004). Once inside the mitochondria, lactate is first converted to pyruvate in the cytosol or intermembrane space by mitochondrial lactate dehydrogenase (mLDH) (Glancy et al., 2020). Pyruvate is then oxidised through the PDH reaction to acetyl-CoA and then continues through the TCA cycle to produce more ATP aerobically (Gladden, 2004). Although this theory remains controversial due to reports of insignificant dehydrogenase activity in the mitochondria (Rasmussen et al., 2002), further research is warranted to fully explore lactate's potential as a key metabolic intermediary.

2.6.2.2 The Intercellular Lactate Shuttle

The intercellular lactate shuttle theory describes the shuttling of lactate out of cells undergoing accelerated glycolysis and taken up by other cells to be used as an energy substrate or as a precursor for gluconeogenesis or glycogenesis (Ferguson et al., 2018). Within muscle, this theory is based on lactate exchanges between low-oxidative and high oxidative muscle fibres within individual contracting muscles; or within contracting muscles and other distant muscles that are at rest or submaximal exercise; or between contracting muscles and the heart; or between tissues of net lactate release and gluconeogenesis or gluconeogenesis (Ferguson et al., 2018). In contracting muscles, as the demand for ATP increases, lactate accumulates and is shuttled via MCT4 from glycolytic to oxidative muscle fibres via MCT1 (Bonen, 2001; Brooks, 2002; Pellerin, et al., 1998). Alternatively, lactate may be transported via the circulation to less or partially active muscle and oxidised, or inactive muscle where it is primarily converted to glycogen, with only some oxidised. Additionally, lactate can be transported to the liver, where it is either oxidised or converted to glucose via gluconeogenesis which is then stored as

glycogen or transported back into circulation (Cori cycle) to the muscle or other tissues such as the heart and brain (Brooks, 2002; Pellerin et al., 1998). The use of lactate for fuel and as a gluconeogenic substrate has been supported by lactate clamp studies (Miller et al., 2002a; Miller et al 2002b; Roef et al., 2003). A plasma lactate clamp (approx.4mM) within exercising subjects (55% $\dot{V}O_{2peak}$) showed a significant increase in lactate oxidation, with a decrease in glucose oxidation, indicating the preferential use of lactate compared to glucose. Furthermore, lactate has been found to be an important gluconeogenic precursor during low and moderate intensity exercise (Miller et al., 2002a; Miller et al 2002b; Roef et al., 2003).

In addition to serving as an energy substrate, through these processes lactate has been shown to function as an extracellular buffer against acidosis (Morris et al., 2011). The utilisation of lactate via direct oxidation or gluconeogenesis consume protons, thus fortifying blood bicarbonate levels, resulting in a subsequent increase in pH (Morris et al., 2011). Multiple studies investigating oral lactate supplementation as an ergogenic aid have documented lactate's role as a buffering agent during exercise in healthy individuals. Significant increases in blood bicarbonate and blood pH levels have been reported following oral lactate supplementation, both in studies of prolonged exercise (Fahey et al., 1991) and in high-intensity exercise (Morris et al., 2011; salles Painelli et al., 2014; van Montfoort et al., 2004).

2.6.3 The Role of Lactate on Glycogen Storage Diseases

The growing recognition of lactate as an alternative energy source and metabolic buffer has generated interest in its potential role in the therapeutic management of GSDs (Bertocci et al., 1993; Ørngreen et al., 2015; Vissing et al., 2005). Lactate supplementation may offer an advantage by providing an alternative oxidative fuel, bypassing metabolic blockages in glycogenolysis and glycolysis. This could enhance energy availability and mitigate metabolic stress during physical activity, potentially improving exercise tolerance and QoL in certain GSD subtypes. Although limited, early research in this area indicates the importance of lactate

within active muscle (Ørngreen et al., 2015) and the beneficial effects of exogenous lactate supplementation (Bertocci et al., 1993; Lewis et al., 1991).

2.6.3.1 Lactate Kinetics in Glycogen Storage Diseases

Lactate plays a significant role in skeletal muscle energy metabolism, being both produced and utilised simultaneously within contracting skeletal muscle; with skeletal muscle being predominantly responsible for clearing lactate from the bloodstream (van Hall, 2003; Jorfeldt & Wahren, 1970; Richter et al., 1988; Stanley et al., 1986). Ørngreen et al. (2015) were the first to specifically investigate the mechanisms of lactate metabolism in skeletal muscle within GSD, specifically in GSD 5, in which there is a complete block in glycogenosis. Individuals with GSD 5 (n=4) and healthy controls (n=7) were studied at rest and during 40 minutes of cycling (60% $\dot{V}O_{2peak}$ of GSD 5 patients, approximately 35 w) using stable isotope techniques and indirect calorimetry. Results showed that patients with GSD 5, were found to produce lactate during exercise as indicated by an increased release of lactate from active muscle and this was found to be comparable to healthy controls exercising at the same workload. However, interestingly, in those with GSD 5, the uptake of lactate exceeded lactate release in contracting muscle, resulting in a net lactate uptake and subsequent oxidation within active muscles. This reveals the importance of lactate as an essential energy source within contracting muscle, where the rate of glycolysis is severely restricted due to the complete metabolic block in glycogenolysis. The lactate released from contracting muscle was exclusively derived from the metabolism of blood glucose in GSD 5 patients, whereas in healthy controls it was most likely produced from glycogenolysis. These findings underscore the importance of lactate within GSD 5 and suggest lactate supplementation could therefore be an important metabolic substrate, particularly in those with complete glycogenolytic and/or glycolytic deficiencies such GSD types 5 and 7.

2.6.3.2 Lactate Supplementation in GSDs

Glycogen storage diseases (GSDs) with glycogenolytic or glycolytic deficiencies, including GSD 3, GSD 5, GSD 7, and GSD 10, involve enzyme defects that impair glycogen breakdown or glycolysis (Smit et al., 2006). These deficiencies restrict the muscle's ability to utilize glucose for energy, especially during high-intensity exercise when glycogen serves as the primary intracellular fuel (Di Mauro, 2007). These impairments can lead to symptoms such as exercise intolerance, muscle cramps, and fatigue. For instance, muscle phosphorylase deficiency in GSD 5 and phosphofructokinase (PFK) deficiency in GSD 7 restrict glycogen and glucose availability respectively, which impairs maximal aerobic power and heightens the reliance on extra muscular oxidative fuels (Haller et al., 1985; Haller & Lewis, 1991). In such cases, patients depend heavily on blood-borne fuels, such as free fatty acids, to sustain energy, particularly under conditions of increased metabolic demand. This reliance has been shown to increase maximal oxygen uptake, work capacity, and normalise the physiological responses associated with muscle oxidative phosphorylation (Preisler et al., 2015). As described previously, lactate can act as an alternative energy source, entering oxidative metabolism and bypassing these metabolic blocks. Thus, lactate supplementation in individuals with glycogenolytic or glycolytic deficiencies may enhance energy availability and muscle function, especially during physical activity, potentially improving QoL and exercise tolerance. For these reasons exogenous lactate supplementation has been explored in a limited number of studies (Bertocci et al., 1993; Lewis et al., 1991; Vissing et al., 2005).

The effect of intravenous infusion of sodium lactate on muscle cellular metabolism has previously been studied in GSD 7 individuals (n=3) and healthy matched controls (n=3) during maximal-effort handgrip exercise (Bertocci et al., 1993). In GSD 7 it was found that during rest there was no effect of lactate. However, during exercise, the lactate infusion, attenuated the decline in phosphocreatine (PCr) and the rise in inorganic phosphate (Pi), indicating a reduced

rate of PCr hydrolysis. This was accompanied by a smaller increase in adenosine di-phosphate (ADP), consistent with an enhanced rate of ADP phosphorylation via oxidative phosphorylation. In post-exercise recovery, venous ammonia levels remained unchanged by lactate infusion in healthy subjects but were reduced in GSD 5 patients compared to control exercise, aligning with the attenuated increase in (ADP). Additionally, lactate infusion reduced the increase in phosphomonoester (PME) in GSD 7 individuals, suggesting a lower glycogenolytic flux. These findings therefore support the role of exogenous lactate in enhancing the rate of oxidative phosphorylation in active muscle by bypassing the enzymatic block in GSD 7. The increase of oxidative metabolism following exogenous lactate has been support by others (Lewis et al., 1991) with lactate infusion in GSD 7 (n=7) leading to higher peak work rate, oxygen uptake ($\dot{V}O_2$), and arteriovenous oxygen difference. Additionally, exogenous lactate was found to normalise the relationship between cardiac output and oxygen consumption, suggesting that lactate helps stabilise metabolic function and enhance energy availability during exercise in these patients (Lewis et al., 1991). In contrast, individuals with GSDs involving partial defects in glycolysis do not appear to benefit from lactate supplementation. Vissing et al. (2005) found no improvement in maximal oxidative capacity with lactate infusion in individuals with GSD 10 (n=2), suggesting that their 2-6% residual PGAM enzyme activity was sufficient to maintain glycolysis, meet oxidative requirements and eliminate any fluctuations in exercise capacity such as a second wind.

Despite evidence suggesting that lactate supplementation can be of benefit in GSDs, specifically those with complete glycogenolytic or glycolytic blocks (Bertocci et al., 1993; Lewis et al., 1991) these findings are derived from a limited number of studies, focusing on acute, short-term intravenous lactate administration during exercise. Although these studies have demonstrated that lactate can bypass metabolic blocks and serve as an alternative fuel source, potentially enhancing energy availability and exercise tolerance in affected individuals,

the reliance on short-term intravenous supplementation limits our understanding of lactate as a dietary therapy in everyday contexts. Intravenous administration is not practical or sustainable for daily use, raising questions about the feasibility, tolerability and effectiveness of alternative routes of administration such as the use of oral lactate supplementation. Certainly, in health, oral lactate administration for exercise performance has presented conflicting reports of gastro-intestinal disturbances (Azevedo et al., 2007; Morris et al., 2011; Morris et al., 2016; Northgraves et al., 2013; Oliveira et al., 2016; Painelli et al., 2014; Péronnet et al., 1997; van Montfoort et al., 2004) with reports of diarrhoea, eructation, stomach ache and flatulence (Oliveira et al., 2016; Péronnet et al., 1997; Painelli et al., 2014), thus highlighting potential concerns regarding the suitability of oral lactate administration.

While initial studies suggest that lactate supplementation holds promise, further research is crucial to establish its tolerability, safety, and effectiveness in healthy individuals before considering its use as a potential dietary intervention within GSD. The majority of evidence within GSD stems from limited studies, that have primarily used short-term intravenous lactate administration. This research approach does not reflect the practical demands of daily supplementation, especially in the form of oral administration, which would be more feasible for routine use. Consequently, in-depth proof-of-concept studies are essential to assess the feasibility, tolerability, safety, and efficacy of oral lactate supplementation in a healthy population. This research would provide foundational data on the efficacy and safety of oral lactate in healthy individuals and provide further insights that may support lactate's use as a novel, supportive therapy for enhancing energy availability and muscle function in individuals with glycogenolytic and/or glycolytic deficiencies. Further preparatory research would lay the groundwork for future clinical trials in GSD patients, bridging an essential gap between preliminary findings and practical application.

2.7 Thesis Aims

In consideration of the reviewed literature, this thesis will investigate the natural progression of GSDs and the factors influencing various clinical, functional, and psychological outcomes in patients with GSD 3a. Given the pervasive exercise intolerance across GSDs and the potential of physical activity interventions, this thesis aims to evaluate the effectiveness of exercise training programs. Additionally, examining current physical activity behaviours and identifying barriers and facilitators is essential for the effective design and implementation of physical activity interventions. Despite current treatments involving diet and exercise, disease progression persists, highlighting the need for adjunct therapies. Therefore, this thesis also investigates the potential of novel dietary treatments for GSDs, such as GSD 3a.

The aims of this thesis are as follows:

- To establish normative reference values for aerobic capacity and strength in individuals with GSD 3a and to investigate the influence of muscle size and quality on exercise impairment.
- To investigate the natural progression of GSD 3a, focusing on skeletal muscle characteristics, functional capacity, and potential mechanisms underlying impairments in muscle strength, physical function, and QoL.
- To systematically review the current literature, explore the broad impact of exercise training programmes across the GSD spectrum and establish the effects of exercise interventions on markers of cardiorespiratory and aerobic performance, muscular strength, functional capacity and overall well-being.
- To quantitatively examine physical activity levels, exercise behaviours, barriers and facilitators to physical activity and physical activity preferences across GSDs.

- To qualitatively explore physical activity behaviours, barriers and facilitators to physical activity and preferences at an individual level, within those with GSDs, aiming to gain deeper, context-specific insights.
- To investigate the feasibility, tolerability, safety and effectiveness of oral lactate supplementation in a healthy population, to inform its potential future use as a novel dietary therapeutic strategy within GSDs.

The thesis does not include a general methods section as each study employed its own specific methodology, which are detailed within the respective chapters.

Chapter 3 - Aerobic capacity and skeletal muscle characteristics in Glycogen Storage Disease 3a

3.1 Introduction

Glycogen storage disease 3a is a rare inherited metabolic disorder caused by pathogenic variants in the *AGL* gene which spans 85 kb of DNA on chromosome 1p21.2 and is composed of 35 exons (Bao et al., 1996). Pathogenic mutations of the *AGL* gene result in glycogen debrancher enzyme deficiency (GDE) which impedes glycogenolysis and results in excessive glycogen storage. The debranching enzyme is a single polypeptide with two catalytic sites, amylo-1,6-glucosidase (EC 3.2.1.33) and 4-alpha-glucanotransferase (EC 2.4.1.25). To date at least 110 disease causing variants have been reported, illustrating a high degree of genetic heterogeneity (Ko et al., 2014). GSD 3a primarily affects the liver, skeletal muscle and the heart, causing hypoglycaemia, hepatomegaly and (cardio)myopathy (Kiechl et al., 1999; Lucchiari et al., 2007). Because of these pathologies, patients suffer from muscle weakness and exercise limitation that worsen through adulthood (Kiechl et al., 1999; Berling et al., 2021) and can result in patients becoming wheelchair bound (Hobson-Webb et al., 2010).

Experts recognise that exercise is likely to be a useful tool for the assessment of functional status and as a treatment strategy to combat some pathophysiological consequences of GSD 3a, such as myopathy, low bone mineral density and hypoglycaemia (Kishnani et al., 2010). However, they also state that they are unable to provide strong guidance related to the prescription of regular exercise for patients due to a lack of information (Kishnani et al., 2010). This lack of information and thus guidance creates difficulties for physicians considering using exercise testing/training in their clinical practice. One such omission in the research literature is the lack of sufficient normative reference data for GSD 3a to aid interpretation of cardiovascular fitness and muscular strength outcomes. At present, normative data for

cardiovascular fitness is limited to 12 individuals (Hoogeveen et al. 2021; Preisler et al. 2013; Preisler et al. 2015) whilst leg strength has been reported in 18 patients (Decostre et al. 2016). The current study adds normative data on skeletal muscle size and quality. Commonly used technologies and techniques were further employed to add to the small literature base providing normative reference values for cardiovascular fitness and quadriceps strength and studied whether these parameters are associated.

Skeletal muscle size and quality are important markers of physical health, predicting physical performance (Lees et al., 2019), gait variability (Shin et al., 2012) and fall risk (Gadelha et al., 2018). In other diseases characterised by myopathy, such as muscular dystrophy, muscle size and quality are lower than predicted for their age and sex, and account for differences in physical capacity (Jacques et al., 2018). As yet, the relationships between markers of physical capacity and muscle structure are largely unstudied in GSD 3a and warrant investigation to help further understand the relative importance of metabolic, muscular, neuromuscular, and cardiorespiratory function on physical capacity in these patients. Furthermore, in other populations, physical activity and sedentary behaviour (SB) are strongly associated with exercise capacity and muscle strength (Chastin et al., 2012; Hughes et al., 2001) but their associations in GSD 3a are unstudied. As such, this thesis examined the association between these movement behaviours and aerobic fitness and leg strength.

3.1.1 Purpose

To produce normative reference values of aerobic capacity and strength in individuals with GSD 3a and to investigate the role of muscle size and quality on exercise impairment.

3.2 Methods

3.2.1 Patients

In this descriptive study, participants were recruited from the Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, London and the Department of Adult Inherited Metabolic Disease, St Thomas' Hospital, London. Adult patients (>= 18 years) with a diagnosis of GSD 3a (confirmed by reduced GDE enzyme activity and/or *AGL* genetic analysis) were eligible for inclusion. Participants were excluded from participating if they were pregnant, had absolute contraindications to exercise testing, as advised by the American Thoracic Society/American College of Chest Physicians statement on cardiopulmonary exercise testing (American Thoracic Society., 2003), or if they were deemed unable to safely mount/ dismount an exercise bike. Following implementation of these criteria, 7 individuals (3 female) provided informed consent to participate in the study **(Appendix B; Appendix C)**. Five of the participants walked independently, one required the use of a walking aid, and one required a wheelchair to travel over longer distances. The study was approved by the South Central—Berkshire B Research Ethics Committee (16/SC/0663).

3.2.2 Protocols

Following informed consent, on the day of testing participants had baseline (non-fasting) blood tests taken (CK, lipid profile, glucose, urate). All exercise tests were conducted in an exercise physiology laboratory in the presence of a medical doctor and an exercise physiologist. Tests were conducted in a specific order to reduce the likelihood of one test affecting another, and to allow adequate time for recovery between exercise bouts. First, resting measures of body composition and pain were taken. Patients then undertook the two exercise bouts. They first completed a CPET and then, following a minimum of two hours rest, during which patients ate lunch and completed questionnaires (described below), they undertook a knee extension

exercise to determine MVC. Patients were not restricted from eating or drinking for the duration of the study. An isotonic sports drink providing 32.5 g carbohydrates (18.0 g sugar) was made available for each participant and, where diet allowed, patients were encouraged to drink it prior to the exercise tests to potentially reduce exercise-induced muscle pain (Preisler et al., 2015). Throughout the day, patients were asked to stop exercise if they believed continuing might result in muscle soreness and damage.

3.2.3 Body composition

On arrival to the laboratory, patients had their height (Seca 217 stadiometer, Seca, Hamburg, Germany), weight (Seca 761 scales, Seca, Hamburg, Germany), and body composition measured using bioelectrical impedance (MC-980MA PLUS, Tanita Corporation, Tokyo, Japan).

3.2.4 Cardio-pulmonary exercise testing

A symptom-limited, incremental ramp cycling protocol to volitional exhaustion was performed to determine $\dot{V}O_{2peak}$ and Anaerobic threshold (AT) using breath-by-breath gas analysis (Vyntus CPX Metabolic Cart, CareFusion, Höchberg, Germany). The test began with 3 min of rest and a 3 min 'unloaded' warm up, then participants performed the ramp section of the test to exhaustion. The workload during the ramp increased by between 5 and 15 watts per minute, depending on the fitness status of the participant. $\dot{V}O_{2peak}$ was defined as the average of the highest exertional oxygen uptake achieved over the last 20 s of exercise. The AT was determined using the modified V-slope method (Beaver et al., 1986) confirmed by patterns of change in ventilatory equivalent and end-tidal gas measurements (Whipp et al., 1986). In addition to expired air gas analysis, continuous heart rate and peripheral oxygen saturation measurements were made, blood pressure was taken every 3 min and a 12-lead ECG was continuously monitored.

3.2.5. Maximum voluntary contraction assessment

During knee extension strength assessment, participants were seated in a supine position on an isokinetic dynamometer (Biodex System 4 Pro, Biodex Medical, Shirley, NY, USA). The patient's right leg was then securely attached via strapping to the dynamometer knee extension lever arm, whilst ensuring the axis of rotation of the knee joint aligned with the rotational axis of the dynamometer. Inextensible straps were fixed across the hip, distal thigh and chest to reduce extraneous synergistic movements undertaken during maximal contraction. Following the initial setup, participants were briefed on the MVC protocol, which was then followed by a series of warm-up knee extension isometric contractions set at 80°. Each contraction lasted two to three seconds in duration and built up towards to a self-perceived 50% maximal exertion, ensuring the participant was warmed up prior to maximal exertion. Prior to commencement of the MVC protocol, the investigators confirmed the participants were feeling no discomfort/pain and instructed them to stop exertion if any discomfort/pain was reported during the main protocol. The MVC protocol consisted of two to three isometric knee extension at 80° with 5–10 min rest between contractions. Torque was acquired from the dynamometer and analysed with supplementary software (Biodex Advantage software, Biodex Medical, Shirley, NY, USA). MVCs were repeated if greater than 10% of their previous effort and optimal torque was selected as the highest MVC. Participant's rate of torque development (RTD) was calculated using the highest recorded MVC, through utilising the slope of the torque curve from the onset of contraction at an interval of 0–200 ms. Isokinetic dynamometry was chosen as it is considered the gold standard technique for the assessment of muscle strength, showing good to excellent reliability (ICC 0.74-0.89) for knee extensors and flexors assessment (Habets et al 2018).

3.2.6 Assessment of skeletal muscle size and quality

Measurement of muscle size was ascertained through the utilisation of validated methodologies of both Vastus Lateralis (VL) muscle volume and fascicle length (Lf) in order to calculate the physiological cross-sectional area (PCSA) (Morse et al., 2007) of the VL, (Muscle Volume ÷ Lf), which is linearly associated with isometric strength (Massey et al., 2015). Quadriceps muscle volume estimated from single MRI scans at 40%, 50%, and 60% of femur length have previously demonstrated strong correlations with measured volumes (R^2 = 0.84, 0.93, and 0.90; all $P < 0.01$) and progressively lower error rates (SEE: 26.8%, 12.5%, and 9.9%, respectively) (Morse et al., 2007). The physiological cross-sectional area was then subsequently used alongside knee extension MVC assessment to calculate muscle quality (MVC ÷ VL PCSA). The vastus lateralis muscle volume was estimated from a single anatomical cross-sectional area (ACSA) slice at 50% of muscle length using B-mode ultrasonography (MyLab Gamma, Esaote Biomedica, Genoa, Italy) (Morse et al., 2005a). Participants lay supine with their knee fully extended for ~ 20 min to avoid fluid shifts (Berg et al., 2004). B-mode ultrasonography was then used to ascertain both the proximal insertion (0% of total length) and distal insertion (100% of total length) of the VL on their right leg, where the location of 50% of VL muscle length (*L*) and a line between medial to lateral border (ultrasound probe path) of the VL were marked upon the participants' leg. VL ACSA was measured using software for panoramic reconstruction of images (VPAN) which has previously been established as a method of ACSA assessment when compared against magnetic resonance imaging (Panoramic ultrasound Inter-experimenter reliability: CV 2.4% to 4.1%, ICC 0.963 to 0.991; MRI Inter-experimenter reliability: CV 2.8% to 3.8%, ICC 0.946 to 0.986) (Scott et al., 2012). The ultrasound probe (7.5 MHz linear array probe, 38 mm wide), was held perpendicular to the muscle and moved with a constant speed and light pressure to avoid compression along the predefined ultrasound path from the lateral to the medial border of the muscle. Analysis of the VL ACSA was

conducted offline using the analysis software IMAGEJ (1.45 s; National Institutes of Health, Bethesda, MD, USA). All scans were performed and analysed by the same researcher. Skeletal muscle Lf of the VL was measured at rest using B-mode ultrasonography with the probe positioned at 50% of the VL length, at mid muscle belly in the sagittal plane. Images were extrapolated from the capturing software and analysed offline. Three clearly visible fascicles with at least 60% of the chosen fascicle visible within the scanning window, defined from the deep to the superficial aponeurosis, were analysed and the mean values of Lf were recorded. Linear extrapolation was undertaken on fascicles that extended beyond the edge of the screen, in line with previous methodology (Morse et al., 2005a).

3.2.7 Physical Activity monitoring

Following completion of the exercise testing protocol, participants were fitted on the anterior thigh (50% of greater trochanter to femoral condyle distance) with a tri-axial GeneActiv Original accelerometer (Activinsights Ltd., Kimbolton, UK) using two waterproof adhesive patches (Tegaderm Film, 3 M, North Ryde, Australia) in line with previous accelerometery physical activity studies (Grant et al., 2020). The accelerometer frequency was recorded at 60 Hz and was worn for between six and seven consecutive days. On return of the accelerometer, the data was downloaded and converted to 60-s epoch files (GENEActiv software version 3.3, Activinsights Ltd., Kimbolton, United Kingdom). Analysis of the data was conducted using GENEActiv macro file version 9, using validated activity cut-off points (Esliger et al., 2011). This has been found to be a robust and accurate tool for measuring and classifying physical activity intensity in adults showing exceptional technical reliability, with intra-device and inter-device coefficients of variation (CVintra = 1.4%, CVinter = 2.1%), as well as strong validity ($r = 0.98$, $P < 0.001$) (Esliger et al., 2011).

3.2.8 Quality of life and Pain assessment

Prior to exercise testing, Health-Related QoL was estimated using the 36-Item Short Form Health Survey questionnaire (SF-36 v1.0) (Ware & Sherbourne., 1992). This questionnaire consists of 36 items, including eight domains of health status measuring physical functioning (10 items); physical role limitations (four items); bodily pain (two items); general health perceptions (five items); energy/vitality (four items); social functioning (two items); emotional role limitations (three items) and mental health (five items). For each domain, scores are coded, summed and transformed to obtain a score from 0 (worst possible health state) to 100 (best possible health state) (Ware & Sherbourne, 1992). The SF-36 was chosen due to its reliability and validity in assessing health related QoL in the general population (Jenkinson et al., 1994) and within those with musculoskeletal disorders (ICC: 0.85 [0.74-0.92]; Beaton et al., 1997). Pain was assessed using the numeric pain rating scale, in which participants were instructed to provide three pain ratings reflecting their current pain, their best pain, and their worst pain experienced over the past 24 hours. The average of these three ratings was then calculated to represent the participant's overall pain level during that period (McCaffery & Beebe., 1989). The day after testing, patients were contacted via telephone to assess if they had any adverse reactions to the exercise trials, including further assessments of pain using the numeric pain rating scale. If an adverse reaction was reported the patient was contacted on subsequent days until symptoms subsided.

3.2.9 Data and statistical analysis

Predicted CPET values were calculated using published normative data; peak work rate (Jones et al., 1985), $\dot{V}O_{2peak}$ (Wasserman et al., 2005), maximum voluntary ventilation (MVV) (Campbell., 1982), maximum heart rate (HR) (220-age) (Fox et al., 1971) and strength (Harbo, et al., 2012). SPSS (v26, IBM) was used for data analysis, with the significance set at $p < 0.05$. Data was checked with a Shapiro–Wilk test (sample n < 50) for normality of distribution. If

parametric assumptions were accepted, paired samples t-tests assessed whether measured values differed from results calculated using prediction equations, Pearson's correlations were used to test the strength of associations, and data are presented as mean (standard deviation). If parametric assumptions were breached, a paired samples Wilcoxon test was used to assess differences, Spearman's rank correlation was utilised, and data are presented as median (IQ range).

3.3 Results

The demographic and clinical characteristics of the seven participants are shown in **Table 3.1.** Briefly, three were female, and the mean (standard deviation) age and height of participants were 37 (11) years and 179 (10) cm, respectively. Median (IQ range) for body mass was 80.6 (8.0) kg. Disease severity (or impact on daily life) varied across the cohort. Participants 1 and 6 had hepatomegaly. Seven participants also had splenomegaly, without imaging evidence of portal hypertension. Ejection fraction (transthoracic echocardiogram) was normal in all patients (range 57–76%). Left ventricle maximum wall thickness (LV MWT) > 1.1 cm, found in two patients, was considered indicative of left ventricular hypertrophy **(Table 3.1)**. All participants had elevated resting creatine kinase (CK) activity. Three individuals did not take any medication, whilst four took one or more of the following: Allopurinol, Vitamin D, Bisphosphonate **(Table 3.1)**. A formal diet diary was not completed as part of this study. Participants were advised to continue with their normal diet and no specific recommendations were made with regard to dietary intake immediately before testing. Whilst our general clinical recommendation is that individuals with GSD 3a consume a diet higher in protein, with a preference for complex carbohydrates rather than simple sugars (Kishnani et al. 2010; Sentner et al., 2016), in practice review of clinical records indicated that the participants' diets did not all follow this approach**.** Five participants consumed a higher protein diet, three with the addition of protein supplementation (these three participants were aiming to consume 2

g/kg/day protein). Two participants included regular additional uncooked cornstarch (UCCS) in their diet (both took 50 g UCCS before bed).

3.3.1 Cardio-respiratory

Peak oxygen uptake ($\dot{V}O_{2peak}$) was lower in participants than predicted based on their demographic data (17.0 (9.0) ml/kg/min, 53 (24)% of predicted, $p = 0.001$), as was peak work rate (Median: 54 (IQ range: 118)) watts, 30 (38)% predicted, $p = 0.018$), and peak heart rate (143 (28) bpm, 78 (13)% predicted $p = 0.005$) **(Table 3.2).** Peak minute ventilation ($\dot{V}E$) was 37 (20) L/min equivalent to 22 (8)% of predicted maximum voluntary ventilation. Anaerobic threshold (AT) was only identifiable in 2 participants. These were 15 and 16 ml/kg/min for participants 1 and 2, respectively. The AT could not be determined in the other participants due to not being reached (participants 4, 5, 6 and 7) and atypical expiratory gas exchanges patterns prohibiting AT determination (participant 3).

Table 3.1 Participant Characteristics of the GSD 3a patients, ordered by $\dot{V}O_{2peak}$

	Patient Demographics				Clinical Characteristics				Dietary Information and Medications			
Participant	**Gender**	**Age (yrs)**	**Height (cm)**	**Body Mass (kg)**	**Cardiac hypertrophy (Y/N)**	**Hepatomegaly (Y/N)**	**Creatine kinase (RR: 26-140 IU/L)**	**Triglycerides (mmol/L)**	**Higher protein diet**	**Protein supplement**	**UCCS**	**Medication**
1	M	27	181.0	81.4	Y	Y	6592	1.2	Y	N	Y	A.
2	F	28	173.1	73.3	N	Y	641	1.1	N	N	N	None.
3	M	26	193.2	80.6	N	Y	3842	1.6	Y	Y	N	A, D.
4	M	48	180.3	69.5	N	Y	1756	2.2	Y	Y (Int)	N	B, D.
5	F	50	173.9	81.1	N	Y	1266	1.4	Y	N	N	None.
6	F	45	162.3	78.9	Y	N	2442	1.1	N	N	N	None.
7	M	32	188.0	112	N	Y	2682	1.5	Y	Y	Y	D.
Mean (SD)	-	37 (11)	179 (10)		-	-	2746 (1987)	1.4 (0.4)	-	-	-	-
Median (IQ range)	-			80.6 (8.0)	-	-		-	-	-	-	-

Int, Intermittent; Cardiac hypertrophy: Y6, Maximal wall thickness 14 mm (asymmetric septal), Y5, Maximal wall thickness 13 mm (basal septal); UCCS: uncooked cornstarch: Y, 50g nightly; A, Allopurinol; D, Vitamin D; B, Bisphosphonate

Table 3.2 Cardio-respiratory properties, ordered by $\dot{V}O_{2peak}$

	Cardio-respiratory characteristics						PA characteristics (min/day)			
Participant	**$\dot{V}O_2$peak (ml/kg/min)**	**Ramp duration (min:sec)**	**Peak Work Rate (W)**	**Peak $\dot{V}$E (L/min)**	**Peak Heart Rate (BPM)**	**Peak RER**	**SB**	**LIPA**	**MPA**	**VPA**
1	27.1	10:40	159	53	179	0.97	410	313	227	0
2	25.9	09:49	146	56	169	0.99	650	170	129	11
3	25.7	10:16	153	63	163	0.91	637	200	124	0
4	15.0	03:39	54	27	130	0.88	669	218	73	0
5	9.4	05:36	41	16	139	0.81	448	459	53	0
6	8.7	03:43	35	21	121	0.93	640	163	157	0
7	7.0	02:32	25	22	102	0.85	678	228	34	0
Mean (SD)	17.0 (9.0)	06:36 (03:32)		37 (20)	143 (28)	0.91 (0.06)	590 (112)	250 (105)	114 (67)	1.6 (0)
Median (IQ range)			54 (118)				640 (221)			0 (0)

$\dot{V}O_2$, oxygen utilisation; $\dot{V}$E, minute ventilation; RER, respiratory exchange ratio; PA, physical activity; SB, sedentary behaviour; LIPA, Light-intensity physical activity; MPA, moderate-intensity physical activity; HPA, High-intensity physical activity

3.3.2 Muscle strength and size

Absolute MVC was markedly lower in participants than predicted (p = 0.045) **(Table 3.3)**. A noticeable difference was also present between MVC relative to body mass and age matched predicted values; however, no significant differences were observed (p = 0.176). Rate of torque development (RTD) could only be determined in 5 individuals and the median (IQ range) was 328 (767) Nm s. Mean muscle volume, PCSA and muscle quality were 516 (240) cm3, 77 (40) cm2, and 1.60 (0.70) Nm cm2, respectively **(Table 3.3)**.

3.3.3 Associations between cardio-respiratory fitness, muscle strength, and muscle characteristics

There was a strong association between aerobic capacity and maximal leg strength. Pearson's correlations identified a significant positive association between $\dot{V}O_{2peak}$ and absolute MVC (r = 0.920; p = 0.003). Spearman's correlations revealed no association between $\dot{V}O_{2peak}$ and MVC relative to body mass (r = 0.679; p = 0.094), or between $\dot{V}O_{2peak}$ and RTD (r = 0.700; p = 0.188). Aerobic capacity was also associated with muscle structural characteristics. Pearson's correlations identified significant positive associations between $\dot{V}O_{2peak}$ and Vastus Lateralis (VL) muscle volume (r = 0.771; p = 0.043), PCSA (r = 0.819; p = 0.024), and muscle quality (r = 0.884; p = 0.008). Pearson correlations revealed VL muscle volume (r = 0.943; p = 0.001), PCSA (r = 0.957; p = 0.001) and muscle quality (r = 0.863; p = 0.012) were all positively correlated with knee extension MVC.

3.3.4 Physical activity, QoL and pain

Participants' physical activity (PA) levels are reported in **Table 3.2**. Analysis revealed that only two (participants 1 and 5) were classified as ambulatory (< 8 h (480 min) of sedentary behaviour) and the remaining as sedentary. Light-intensity physical activity (LIPA) and moderate-intensity physical activity (MPA) accounted for the majority of movement, 60% and

28%, respectively. High-intensity physical activity (HPA) was not achieved by six of the seven participants, and the remaining participant recorded an average of 11 min of HPA per day.

Self-reported health status results taken from the SF-36 are reported in **Table 3.4**. All physical and emotional outcomes were lower in participants than would be expected for their age and gender (Jenkinson et al., 1993). Mental health variables were less affected, with emotional wellbeing and role limitations due to emotional problems with median values of 100% and 65% of their predicted values, respectively. In contrast, variables related to physical health were much lower than predicted (median physical functioning, 41% predicted; role limitations due to physical health, 0% predicted; energy/fatigue, 29% predicted).

Current pain intensity at baseline (taken pre-exercise) was 1.6 (1.8) and did not alter when assessed the day after the exercise trials (1.6 (1.6), $p = 1.000$). Maximum pain endured over the past 24 h was also no different the day following exercise when compared to baseline, 2.9 ± 2.1 and 3.0 ± 2.8 ($p = 0.846$), respectively.

In comparison to predicted normative values, participants had substantially lower aerobic fitness ($\dot{V}O_{2peak}$) and muscle strength (MVC). However, within the group, substantial inter-individual variation was present across these variables, such that two separate groups of patients emerged. A higher physical capacity group, comprised of participants 1, 2, 3, that maintained normal maximal leg strength (MVC: 101% of predicted) and relatively high aerobic capacity ($\dot{V}O_{2peak}$: 73% of predicted), and a lower physical capacity group, comprised of participants 4, 5, 6, 7 who achieved 24% and 38% of their predicted values for MVC and $\dot{V}O_{2peak}$, respectively. The subgroup with greater physical capacities had greater muscle volume (737 vs. 352cm^3), PCSA (115 vs. 48cm^2) and muscle quality (2.38 vs. 1.18 $Nm \cdot cm^2$). They were younger (27 ± 1 yrs) than those with less strength (44 ± 8 yrs), tended to self-report higher

physical functioning **(Table 3.4)** and spent more time undertaking moderate to vigorous physical activity (MVPA) **(Table 3.2)**.

Table 3.3 Descriptive skeletal muscle structural and functional characteristics, ordered by $\dot{V}O_2$peak

	Functional characteristics							Structural characteristics		
Participant	**MVC (Nm)**	**Predicted MVC (Nm)**	**Percentage achieved (%)**	**MVC/BM (Nm/kg)**	**Predicted MVC/BM (Nm/kg)**	**Percentage achieved (%)**	**ROTD 0-200ms (Nm·s)**	**Vastus Lateralis Muscle Volume (cm^3)**	**Vastus Lateralis PCSA (cm^2)**	**Muscle Quality ($Nm \cdot cm^2$)**
1	267	281	95	3.28	2.67	123	975	726	126	2.13
2	225	210	107	3.07	2.87	107	-	544	81	2.77
3	309	302	102	3.83	3.75	102	965	940	139	2.23
4	47	226	21	0.68	3.25	21	214	273	36	1.32
5	56	198	28	0.64	2.44	26	-	323	48	1.17
6	43	174	25	0.54	2.21	24	192	393	54	0.79
7	77	339	23	0.69	3.03	23	328	419	54	1.44
Mean (SD)	146 (116)	247 (61)	57 (42)		2.89 (0.52)	61 (47)		516 (240)	77 (40)	1.60 (0.70)
Median (IQ range)			28 (80)	1.82 (2.64)		26 (84)	328 (767)			

MVC, maximum voluntary contraction; BM, body mass; ROTD, Rate of Torque Development; PCSA, physiological cross-sectional area

Table 3.4 Self-reported health-related QoL, ordered by $\dot{V}O_2$peak

Participant	Physical functioning	Role limitations due to		Energy/fatigue	Emotional well-being	Social functioning	Pain	General health
		Physical health	Emotional problems					
1	70	75	100	35	92	100	77.5	50
2	70	0	100	45	48	75	22.5	45
3	90	0	0	-	-	-	45	30
4	10	0	100	25	68	50	90	35
5	0	0	33	5	56	12.5	10	10
6	35	50	100	60	88	62.5	90	35
7	10	0	0	5	40	12.5	32.5	10
Mean (SD)	41 (36)			29 (22)	65 (21)	52 (35)	53 (33)	31 (16)
Median (IQ range)		0 (50)	100 (100)					

3.4 Discussion

This study demonstrates that $\dot{V}O_{2peak}$ and knee extension strength are lower in individuals with GSD 3a than predicted based on their demographic data. Muscle size and quality were positively associated with both $\dot{V}O_{2peak}$ and MVC, implicating muscle atrophy and neuromuscular impairment for the functional decline observed in this cohort. Interestingly, a high physical capacity group emerged that had normal leg strength (MVC) and relatively high $\dot{V}O_{2peak}$, and a low physical capacity that display impaired strength and substantially lower $\dot{V}O_{2peak}$. The higher physical capacity sub-group were younger, had superior muscle size and quality, and tended to undertake more PA and report higher health-related QoL. This study demonstrates that $\dot{V}O_{2peak}$ and isometric maximal strength measurements can be undertaken safely in this population and provides normative values of these important markers of physical capacity.

$\dot{V}O_{2peak}$ in this cohort was 17.0 (9.0) ml/kg/min, which is somewhat lower than previously reported in six patients with GSD 3a (25.4 ± 5.1 mL/kg/min) (Preisler et al., 2013). The difference between studies is removed when patients are compared to control/normative values, with the current sample achieving 54% of predicted based on the demographic information and the sample collected by Preisler et al. (2013) achieving 55% that of their matched control. This indicates that the difference in $\dot{V}O_{2peak}$ between studies is likely due to the current study recruiting older individuals (37 (11) vs 27 (8) years) with higher disease severity. The deficit in $\dot{V}O_{2peak}$ was different amongst the group, with participants achieving between 22 and 91% of their predicted value. Hoogeveen et al. (2021) also identified a large range in $\dot{V}O_{2peak}$ but with values generally higher than the current study (range: 46–105% of predicted). A key factor explaining this variation in the current study appears to be age/disease progression, with those achieving a higher $\dot{V}O_{2peak}$ tending to be younger. However, in contrast, Hoogeveen et al. (2021) found older participants had the highest $\dot{V}O_{2peak}$ relative to predicted. This discrepancy could

be attributable to differences in the genetic and environmental characteristics of the two samples.

The cause of lower $\dot{V}O_{2peak}$ in GSD 3a will reflect the underlying pathophysiology of the disease, and these are likely different from those in healthy people. In healthy individuals, the attainment of $\dot{V}O_{2peak}$ is typically attributed to cardiovascular limitation (Bassett & Howley., 2000) with heart rate reaching maximal levels when exercise ceases. In the current study, no participants with GSD 3a reached their predicted maximum heart rate, indicating that factors other than cardiovascular limitations were responsible for exercise cessation. Furthermore, the associations between $\dot{V}O_{2peak}$, MVC and muscle size provides evidence of the role muscle weakness has on limiting aerobic capacity, whilst the low peak respiratory exchange ratio (RER) supports previous studies demonstrating impaired skeletal muscle glycogenosis impedes exercise performance (Preisler et al. 2013; Preisler et al., 2015).

The sensitivity of $\dot{V}O_{2peak}$ to impairments in cardiovascular, respiratory, metabolic and neuromuscular function make it an ideal tool for the assessment of physical function in diseases with complex pathology, such as GSD 3a. In other forms of GSD, CPET has been successfully used to assess the effectiveness of various therapeutic interventions, with improvements in $\dot{V}O_{2peak}$ noted following ERT in GSD 2 (Marzorati et al., 2012) and exercise training in GSDs 2 and 5 (Ørngreen & Vissing., 2017). Now that new therapies are in development for GSD 3a (Clinical Trial database., 2021; Kishnani, Sun & Koeberl., 2019) and exercise training is increasingly recognised as an adjunct therapy (Kishnani et al., 2010), future studies should consider measuring $\dot{V}O_{2peak}$ to evaluate the efficacy of these interventions. Overall, study participants achieved 57% of their predicted MVC. However, results indicate that 3 of the study participants (participants 1–3) would be classed as having a normal maximal strength capacity compared with their predicted age and sex matched counterparts (101% of predicted) (Harbo et al., 2012), whilst 4 people (participants 5–8) had impaired knee extensor strength (24% of

predicted). This phenotypic variation in leg strength was also noted by Decoste et al. (2016), whose patients' strength ranged from approximately 5 to 80% of predicted. In the current study, those with higher strength tended to be younger (27 ± 1 years) than those with less strength (44 ± 8 years) indicating disease progression is a primary cause. These findings of a reduction in strength with age would be consistent with the cross-sectional study by Decostre et al. (2016) which noted a drop in muscle function around the 3rd decade of life at a rate of 0.7% per year. Knee extensor strength is an important health marker as it contributes to habitual functional activities such as gait speed (Bohm et al., 2018), rising from a chair (Crockett et al., 2013) and stair negotiation (Fukagawa et al., 1995). As such, individuals with GSD 3a may benefit from interventions designed to increase/maintain leg strength, such as resistance training, which have been successful with other low strength cohorts such as in adults with GSD 2 (van den Berg et al., 2015) and limb-girdle, Becker, and facioscapulohumeral dystrophies (Bostock et al., 2019).

This is the first study to examine the link between muscle size and MVC capacity in individuals with GSD 3a and interestingly both variables were shown to positively correlate with each other, in line with previous literature that isometric MVC is proportional to the PCSA (Arnold et al., 2010). This suggests that smaller muscle size is partially responsible for the lower maximal strength alongside potential neuromuscular deficiencies in agonist activation noted during healthy ageing (Tomlinson et al., 2014a) and neuropathy previously observed in GSD 3a (Hobson-Webb et al., 2010), however these hypotheses need to be confirmed in future longitudinal investigations.

Muscle quality (MQ) is the ability to produce force relative to contractile tissue mass/volume and is a key determinant of physical function and mobility in later life (McGregor et al., 2014). Interestingly, muscle quality was lower in participants when compared against age and sex matched normative data (Sims et al., 2018). These findings support a decrease in the intrinsic

fibre properties especially as individuals with GSD 3a age, and this explanation is additionally supported by a greater decrement in RTD. Potential mechanisms to explain this decrement include neuromuscular and myopathic manifestations in skeletal muscle which become exacerbated with age (Hobson-Webb et al., 2010) . The functional consequence for a reduction in muscle quality could lead to functional impairment (Lees et al., 2019), gait variability (Shin et al., 2012) and fall risk (Gadelha et al., 2018).

The participants with GSD 3a had low PA levels with the majority of the study sample classed as sedentary (> 8 h of SB) (Ekelund et al., 2019; Matthews et al., 2012). Self-reported health status of our cohort was also lower than the general population (Jenkinson et al., 1993). The GSD 3a group with higher physical capacity, those with normal leg strength and relatively high aerobic capacity, undertook noticeably more MVPA (164 (55) min/day) than those with lower physical capacity (79 (54) min/day). They also tended to self-report higher levels of physical health, though levels still tended to be lower than age and sex matched normative values. These results indicate that individuals with GSD 3a with high physical capacity undertake more PA and enjoy better health, or conversely, it indicates that high PA and better health status led to greater physical capacity in these patients. Using the current cross-sectional study design, it is impossible to know the direction of this association, though both these scenarios are likely true to some extent. Longitudinal assessment of changes in movement behaviour, physical capacity and health will help us more clearly understand the interplay between these important behaviours and health outcomes, whilst also informing potential exercise interventions.

3.4.1 Implications

Expert guidelines highlight the need for regular assessments of strength and aerobic capacity in individuals with GSD 3a to monitor status and guide exercise training (Kishnani et al., 2010). However, to fully interpret any exercise results, clinicians require normative data in the populations of interest. This study shows that aerobic capacity and maximal strength are

plausible outcome markers of physical function in GSD 3a and may be useful given exercise intolerance is a major complication associated with the disease.

3.4.2 Strengths and limitations

The current study employed a relatively small sample size (n=7) which reflects the rare nature of the disease and the difficulties this creates for recruitment. Small sample sizes limit the utility of data for the provision of normative physical capacity values in rare disorders. To combat this, our tests were conducted using standard techniques and equipment that are available in many hospitals and universities, and we presented the results at an individual level. Our hope is that future studies will use similar testing techniques to those used here and combine our data with theirs to create a larger, more representative, data set.

A strength of the current study is that we were able to demonstrate that assessment of aerobic capacity and leg strength was achievable in individuals with GSD 3a. However, our first participant reported suffering from leg pain and contractures following the test, which resulted in an elevation in CK concentration that resolved after 1 week. The patient felt that these symptoms were brought on by the strength tests, which at the time consisted of three knee extension isometric contractions at 70°, 80° and 90°, and two isokinetic knee extension and flexion at 60°/sec and 120°/sec (both concentric contractions) with 90–120 s rest between contractions. Muscle pain was noted following isokinetic contractions in the participant and may have implications for developing future training protocols (low %1RM and low volume). However, in response to this incident we extended the rest time between contractions to 5–10 min and excluded isokinetic contractions from the trial and no further patient reported any adverse side effects.

The current study compared the physiological responses of participants with GSD 3a with predicted values, rather than using a control group. Though comparing patients' results to

normative data is not optimal, selecting appropriate controls to compare with this small sample of individuals with GSD 3a would have been problematic and open to selection bias. We concluded that the benefit of comparing our results with data collected on hundreds of healthy controls and being able to adjust for age, height, weight and sex warranted the comparison to normative values in our study.

The measurement of $\dot{V}O_{2peak}$ is effort dependent so it is difficult to know with certainty if the values we obtained actually represent the participants' aerobic capacity. To verify $\dot{V}O_{2peak}$, the participant can perform a second, constant work rate test at a severe intensity to determine if an equivalent $\dot{V}O_2$ is achieved (Poole & Jones., 2017). We did not employ this additional severe-intensity phase as we believed it may encourage muscle damage and contractures in our cohort. However, we believe our cohort was highly motivated to exercise and that the measure of $\dot{V}O_{2peak}$ is reflective of their exercise capacity.

Finally, activity monitoring was performed in the week following the exercise trials. It is possible that completing the exercise tests had residual fatiguing effects and lead us to underestimate PA. Future studies should avoid this oversight by monitoring PA at a different time or by allowing a recovery period prior to starting PA monitoring.

3.5 Conclusion

$\dot{V}O_{2peak}$ and MVC are lower in individuals with GSD 3a than would be expected. The data is intended to provide some normative reference data of cardiovascular fitness and muscular strength outcomes in GSD 3a. The mechanisms responsible for the impairment in $\dot{V}O_{2peak}$ in GSD 3a are yet to be fully determined, but the associations between $\dot{V}O_{2peak}$, MVC, muscle size and quality highlight the role of muscle weakness. The deficit in physical capacity was highly variable in the cohort and though older age accounts for some of the decline more

research is needed to understand the impact of lifestyle/ treatment choices, such as diet and PA on exercise capacity.

Chapter 4 - Longitudinal Assessment of the Impact of Glycogen Storage Disease 3a on Load Bearing Skeletal Muscle Structural and Functional Characteristics: A Case Series

4.1 Links to previous chapters

Findings from **Chapter 3** revealed a marked reduction in aerobic capacity and strength in individuals with GSD 3a compared to predicted values. However, these findings showed significant variability between participants. Due to the cross-sectional design of the study, the underlying mechanisms and associated factors could not be fully explored. **Chapter 4**, therefore, adopts a longitudinal approach, aiming to investigate the natural progression of GSD 3a over several years in order to gain a deeper understanding of the impact of lifestyle factors, including diet and physical activity, on exercise capacity.

4.2 Introduction

Glycogen storage disease 3a is a rare autosomal recessive metabolic disorder, caused by pathogenic variants in the *AGL* gene, located on chromosome 1p21.2 (Bao, Dawson & Chen, 1996). This causes a deficiency in the glycogen debrancher enzyme (GDE), which impairs glycogenolysis and leads to excessive glycogen accumulation. The debranching enzyme is a single polypeptide containing two catalytic sites: amylo-1,6-glucosidase (EC 3.2.1.33) and 4-alpha-glucanotransferase (EC 2.4.1.25), in which over 110 disease-causing variants have been identified, resulting in significant genetic heterogeneity (Ko et al., 2014). The liver, skeletal muscle and the heart are primarily affected, resulting in hypoglycaemia, hepatomegaly and (cardio)myopathy (Kiechl et al., 1999; Lucchiari et al., 2007). Myopathy is the main presentation in adulthood, particularly around the third and fourth decade (Coleman, et al.,

1992) with progressive muscle weakness, muscle wasting and exercise intolerance (Berling et al., 2021; Hicks et al., 2011; Kiechl et al., 1999).

Despite progressive muscle weakness being well established in GSD 3a, the majority of data supporting this contention is from a limited number of cross-sectional studies (Decostre et al., 2016; Hennis et al., 2022; Hobson-Webb et al., 2010; Verbeek et al., 2016), with Decostre et al. (2016) detailing a 0.7% reduction in muscle strength per year around the third decade of life. Due to the rarity of the disease and difficulties collecting data (validity of maximal strength measures), longitudinal studies are extremely rare. Where available, preliminary longitudinal data suggests a progression in the decline in muscle strength and motor function with advancing age (Decostre et al., 2017). However, longitudinal studies detailing the progression of myopathy with the quantification of muscle strength remain scarce, in which potential mechanisms such as muscle size and architecture underpinning muscular impairments have not been previously investigated. The structural characterisitics of distal muscle including pennation angle, fascicle length and cross-sectional area (CSA) to calculate gold standard measures of muscle size, such as physiological cross-sectional area (Stokes et al., 2020) are necessary to aid the interpretation of muscular strength outcomes, particularly given their association with functional and mobility limitations (Rantanen, Era & Heikkinen, 1994; Vieira et al., 2013). In reference to other populations, skeletal muscle size and architecture, along with physical activity and sedentary behaviour are strongly associated with exercise capacity and muscle strength (Aagaard et al., 2001; Chastrin et al., 2012; Hughes et al., 2001; McLeod et al., 2016; Tomlinson et al., 2018). However, longitudinal associations in GSD 3a have yet to be explored and given the known progressive muscle weakness in adulthood (Di mauro et al., 1979; Keichl et al., 1999), examining changes in maximal strength, and associated changes in muscle architecture of the knee extensors are of upmost importance; particularly given their

weight-bearing role and contribution towards functional activities including gait speed and sit-to-standing (Bohm et al., 2018; Crockett et al., 2013).

In this case series, we present longitudinal data on skeletal muscle structural and functional characteristics in three individuals with GSD 3a, aiming to investigate potential mechanisms underpinning impairments in muscle strength, measures of physical function, and consequently QoL. Identifying the mechanisms underlying these impairments may guide the optimal design of interventions aimed at limiting the rapid decline in muscle function, thereby preserving functional capacity and QoL in individuals with GSD 3a.

4.3 Materials and Methods

4.3.1 Participants

This case series includes the follow-up of three adults with GSD 3a, who had previously been assessed 4-7 years ago in **Chapter 3**. Two of the participants walked independently, one required the use of a walking aid. The study followed the Declaration of Helsinki and was approved by the South-East Scotland Research Ethics Committee 01 (22/SS/0069) **(Appendix D, Appendix E; Appendix F).**

4.3.2 Protocols

All exercise tests were conducted in an exercise physiology laboratory in the presence of a medical doctor and an exercise physiologist as previously detailed (**Chapter 3**). Assessments included anthropometry, the structural characteristics of the vastus lateralis using B-mode ultrasonography (Siemens Acuson p500, Siemens Healthcare Ltd, Surrey, UK), CPET, Knee-extensor maximum voluntary contractions using an isokinetic dynamometer (Cybex Humac Norm, Cranlea, Birmingham, UK), physical activity monitoring (GENEActiv, Activinsights Ltd., Cambridgeshire, UK) processed using the GGIR package (R package version 1.6-0, URL: https://cran.r-project.org/web/packages/GGIR/index.html; Migueles et al. 2019) in R (R

package version 3.1.2, URL: https://cran.r-project.org) using previously defined cut off points (Esliger et al., 2011) and the assessment of QoL (Ware & Sherbourne, 1992) and pain (McCaffery & Beebe, 1989). Furthermore, this study included additional measures to those previously assessed (**Chapter 3**). Nutritional intake was assessed using a 7-day diet diary (7dDD) and analysed using Nutritics (Nutritics Professional Diet Analysis version 3.06, Nutritics Ltd., Ireland). Muscle activation of the vastus lateralis and co-contraction of the biceps femoris was assessed during knee extension and flexion respectively using surface electromyography (sEMG) (Biopac Acknowledge 5.0, Goleta, USA). Prior to electrode placement, the skin was shaved, lightly abrased and cleaned with alcohol wipes to help reduce skin impedance. An electrode was then placed at the location of 50% of VL muscle length and another at the distal third of the lateral hamstring. A common reference electrode was also secured over the patella. All sEMG signals were collected and analysed through data acquisition software (Biopac Acknowledge 5.0, Goleta, USA). Moreover, bone mineral density and body composition was assessed via dual energy X-ray absorptiometry (DEXA) (Lunar enCORE iDXA, GE Healthcare, UK). DEXA is recognised as the gold standard for bone mineral density and body composition analysis, validated against anatomical imaging (CT/MRI), chemical analysis and dissection. (Clarys et al., 2010; Kim et al., 2002; Scafoglieri et al., 2013). The numeric pain rating scale (McCaffery & Beebe, 1989) was conducted on days 1, 3 and 7 to establish if participants had any adverse reactions following the exercise tests.

4.4 Case series description

We report the longitudinal changes in skeletal muscle structural and functional characteristics in 3 individuals with GSD 3a. Demographic, clinical and dietary information are summarised in **Table 4.1**. The structural and functional characteristics of skeletal muscle are presented in **Table 4.2** and **Table 4.3**.

4.4.1 Participant #1

Initial investigation: This Caucasian 48-year-old male had a BMI of 21.4 kg/m^2, with lean mass of 52.7 kg and 20.9% body fat. Clinically he had hepatomegaly and substantially elevated resting creatine kinase (1756 IU/L) and was advised a high protein diet with an intermittent protein supplement **(Table 4.1)**. Physically, he was classified as sedentary (>8h sedentary behaviour: 669 mins/day) with low amounts of light (218 min/day) and moderate activity (73 min/day). No vigorous activity was achieved **(Table 4.4)**. Muscle structural characteristics detailed a fascicle length of 7.63cm, pennation angle of 16.91°, muscle volume of 273 cm^3 and physiological cross-sectional area (PCSA) of 36cm^2 **(Table 4.2)**. Functionally he only achieved 21% predicted muscle strength and 21 % predicted muscle strength relative to body mass, with a rate of torque development of 214 Nm.s and muscle quality of 1.32 Nm.cm^2 **(Table 4.3)**. Furthermore, he only achieved a peak oxygen uptake ($\dot{V}O_{2peak}$) of 46% predicted, with a peak work rate of 25% predicted **(Table 4.4)**. Self-reported QoL scores were particularly low for the domains related to physical functioning, physical health, energy and fatigue and overall general health. In contrast, emotional problems and emotional wellbeing scores were much higher **(Table 4.5)**.

Follow up: The participant's BMI had reduced to 19.8 kg/m^2, with an 18% reduction in lean mass. However, in contrast, his body fat percentage increased by 10%, remaining high at 30.6%. Clinically, although creatine kinase levels decreased to 1232 IU/L, they remained elevated, and hepatomegaly persisted. He had changed to a ketogenic diet over the last 3 years, in which dietary analysis detailed an intake of 1705 kcals per day, comprising of 8% carbohydrate, 23% protein and 66% fat **(Table 4.1)**. Physically, his mobility had further deteriorated and he could now only mobilise short distances with the use of a walking stick. Accelerometery data showed he was still classified as sedentary (>8h sedentary behaviour), in which his sedentary behaviour had further increased (+78 min/day). Moreover, there were reductions in light (-118 min/day)

and moderate (-7min/day) intensity exercise **(Table 4.4)**. Assessment of skeletal muscle architecture revealed a 38% reduction in fascicle length and 3% increase in pennation angle. Furthermore, assessment of skeletal muscle structure showed marked reductions in muscle volume (52%) and muscle PCSA (23%) **(Table 4.2)**. Functional assessment subsequently demonstrated a substantial decline in maximal strength (49%) and maximal strength relative to body mass (45%), which equated to achieving 11% of predicted values and a 7% decline in muscle strength per year. Similar reductions were found in the rate of torque development (47%) **(Table 4.3)**. Furthermore, there was a 34% reduction in muscle quality and sEMG found simultaneous contraction of the vastus lateralis and bicep femoris, with 14% coactivation (Comparable to healthy controls:11.8 [6.2] % and others with neurological impairment and weakness: 7-17%; Busse et al., 2006). These muscular impairments lead to associated reductions in peak work rate (-30w) during the cycling exercise test, achieving only 11% of predicted and a $\dot{V}O_{2peak}$ which remained at 46% of predicted values **(Table 4.4)**. Despite slight changes, self-reported health-related QoL scores remained particularly low for the domains related to physical functioning, physical health, energy/fatigue and general health **(Table 4.5)**.

4.4.2 Participant #2

Initial investigation: On initial investigation this 27-year-old Caucasian male had a BMI of 24.9kg/m^2. Clinically he had hepatomegaly, substantially elevated resting creatine kinase (6592 IU/L) and was advised a high protein diet **(Table 4.1)**. Physically, he was classified as ambulatory (<8h sedentary behaviour) with accelerometery data recording 410 min/day of sedentary behaviour. All activity was either light activity (313 min/day) or moderate activity (227 min/day) with no vigorous activity recorded **(Table 4.4)**. Muscle structural characteristics detailed a fascicle length of 5.78cm, pennation angle of 22.12°, muscle volume of 726cm^3 and PCSA of 126cm^2 **(Table 4.2)**. His muscle strength was normal predicted values (95% of predicted muscle strength and 123% of predicted muscle strength relative to body mass) with

a rate of torque development of 975Nm.s and muscle quality of 2.13Nm.cm^2 **(Table 4.3)**. However, his cardio-respiratory fitness was lower than predicted, in which he achieved a $\dot{V}O_{2peak}$ of 67% predicted, with a peak work rate of 63% predicted and minute ventilation of 29% predicted **(Table 4.4)**. Self-reported QoL scores were lower for the domains relating to physical health and energy/fatigue compared to emotional and social functioning domains **(Table 4.5)**.

Follow up: The participant's BMI had reduced to 23.6 kg/m^2, with 44.59 kg of lean mass and 26.9% body fat. Clinically hepatomegaly was still present and despite a reduction, creatine kinase remained elevated (4226 IU/L). He continued to be advised a high protein diet, with the addition of a daily protein shake (15-25g protein) and dietary analysis showed a daily intake of 1938 kcals, comprising of 20% protein, 43% carbohydrate and 37% fat **(Table 4.1)**. He was employed full-time as a tradesman and his physical activity data detailed a marked reduction in sedentary behaviour following previous assessment (-125 min/day). Furthermore, there were reductions in light intensity exercise (-80 min/day) and moderate intensity activity (-132min/day) but a slight increase in vigorous activity (+5 min/day) **(Table 4.4)**. Architectural changes detailed minimal changes in fascicle length (1%) and a 19% reduction in pennation angle with structural changes including a reduction in muscle volume (13%) and PCSA (14%) **(Table 4.2)**. Functionally, muscle dynamometry demonstrated marked reductions in maximal strength (21%) and maximal strength relative to body mass (14%), which equated to achieving 81% of predicted values and a 4.85% decline per year in muscle strength. Furthermore, there was a reduction of 28% in RTD and a 9% decrease in muscle quality **(Table 4.3)**. Surface EMG found simultaneous contraction of the vastus lateralis and bicep femoris with 8% coactivation (Comparable to healthy controls:11.8 [6.2] % and others with neurological impairment and weakness: 7-17%; Busse et al., 2006). On assessment, he did reveal that he had started to limp on the left side and that there had been initial conversations with his medical team regarding

the transition to a sedentary desk-based job in the future. The muscular changes observed, lead to further reductions in peak work rate (-26 watts), achieving 56% of predicted and a 4.3 ml/kg/min reduction in $\dot{V}O_{2peak}$, with the present value of 22.8 ml/kg/min being 58% of predicted **(Table 4.4)**. Self-reported health-related QoL scores highlighted reductions in physical functioning, particularly limitations due to physical health, as well as emotional well-being and social functioning. Whereas there were slight improvements in energy/fatigue and pain compared to previous assessment **(Table 4.5)**.

4.4.3 Participant #3

Initial investigation: This Caucasian 26-year-old male had a BMI of 21.6 kg/m^2, with a lean mass of 66.8kg and 13.2% body fat. Clinically he had hepatomegaly and substantially elevated resting creatine kinase (3842 IU/L) and was advised a high protein diet with a protein supplement **(Table 4.1)**. Physically, he was classified as sedentary (637 min/day). Physical activity data showed low amounts of light activity (200 min/day) and moderate activity (124 min/day), with no vigorous activity achieved **(Table 4.4)**. Muscle structural characteristics detailed a fascicle length of 6.78cm, pennation angle of 12.99°, muscle volume of 940cm^3 and PCSA of 139cm^2 **(Table 4.2)**. Functionally he had normal maximal leg strength (achieving 102% of predicted muscle strength and 102% of predicted muscle strength relative to body mass) with a rate of torque development of 965 Nm.s and muscle quality of 2.23Nm.cm^2 **(Table 4.3)**. However, his cardiorespiratory fitness was lower than predicted, in which his $\dot{V}O_{2peak}$ was reduced (63% predicted), along with peak work rate (52% predicted) and minute ventilation (27% predicted) **(Table 4.4)**. Self-reported QoL scores were particularly low for the domains related to role limitations due to physical health and emotional problems, energy/fatigue, social functioning and general health. Whereas physical functioning in particular, along with emotional wellbeing and pain were less affected **(Table 4.5)**.

Follow up: Despite the participant's BMI remaining stable, there were however notable changes in his body composition, with a 15% reduction in lean mass and 12% increase in body fat. Clinically hepatomegaly was still present and despite a marked reduction in creatine kinase, this remained high (864 IU/L). He remained on a high protein diet with an intermittent protein shake (40-50g protein), in which dietary analyses showed an intake of 2666 kcals/day, comprising of 22% carbohydrate, 31% protein and 47% fat **(Table 4.1)**. On arrival he reported that had been suffering from knee pain in which his medical team had suggested was due to increased progression of the disease. Physical activity data showed he was still classified as sedentary, with a marked increase in sedentary behaviour (+105 mins/day). Furthermore, there was a reduction in light activity (-102 mins/day) and moderate activity (-57 min/day) compared to previous assessment, with no vigorous activity achieved **(Table 4.4)**. Assessment of skeletal muscle showed minimal architectural changes, with a 7% increase in fascicle length and 1% reduction in pennation angle. In contrast there were notable structural reductions in muscle volume (42%) and PCSA (46%) **(Table 4.2)**. Due to increased knee pain, he was unable to undertake the maximal exercise tests thus we were unable to quantify changes in muscle function and cardio-respiratory fitness. Self-reported health-related QoL scores detailed a marked reduction in physical functioning in comparison to previous assessment with a smaller reduction in general health and an increase in pain **(Table 4.5)**.

Table 4.1 Participant characteristics (*n*=3)

	Participant Demographics						Clinical Characteristics			Dietary Information & Medication						
										Dietary Intake			Diet type reported by participant	Protein supplement	UCCS	Medication
Participant	**Gender**	**Age (yrs)**	**Height (cm)**	**Body mass (Kg)**	**Body fat (%)**	**Lean mass (Kg)**	**Cardiac hypertrophy (Y/N)**	**Hepatomegaly (Y/N)**	**Creatine kinase (RR:26-140 IU/L)**	**EI (kcals)**	**Carbohydrate (% EI)**	**Protein (% EI)**	**Fat (% EI)**				
1	M	54	180.1	64.3	30.6	43.40	N	Y	1232	1705	8.0	22.5	66.4	Ketogenic	N	N	Al, C
2	M	31	177.6	74.4	26.9	44.59	N	Y	4226	1938	42.7	20.1	37.2	High protein	Y	N	A, M
3	M	33	191.6	78.2	25.5	56.57	N	Y	864	2666	22.2	30.7	47.1	High protein	Y (Int)	Y	Al, A, P

Yrs, Years; EI, Energy Intake; Int, Intermittent; UCCs, Uncooked cornstarch; Al, Alendronic acid; C, Cholecalciferol; Al, Allopurinal; M, Multivitamins with minerals, gingko biloba + ginseng; P, Phlexyvits.

Table 4.2 Skeletal muscle structural characteristics (*n*=3)

Participant	Structural Characteristics																	
	Pre Fascicle Length (cm)	**Present Fascicle Length (cm)**	**Δ**	**Change (%)**	**Pre Pennation Angle (°)**	**Present Pennation Angle (°)**	**Δ**	**Change (%)**	**Pre VL Muscle volume (cm^3)**	**Present VL Muscle volume (cm^3)**	**Δ**	**Change (%)**	**Change per year (%)**	**Pre VL PCSA (cm^2)**	**Present VL PCSA (cm^2)**	**Δ**	**Change (%)**	**Change per year (%)**
1	7.63	4.73	-2.90	-38.01	16.91	17.40	0.49	2.93	273	131	-143	-52.22	-8.70	36	28	-8	-22.92	-3.82
2	5.78	5.86	0.08	1.38	22.12	17.92	-4.20	-18.99	726	635	-91	-12.57	-2.90	126	108	-17	-13.77	-3.18
3	6.78	7.28	0.49	7.28	12.99	12.83	-0.16	-1.23	940	548	-392	-41.71	-5.96	139	75	-63	-45.67	-6.52

Table 4.3. Skeletal muscle functional characteristics (*n*=3)

Participant	Functional Characteristics																	
	Pre MVC (Nm)	**Present MVC (Nm)**	**Δ**	**Change (%)**	**Change per year (%)**	**Pre MVC/ BM (Nm/kg)**	**Present MVC/ BM (Nm/kg)**	**Δ**	**Change (%)**	**Change per year (%)**	**Pre RTD 0-200ms (Nm.s)**	**Present RTD 0-200ms (Nm.s)**	**Δ**	**Change (%)**	**Pre Muscle Quality ($NM.cm^2$)**	**Present Muscle Quality ($NM.cm^2$)**	**Δ**	**Change (%)**
1	47	24	-23	-49.26	-8.21	0.68	0.37	-0.31	-45.16	-7.53	214	114	-100	-46.87	1.32	0.87	-0.45	-34.17
2	267	210	-57	-21.28	-4.91	3.28	2.83	-0.46	-13.93	-3.22	975	704	-271	-27.78	2.13	1.94	-0.19	-8.75
3	309	-	-	-	-	3.83	-	-	-	-	965	-	-		2.23	-	-	-

Table 4.4. Cardio-respiratory properties and physical activity (*n*=3)

Participant	Cardio-respiratory characteristics											PA characteristics (min/day)								
	Pre $\dot{V}O_{2peak}$ (ml/kg/min)	Present $\dot{V}O_{2peak}$ (ml/kg/min)	Δ	$\dot{V}O_{2peak}$ (% of predicted)	Pre Peak WR (W)	Present Peak WR (W)	Δ	Peak WR (% of predicted)	Pre SB	Present SB	Δ	Pre LIPA	Present LIPA	Δ	Pre MPA	Present MPA	Δ	Pre VPA	Present VPA	Δ
1	15.0	14.2	-0.8	46	54	24	-30	11	669	747	+78	218	100	-118	73	66	-7	0	0	0
2	27.1	22.8	-4.3	58	159	133	-26	56	410	285	-125	313	233	-80	227	95	-132	0	5	+5
3	25.7	-	-	-	153	-	-	-	637	742	+105	200	98	-102	124	67	-57	0	0	0

Table 4.5. Self-reported health-related QoL (*n*=3)

Participant	Pre Physical Functioning	Present Physical Functioning	Pre Role limitations due to:		Current Role limitations due to:		Pre Energy/ fatigue	Present Energy/ fatigue	Pre Emotional well-being	Present Emotional wellbeing	Pre Social functioning	Present Social functioning	Pre Pain	Present pain	Pre General health	Present General Health
			Physical health	Emotional problems	Physical health	Emotional problems										
1	10	10	0	100	25	100	25	35	68	68	50	63	90	90	35	20
2	70	65	75	100	0	100	35	40	92	60	100	88	78	90	50	50
3	90	30	0	0	0	0	-	30	-	48	-	25	45	33	30	25

4.5 Discussion

This case series is the first to present the longitudinal decline in skeletal muscle structural and functional characteristics in adults with GSD 3a using gold standard measures of muscle strength, size and physical activity data. Consistent with previous cross-sectional data, this case series particularly highlights the progression of the disease after the age of 30, with a notable decline in muscle volume and muscle quality, accompanied by marked reductions in maximum knee extensor strength and rate of torque development. Furthermore, undesirable changes in body composition were observed, with increased body fat and reductions in lean mass. However, contrary to predictions derived from previous literature, the rate of decline in skeletal muscle structure and function does not appear to follow a linear trajectory. Instead, the decline appears progressive, with substantial heterogeneity, not only between those of different ages and disease stages, but also between those of similar ages. This variability underscores the complex and individualised progression of GSD 3a and the potential influence of lifestyle factors, such as physical activity on disease outcomes. Notably, among individuals of similar age, those with higher levels of physical activity and reduced sedentary behaviour demonstrated less of a reduction in muscle mass and strength, along with improved self-reported QoL related to physical health. This potentially highlights the importance of physical activity to preserve muscle mass and strength and mitigate reductions in QoL.

When comparing individuals of different ages and disease stages, notable differences in muscular strength were observed. On initial assessment, Participant 2, a 27-year-old, demonstrated near-normal maximal strength capacity compared to their predicted age- and sex-matched counterparts, achieving 95% of the predicted value (Harbo et al., 2012). As expected, this was in contrast to Participant 1, who was significantly older (48 years) and as such presented with a more advanced disease stage, only achieving 21% of predicted values. These results align with previous cross-sectional data, showing a reduction in strength observed with

age, indicative of the progression of the disease (Decostre et al., 2016). Specifically, Decostre et al. (2016) reported a projected annual muscle mass decline of 0.7% following 30 years of age. However, contrary to cross-sectional predictions, our data suggest that disease progression does not follow a linear trajectory. Instead, the decline in muscular strength appears to accelerate with advancing age and disease stage. Despite muscular strength being already significantly impaired in participant 1, there was a greater decline in muscular strength (49%) compared to that observed in the younger participant 2 (21%). Notably, the rate of decline increased from approximately 5% per year during the third and fourth decades of life to 8% per year during the fifth and sixth decades. This accelerated decline far exceeds cross-sectional predictions, highlighting the limitations of using age as a sole indicator of functional decline and underscoring the considerable heterogeneity in disease progression as acknowledged by others (Ben Chehida et al., 2018; Decostre et al., 2017; Lucchiari et al., 2007; Sentner et al., 2016).

The marked reduction in muscle strength may be explained by architectural and structural changes observed within the skeletal muscle. Architecturally, Participant 1 exhibited a pronounced reduction in fascicle length (38%), which likely reflects a decrease in the muscle's contraction speed, as shorter fascicles contain fewer in-series sarcomeres, thereby reducing the muscle’s shortening velocity and power output (Degens et al., 2009). This may stem from a combination of physiological, mechanical, and pathological factors. Chronic immobility and disuse in this participant likely caused the fascicles to operate at shorter lengths. Additionally, ageing and disease progression contributed to muscle atrophy, reducing both muscle mass and sarcomere number, which further shortens fascicle length (Morse et al., 2005b; Power et al., 2021). Alterations in tendon stiffness and shifts in muscle fibre type may have exacerbated these changes, ultimately diminishing the muscle's contractile capacity (Narici et al., 2008). Changes in pennation angle were also observed, which is the angle of insertion of muscle fibres

into the aponeurosis and provides information on muscle strength in which a greater pennation angle can signify more contractile material and increased force generating capacity (Strasser et al., 2013). Notably, Participant 2 showed the greatest loss in pennation angle (-19%), however, given the marked decline in MVCs, particularly in participant 1, the pennation angle across participants is likely to have been artificially maintained to some extent by an increase in intramuscular fat, particularly in light of observed increases in body fat (Malenfant et al., 2001; Rahemi et al., 2015; Tomlinson et al., 2014b) or an accumulation of non-contractile material (Akima et al., 2012). Although non-contractile material such as intramuscular fat or connective tissue cannot generate force, it may indirectly influence muscle architecture and give the impression of preserved strength. Intramuscular fat can increase tissue stiffness and alter fibre stress distribution, potentially masking losses in contractile tissue (Rahemi et al., 2015). In addition, connective tissue plays an important role in transmitting force laterally and longitudinally between fibres and to surrounding structures (Gillies & Lieber, 2011; Purslow, 2020). As such, the infiltration of non-contractile material may artificially maintain pennation angle and provide passive support to force transmission, even as maximal voluntary contractions decline.

Structurally, pronounced reductions in muscle volume were observed, particularly when comparing between the older Participant 1 and younger Participant 2, with subsequent reductions in PCSA. Muscle size and MVC in GSD 3 have previously been shown to positively correlate (Arnold et al., 2010; **Chapter 3**) suggesting that the accelerated decrease in muscle volume, thus muscular atrophy is partially responsible for the decline in MVC observed. The marked muscle loss in Participant 1 and 2 was found to vary, with muscle volume losses of 3% (3% PCSA per year) between 3rd-4th decade and 9% between the 5-6th decade of life (4% PCSA per year), which is considerably higher than in a healthy population following the 5th decade of life (~1% PCSA per year) (Frontera et al. 1985). In Participant 2, the loss of muscle volume

is disproportionate to the loss observed in MVC, in which there was a reduction of 5% per year in MVC compared to the 3% per year reduction in muscle volume in the 3nd to 4th decade of life. The accelerated loss of muscle strength found in GSD 3a within the 3nd and 4th decade of life appears to contrast to a healthy population, in which this is only observed following the 5th and 6th decade of life (-3% MVC per year vs. -1% per year muscle volume) (Goodpaster, *et al*., 2006). This supports the theory that the decline in MVC is not only attributable to muscle atrophy, but potentially neuropathy as previously observed in GSD 3a (Hobson-Webb et al., 2010) and potential neuromuscular deficiencies in agonist muscle activation noted during healthy aging (Tomlinson et al., 2014a). Furthermore, intramuscular fat, which was not assessed within this study could have resulted in a stiffer base material and resultant contractile performance (Rahemi et al., 2015). Subsequently, reductions in muscle quality were observed, which is the ability to generate force relative to the contractile tissue/mass (Metter *et al*., 1999). This was particularly evident in Participant 1 and supported by previous evidence documenting a decline in intrinsic fibre properties with age and reduced RTD (**Chapter 3**) with increased neuropathy, myopathy (Hobson-Webb et al., 2010) and fatty infiltration (Rahemi et al., 2015) as potential mechanisms. Given muscle quality is a key factor in physical function this may explain the reduced mobility observed (Lees et al., 2019). Given the evidence of muscular weakness, it is unsurprising participants had vastly limited aerobic capacity, only achieving a $\dot{V}O_{2peak}$ between 46-58% of predicted values, which has previously been documented in **Chapter 3** and by others (Preisler et al., 2013; Preisler et al., 2015).

Even in those of a similar age (Participants 2 and 3), there were marked differences, specifically in the decline in muscle volume. Interestingly, where higher physical activity and lower sedentary behaviour was maintained, there was less of a reduction in muscle mass and strength (Participant 2), compared to those who undertook noticeably less physical activity and were classified as sedentary (>8 h of Sedentary behaviour) (Participant 3). Furthermore, those with

a sedentary lifestyle tended to self-report greater reductions in QoL related to physical health outcomes and a worse health status. Notably, the individual with a greater physical capacity and less of a decline in muscle mass and strength (Participant 2) engaged in noticeably more physical activity and exhibited lower levels of sedentary behaviour. Furthermore, they tended to report less of a reduction in QoL related to physical health outcomes and a better health status. These findings suggest that those with an increased physical capacity undertake more physical activity and have improved QoL, or alternatively it may imply that greater physical activity and improved QoL contribute to maintaining higher physical capacity. Within the current study design the direction of this association is unclear, although it is likely that both scenarios play a role. The use of physical activity interventions promoting increasing muscle mass may therefore be considered, particularly between the 3 - 4th decade of life, where there is a potential to develop greater physiological reserve, muscle quality and functional capacity. In healthy older adults' the association of physical activity and knee extensor muscle strength has been documented (Aniansson et al., 1983; Reed et al., 1991) with longitudinal analysis showing that maintaining or increasing activity prevented or attenuated decline in strength with age (Rantanen et al., 1997). Despite the limitation imposed by the condition, people with GSD have the capacity to increase strength through resistance training, which has been shown to increase strength and function in the healthy (Kraemer & Ratamess, 2004; Williams et al. 2007), elderly (Morse et al*.,* 2005c) and other degenerative cohorts including GSD 2 (van den Berg et al., 2015) and muscular dystrophies (Bostock et al., 2019). Further studies are necessary to investigate the effectiveness of resistance training in GSD 3, specifically to maintain habitual functional tasks and mobility.

4.5.1 Strengths and Limitations

This case series provides valuable insights to add to the small literature base on the progression of exercise limitation in GSD 3a. This work challenges previous projections of a linear decline

by uncovering an accelerating deterioration in physical capacity and significant individual variability. These findings underscore the critical need for further longitudinal studies to better understand the disease trajectory and highlight the importance of initiating therapeutic interventions early.

It is important to acknowledge that this case series included a small sample size (n=3), which may not adequately represent the broader GSD 3a population. Given the rarity of the disease and physical requirements of testing, such limited sample sizes were to be expected but introduce a risk of selection bias. This could have skewed the results toward fitter, healthier individuals, thereby reducing the generalisability of the findings. To address this, we conducted our tests using standard techniques and equipment, commonly available in hospitals and universities, and we reported the results on an individual basis. It is our hope that future studies will adopt similar testing methods and integrate their findings with ours to include a larger, more representative dataset that could be continually built upon in future research.

Furthermore, this case series compared the physiological responses of participants with GSD 3a to predicted normative values as opposed to a control group. While comparing participant results to normative data is not ideal, selecting an appropriate control group for this small sample of individuals with GSD 3a would have been challenging and susceptible to selection bias. We determined that the advantage of utilising data from hundreds of healthy individuals and the ability to adjust for factors such as age, height, weight, and sex justified the use of normative values in our analysis.

It should also be acknowledged that accelerometery data were processed using cut-off thresholds established for the general population (Esliger et al., 2011), and their validity in individuals with GSD 3a is uncertain. This represents a potential source of measurement bias that should be addressed in future research. Additionally, standardised QoL and pain

assessment tools were employed due to their reliability and validity within those with musculoskeletal disorders (Beaton et al., 1997; Ferraz et al., 1990); however, these instruments have not been formally validated for use in GSD 3a, and may therefore limit the precision with which disease-specific experiences are captured. Given the limitations, future research should prioritise a collaborative, multicentre approach to establish data from a larger, more diverse cohort, thereby improving the generalisability of findings within GSD 3a.

4.6 Conclusion

This case series highlights the decline in muscle mass and strength in individuals with GSD 3a, offering new insights into the progression of the disease. While previous cross-sectional data have suggested a linear trajectory of decline beyond the age of 30, this case series reveals that the disease trajectory may actually accelerate with age, resulting in significantly reduced functional capacity compared to that predicted. Moreover, there is notable heterogeneity in disease presentation, even among individuals of similar ages, suggesting the influence of additional factors, such as lifestyle behaviours. Physical activity, in particular, may play a role in attenuating the decline in physical capabilities, notably the decline in muscle structural and functional characteristics. Individuals with GSD 3a may therefore benefit from physical activity interventions designed to increase or maintain muscle mass and subsequent strength such as resistance training, however further research is required to ensure timely, safe and effective implementation. This case series underscores the need for longitudinal assessments utilising robust and validated disease-specific methodologies to accurately capture individual disease trajectories, with linear projections derived from cross-sectional data failing to account for the heterogeneity of the disease.

Further longitudinal assessment will not only provide a clearer understanding of the variability and progression of the disease but will also serve as a foundation for developing more effective

disease management and intervention strategies, ultimately improving outcomes for individuals with GSD3a.

Chapter 5 - A Systematic Review investigating the Effectiveness of Exercise training in Glycogen Storage Diseases

5.1 Links to previous chapters

The marked exercise intolerance and significant progression of GSD 3a were detailed in **Chapter 3** and **Chapter 4**. However, these challenges are not unique to GSD 3a but are observed across the spectrum of GSDs, presenting opportunities for targeted interventions. Given the potential therapeutic benefits of exercise, **Chapter 5** aims to provide a comprehensive exploration of the existing evidence.

5.2 Introduction

GSDs can present from early childhood to late adulthood, with symptoms and the severity of symptoms varying greatly between different types of GSDs (Bhengu et al., 2014; Chien et al., 2013; Schoser et al., 2017). They are broadly categorised into those with hepatic involvement (GSD 0a, GSD 1a, GSD 1b, GSD 6, GSD 9A1, GSD 9A2, GSD 9c), those with skeletal muscle involvement (GSD 0b, GSD 2, GSD 5, GSD 7, GSD 9D, GSD 10, GSD 11, GSD 12, GSD 13, GSD 14, GSD 15) and those with both hepatic and skeletal muscle involvement (GSD 3, GSD 4, GSD 9b) (Kanungo et al., 2018). Those with hepatic involvement commonly present with fasting hypoglycaemia, with or without hepatomegaly and liver disease (Tarnopolsky, 2018). This can influence exercise tolerance due to the direct effects of liver glycogen content on exercise capacity as shown in rodents (Lopez-Soldado et al., 2021) and the indirect effect of glycogen via its role in the maintenance of blood glucose homeostasis (Gozalez et al, 2016). In contrast where there is skeletal muscle involvement, skeletal myopathy is present (Tarnopolsky, 2018). Those with skeletal muscle involvement can typically be divided into those showing static symptoms with loss of muscle mass and strength (GSD 2, GSD 3) and those with dynamic exercise-related symptoms of fatigue, muscle pain and contractures, often

associated with exercise-induced muscle damage (GSD 5, GSD 7, GSD 9D, GSD 10, GSD 14) (Preisler et al., 2015). However, clinically these phenotypes can overlap, and precise classification can be challenging (Preisler et al., 2015). In the GSDs with muscle involvement, exercise intolerance can lead to compromised habitual functioning, with increased morbidity and even premature death in some (Haller & Lewis, 1991; Mate-Munoz et al., 2007; Preisler et al., 2012; Preisler et al., 2013; Vissing, 2016). In addition, as a likely consequence of exercise intolerance, many people with GSDs lead a sedentary lifestyle, which itself is associated with unwanted metabolic adaptations and further health issues (Stein & Wade, 2005).

Primary therapeutic treatments for GSDs consist of diet and exercise. Dietary treatment varies based on the underlying enzyme defect and pathophysiology. Within hepatic GSDs nutritional therapy focusses upon preventing hypoglycaemia although there is a lack of general consensus on the optimal treatment (Heller et al., 2008; Ross et al., 2020). ERT is an emerging drug treatment, which has proven benefits in GSD 2 but is not currently available for most GSD subtypes (Van der Ploeg et al., 2010). Other supportive measures such as non-invasive ventilation (NIV) and cough assist devices are also employed for respiratory support and airway clearance in GSD 2 and GSD 3 (Chien et al., 2013; Gaeta et al., 2015). Although the primary treatments of diet modification are beneficial for GSDs with hepatic and skeletal involvement (particularly in Types 0, 1, 3, 6, 9 and 11) and ERT is relatively successful in reducing symptoms, impairments in functional capacity and QoL still persist (Heller et al., 2008; Ross et al., 2020). As such, there is a need to identify other treatments to accompany diet and ERT to further improve the health outcomes of people with GSDs. One such intervention is physical exercise training.

Exercise as an intervention may seem counterintuitive to many patients and clinicians given the severe exercise intolerance associated with many GSDs (Vissing, 2016). However, increasingly, evidence suggests exercise can be beneficial in reducing symptoms and increasing

QoL, rather than accelerating the disease (Preisler et al., 2015). The three primary exercise interventions considered as treatments for GSDs are aerobic, resistance and respiratory muscle training.

Endurance exercise acts as a powerful inducer of metabolic changes in skeletal muscle. Chronic adaptations associated with training include improvements in substrate delivery to contracting muscles and an increased ability to oxidise non esterified fatty acids (Preisler et al., 2015) at the same absolute and relative intensity post training (Achten & Jeukendrup, 2004). For this reason, in GSD 5, improvements in aerobic capacity and work rate have been found, leading to greater exercise tolerance (Haller et al., 2006; Mate-Munoz et al., 2007; Oliver et al., 2005). Theoretically, endurance exercise could potentially have important benefits to those GSDs with hepatic involvement too, as this shift towards an increased reliance on fat as a fuel and the reduction in plasma glucose oxidation rates would subsequently be protective against hypoglycaemia. Meanwhile, strength training can reverse muscle weakness and atrophy, attenuating disease severity (Santalla et al., 2014). Respiratory muscle training (RMT) is an emerging treatment in GSD 2, involving resistance exercise specifically targeting the respiratory muscles, aiming to alleviate significant respiratory weakness (Gozal & Thiriet, 1999). These exercise interventions will also combat the physical inactivity seen across the GSD spectrum and in doing so may improve overall general health, fitness and QoL (Blair et al., 1995; Pedersen & Saltin, 2006).

Researchers and clinicians have promoted the potential therapeutic benefits of exercise training for people with GSDs for many years. Supervised training programmes have even been included in consensus guidelines for those with GSD 2 (Cupler et al., 2012; Kishnani et al., 2006). However, despite the beneficial effects of exercise training in GSDs being acknowledged, the research supporting the utility of exercise training in GSDs is sparse and heterogeneous, most likely due to the rarity of these diseases. To date, the only previous

systematic review identified three studies and concluded that aerobic exercise effectively induces adaptations in cardiac, metabolic and skeletal muscle activity without adverse events in those with GSD 5 (Quinlivan et al., 2011). However, no other GSDs were reviewed by Quinlivan et al. (2011) and since its publication a number of exercise intervention studies have been published, including a randomised controlled trial (RCT) (Jones et al., 2020). As such, several questions remain, which include: Does current literature support the use of exercise training for people with GSD? Which GSD subtypes benefit from exercise training? Which training modalities are effective? And do patients adhere to prescribed exercise interventions? We aim to systematically review the current literature using a defined and reproducible strategy to investigate the broad impact of exercise training programmes across the GSD spectrum and establish the effects that various exercise interventions have on markers of cardiorespiratory and aerobic performance, muscular strength, functional capacity and well-being. In doing so, we aim to determine the feasibility and utility of using exercise training as a treatment option in those with GSDs to inform further research, clinical guidelines and practical recommendations.

5.3 Methods

This systematic review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2020; **Appendix G).**

5.3.1 Eligibility

Criteria for inclusion of publications within this review

Eligibility criteria were based on the PICO approach. Inclusion was based on the following criteria:

- A study population with a medical diagnosis of GSD, adults (⩾18 years).

- Studies comparing the effects of all forms of physical training programmes including aerobic training in the form of swimming, cycling, walking, jogging, flexibility, strength and respiratory muscle training.
- Interventions undertaken for a period of at least 4 weeks to ensure sufficient time for aerobic or respiratory conditioning to occur, but no upper limit on study duration.

Papers were excluded that were unrelated, duplicated, non-human subjects, subject requiring continuous invasive/continuous NIV, unavailable full texts, abstract only papers, editorials, reviews, authors responses and books.

5.3.2 Search strategy

We searched SCOPUS (1966 to February 2020) using the following search terms: {glycogen storage disease} AND 'exercise' OR 'endurance training' OR' aerobic exercise' OR 'physical fitness' OR 'muscle training' OR 'resistance training' OR ' aerobic conditioning' OR 'respiratory training' OR 'walk*' OR 'swim*' OR 'cycl*' OR 'jogging'. Limited to human/humans' papers.

We searched MEDLINE (1950 to February 2020) using a modified search strategy to include exploded MeSH Headings: (MeSH HEADING: exp: ((((((((((glycogen storage disease) OR Fanconi Syndrome) OR Glycogen Storage Disease Type I) OR Glycogen Storage Disease) OR Glycogen Storage Disease Type II) OR Glycogen Storage Disease Type III) OR Glycogen Storage Disease Type IV) OR Glycogen Storage Disease Type V) OR Glycogen Storage Disease Type VII) OR Glycogen Storage Disease Type VI) OR Glycogen Storage Disease Type VIII) OR Glycogen Storage Disease Type IIb) *AND* MeSH HEADING:exp: ((((((exercise) OR Exercise Test) OR Exercise Therapy) OR Exercise) OR Exercise Tolerance) OR Muscle Stretching Exercises) OR Resistance Training)) *OR* MeSH HEADING:exp: (respiratory training OR Breathing Exercises). All searches were conducted on 11 February 2020.

5.3.3 Selection of studies

Two authors (P.H., C.B.) independently reviewed abstracts in order to identify potential studies for inclusion. Full texts were downloaded and screened for inclusion according to eligibility criteria by two researchers independently. Any disagreement was resolved by consensus agreement following discussion with another author (I.V.). In addition, the reference list of eligible papers was checked to ensure that all potential eligible papers had been identified. Foreign language studies were translated into English.

5.3.4 Quality assessment

Publications were assessed for quality by considering characteristics that could introduce bias using the NIH Quality Assessment Tool for Before- After (Pre-Post) Studies with no control group and the NIH Quality Assessment Tool for controlled intervention studies (NHLBI, 2021) **(Appendix H).**

5.3.5 Data extraction

Data from the included studies were extracted into defined tables by a single reviewer. Information was recorded on population characteristics, study design, intervention and outcomes. For Aerobic and Strength training, outcomes were categorised into the following groups: Cardiorespiratory fitness; Muscular strength; Functional capacity and Well-being; and Ventilatory function (where data available). For Respiratory Muscle Training, outcomes were categorised into the following groups: Muscular strength; Ventilatory function; and Functional capacity and Well-being. Data presented in graphs were extracted by Web plot digitiser (Rohatgi, 2020).

5.4 Results

5.4.1 Search results

A total of 4868 titles and abstracts were screened following the search, 121 of which were included for full test screening. Twenty-three articles were subsequently selected for final inclusion in this review **(Figure 5.1).** All identified studies included adult patients with GSD 5 or GSD 2 disease. Eight studies of adults with GSD 5 were identified, with seven studies investigating aerobic exercise (Cakir et al., 2017; Haller et al., 2006; Lucia et al., 2007; Mate-Munoz et al., 2007; Olivier et al., 2005; Perez et al., 2007; Porcelli et al., 2016) and one study investigating strength training (Santalla et al., 2014). Fifteen studies of adults with GSD 2 were identified, with six investigating a combination of aerobic and muscular training (Favejee et al., 2015; Khan et al., 2009; Leutholtz & Ripoll, 1996; Montagnese et al., 2016; Terzis et al., 2011; van den Berg et al., 2015) two investigating aerobic and nutrition interventions (Sechi et al., 2020; Slonim et al., 2007) and seven investigating RMT (Aslan et al., 2014; Jones et al., 2020; Jones et al., 2011; Jones et al., 2016; Martin et al., 1983; Mitja et al., 2015; Wenninger et al., 2019). No studies including adults with other GSDs were identified. The 23 included publications were largely uncontrolled intervention trials. Other publications included single-arm A-B-A experimental design (Jones et al., 2016), a double-blind RCT (Jones et al., 2020), a A-B-C single-arm experimental design (Wenninger et al., 2019), a longitudinal observation study (Mitja et al., 2015), an uncontrolled prospective study (Slonim et al., 2007) and a quasi-experimental reversal design study (Santalla et al., 2014).

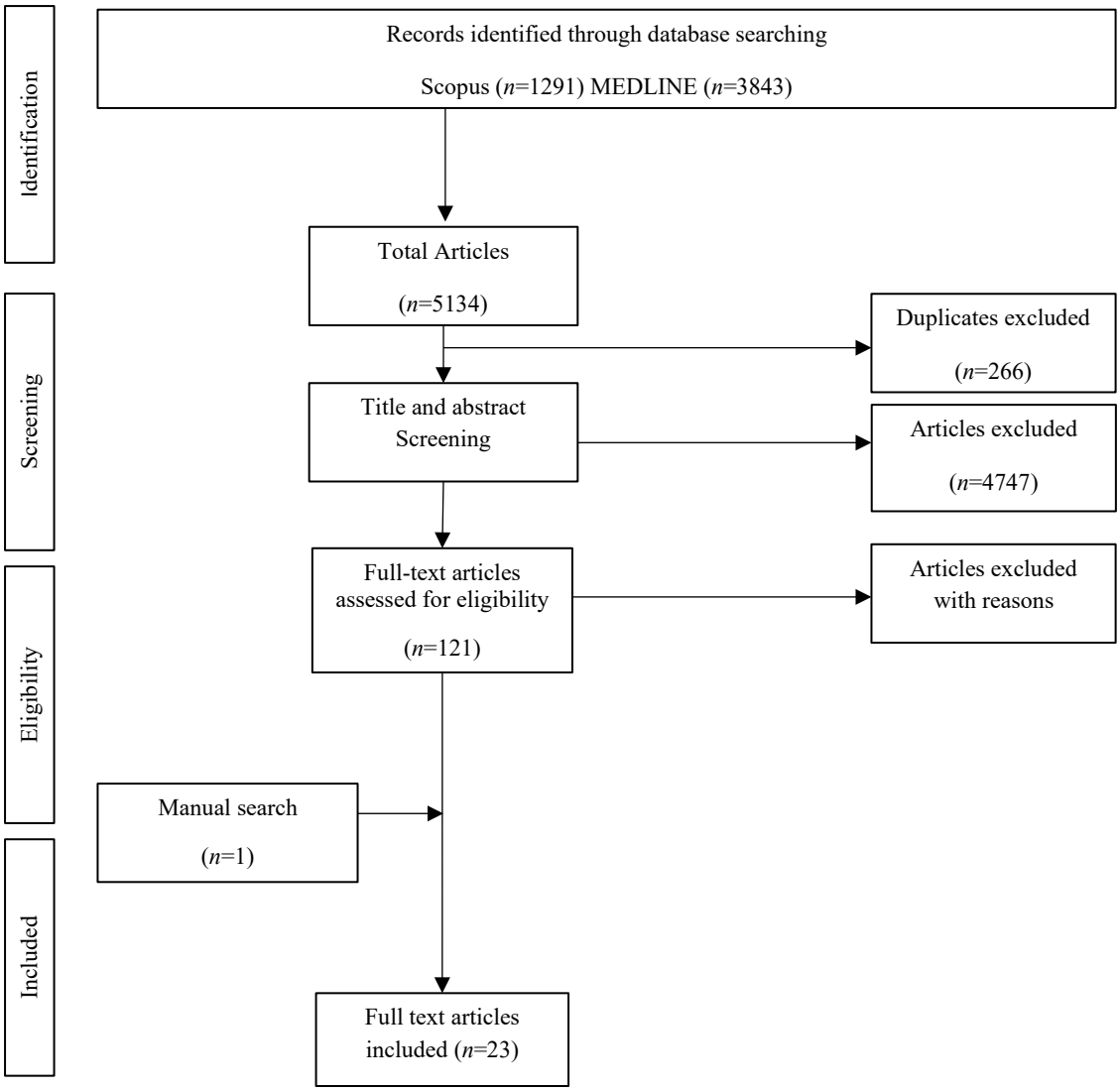


Figure 5.1 PRISMA flow diagram of literature screening and selection.

Outcomes reported in patients undergoing aerobic and muscular training included markers of cardiorespiratory fitness, muscular strength and functional capacity and well-being. Markers of cardiorespiratory fitness included maximum work rates, $\dot{V}O_{2peak}$, submaximal $\dot{V}O_2$ ventilatory threshold (VT), gross efficiency (GE), heart rate (HR) and cardiac output. Markers of muscular strength included peak power, Medical Research Council sumscore (MRCss), isometric strength and repetitions of weights. Markers of ventilatory function included vital capacity (VC). Markers of functional capacity included grip strength, timed function tests

(TFTs), functional status (Walton & Gardner-Medwin Scale) and muscle function deterioration. All well-being outcomes were self-reported, with validated surveys such as Short Form-36 (Cakir et al., 2017; Favejee et al., 2015; Porcelli et al., 2016; Sechi et al., 2020), Fatigue Severity Scale (FSS) (Favejee et al., 2015) and Phenotype Severity Scale used (Santalla et al., 2014). In patients undergoing RMT, markers of respiratory muscle strength included maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and diaphragm thickness. Markers of ventilatory function included peak cough flow (PCF), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), MMRC-Dyspnoea and capillary capnometry. Functional capacity and well-being markers included functional status (WGMS), TFTs, QoL using the Nottingham Health profile (NHP), Quality of sleep using the Pittsburgh Sleep Quality Index (PSQI), reported outcomes of fatigue (FSS) and daytime sleepiness (ESS) and Dyspnoea (SRGQ and MMRC Dyspnoea Scale).

5.4.2 Findings

The following analysis focusses on the effectiveness of exercise in GSD 5 and GSD 2. The main exercise interventions identified were aerobic training, muscular training and respiratory muscle training.

5.4.2.1 Aerobic training in GSD 5

5.4.2.1.1 Characteristics and quality

Aerobic training involving 34 adults with GSD 5 was included in 7 studies, 3 of which were deemed fair quality (Haller et al., 2006; Mate-Munoz et al., 2007; Porcelli et al., 2016), with the remaining 4 studies being deemed of poor quality (Cakir et al., 2017; Lucia et al., 2007; Olivier et al., 2005; Perez et al., 2007). The basic characteristics of these are shown in **Table 5.1**. All of these were nonrandomised intervention studies, with two studies including controls of clinically healthy subjects; however, these were only included for comparison of acute

exercise responses at baseline (Mate-Munoz et al., 2007; Olivier et al., 2005). The duration of training varied from 4 to 32 weeks, with the frequency of training between 3 and 5 times per week and protocols including 60 min or less of walking and running and cycling, with the majority at an intensity of between 60% and 85% max HR (Cakir et al., 2017; Haller et al., 2006; Lucia et al., 2007; Mate-Munoz et al., 2007; Olivier et al., 2005; Perez et al., 2007; Porcelli et al., 2016).

Table 5.1 GSD 5: Population Characteristics and Study Design

Author (year)	Quality Rating	Population (age)	Study design
Olivier et al. (2005)	Poor	5 McArdle patients (35±11 years)	Nonrandomised intervention
Haller, et al. (2006)	Fair	8 McArdle patients (33-61years)	Nonrandomised uncontrolled intervention
Lucia, et al. (2007)	Poor	1 McArdle and Myasthenia gravis patient (29 years)	Nonrandomised uncontrolled intervention
Mate-Munoz, et al. (2007)	Fair	10 McArdle patients (36±5 years)	Nonrandomised intervention
Perez, et al. (2007)	Poor	1 McArdle patient (38 years)	Nonrandomised uncontrolled intervention
Porcelli, et al. (2016)	Fair	7 McArdle patients (41±13years)	Nonrandomised uncontrolled intervention
Cakir, et al. (2017)	Poor	2 McArdle patients (33 years, 42 years)	Nonrandomised uncontrolled intervention
Santalla, et al. (2014)	Fair	7 McArdle patients (23-58 years)	Quasi experimental reversal

5.4.2.1.2 Outcomes

5.4.2.1.2.1 Cardiorespiratory fitness:

Aerobic capacity was shown to improve with increased $\dot{V}O_{2peak}$ observed in five studies **(Table 5.2)** (Haller et al., 2006; Lucia et al., 2007; Mate-Munoz et al., 2007; Perez et al., 2007; Porcelli et al., 2016). Greatest improvements were found by Perez et al. (2007) (14.6 to 30.8 ml/kg/min), Lucia et al. (2007) (8.5 to 17.0 ml/kg/min) and Mate-Munoz et al. (2007) (13.0 ± 3.8 to 18.8 ± 5.9 ml/kg/min). Smaller differences were seen by Haller et al. (2006) (1.3 to1.5 L/min) and Porcelli et al. (2016) (18.5 ± 1.8 to 21.6 ± 1.9 ml/kg/min). In contrast, no differences were found by Olivier et al. (2005) VT increased in Lucia et al. (2007) (6.1 to 11.8 ml/kg/min) and Mate-Munoz et al. (2007) (9.4 ± 1.8 to 12.8 ± 3.7 ml/kg/min). Gross muscle efficiency was only found to increase by Perez et al. (2007) (13.8% to 17.2%). Three studies showed improvements in peak heart rate (Perez et al. (2007) 140 to 166 bpm; Mate-Munoz et al. (2007)146 ± 22 to 156 ±19 bpm; Lucia et al. (2007) 141 to 163 bpm), whereas others found no differences (Porcelli et al., 2016). Similar increases were found in cardiac output (Haller et al. (2006) 13.1 to 15.0 L/min; Porcelli et al. (2016) 15.2 ±1.3 to 18.9 ± 1.1 L/min). Peak work rate in an incremental test increased in all five studies that measured this (Haller et al., 2006; Lucia et al., 2007; Mate-Munoz et al., 2007; Perez et al., 2007; Porcelli et al., 2016) with the highest overall increase being 59 to 120 W (Perez et al., 2007). Significant increases were reported by Haller et al. (2006) (59 to 78 W), Mate-Munoz et al. (2007) (0.8 ± 0.2 to 1.1 ± 0.3 W/kg) and Porcelli et al. (2016) (73 ± 13 to 89 ± 12 W).

5.4.2.1.2.2 Functional capacity and well-being:

Improvements in functional capacity (grip strength and 10 m walk) were observed by Cakir et al. (2017) (Right grip: 21.5 to 23.5 kg; Left grip: 20.5 to 22.5 kg; 10 m walk: 7.0 to 5.9 s). Improvements in well-being were reported in three studies (Cakir et al., 2017; Lucia et al., 2007; Perez et al., 2007) with two studies documenting self-reported improvements in well-

being (Lucia et al., 2007; Perez et al., 2007) and others reporting improvements in all QoL scores (Cakir et al., 2017).

5.4.2.1.2.3 Adherence

In the only study to report this outcome, Porcelli et al. (2016) observed 96% adherence to their training programme.

5.4.2.2 Strength training in GSD 5

5.4.2.2.1 Characteristics and quality

Strength training was included in one study consisting of seven patients with GSD 5 (Santalla et al., 2014) **(Table 5.1)**. This was a quasi-experimental reversal trial deemed of fair quality, consisting of resistance training including a warmup, circuit training of large muscle groups followed by passive stretching, carried out twice per week for 16 weeks.

5.4.2.2.2 Outcomes

5.4.2.2.2.1 Muscular Strength

Muscular power was shown to increase after resistance training **(Table 5.2**; Bench press: 51 to 103 W; Half Squat: 116 to 290 W) (Santalla et al., 2014).

5.4.2.2.2.2 Adherence

Adherence to training was reported to be between 84% and 100% (Santalla et al., 2014).

Table 5.2 Aerobic and Strength training in GSD 5.

Author	Duration (weeks)	Frequency (days/week)	Protocol of sessions	Outcomes Cardiorespiratory Fitness	Muscular Strength	Functional Capacity and Wellbeing
Aerobic Training						
Olivier et al. (2005)	8	3	Cycling 35-45 min Intensity 60-70% max HR Then 60 min recovery	**Submaximal** $\dot{V}O_2$: No differences **HR**: Decrease at submaximal workloads	-	-
Haller et al. (2006)	14	4	Cycling 30-40 min Intensity 60-70% max HR.	**Peak Work rate** Increased 36% (+19 watts) ($p<0.002$) $\dot{V}O_{2peak}$ **during prolonged test:** Increased 14% (+0.2 L/min) **Peak Cardiac output (Q):** Increased 15% (+2 L/min) ($p<0.02$)	-	-
Lucia et al. (2007)	12	5	Walking ≤60 min Intensity 60% max HR.	**Peak Work rate** Increased 61% (+38 watts) $\dot{V}O_{2peak}$ Increased 100% (+8.5 ml/kg/min) **VT:** Increased 93% (+5.7 ml/kg/min) **Peak HR:** Increased 16% (+22 bpm)	-	Self-reported improved sense of wellbeing and ability to perform activities of daily living.
Mate-Munoz et al. (2007)	32	5	Walking and/or cycling and or gentle running ≤60min at 60% peak HR	**Peak Work rate:** Increased 38% (+0.3 W/Kg) ($p=0.014$) $\dot{V}O_{2peak}$**:** Increased 45% (+5.8 mL/kg/min) ($p=0.006$) **VT:** Increased 36% (+3.4 mL/kg/min) ($p=0.012$) **GE:** No differences ($p=0.476$) **Peak HR:** Increased 7% (+10 bpm) ($p=0.05$)	-	-

Perez et al. (2007)	28	3-4	Running ≤60min Intensity ≤80-85% max HR.	**Peak Work rate:** Increased 103% (+61 watts) **$\dot{V}O_{2peak}$:** Increased 111% (+16.2 ml/kg/min) **GE:** Increased 3.4% **Peak HR:** Increased 19% (+26 bpm)	-	Self-reported improvement in well-being and ability to perform activities of daily living.

				Outcomes		
Author (year)	**Duration (weeks)**	**Frequency (days/week)**	**Protocol of sessions**	**Cardiorespiratory fitness**	**Muscular strength**	**Functional Capacity and Wellbeing**
Porcelli et al. (2016)	12	4	1)10-15 min Stretching exercises 2) 30-45 min cycling 65-70% max HR.	**Peak Work rate:** Increased 22% (+16 watts) (p=0.02) **$\dot{V}O_{2peak}$:** Increased 17% (+3.1 ml/kg/min) (p=0.02) **GE:** Increased 0.8% **Peak HR:** No differences **Peak SV:** Increased 22% (19.9 ml) (p<0.05) **Peak Cardiac Output (Q):** Increased 24% (+3.7 L/min) (p=0.04)	-	**QoL:** No differences
Cakir et al. (2017)	4	5	1)Walking 30-45 min Intensity 5-44% 2) 3 reps of static stretching 3) Diaphragmatic breathing also included.	-	-	**Grip strength:** R: Increased 9% (+2.0 kg) L: Increased 14% (+1.8 kg) **10m walking time:** Decreased 15% (-1.08 s) **Time to climb 4 steps:** Decreased 7% (-0.17 secs) **Sit to stand within 30 secs:** Increased 14% (+1.5 s). **QoL:** Improvement in all scores, except for physical function, vitality, and emotional role in one patient.

Strength Training						
Santalla et al. (2014)	16 (+8 detraining)	2	1) Warm up (12 min on arm crank ergometer and 12 min on cycle ergometer) 2) Circuits using large muscle groups, 5-6 reps, using load(kg) eliciting RPE of 6-7. Bench press, leg press, lateral pull down, abdominals) 3) Passive stretching (3 x 30secs for each muscle group)	-	**Peak Power:** **Bench press:** Increased 100% (+52 watts) (p=0.018) **Half Squat:** Increased 151% (+173 watts) (p=0.018)	All changed to a lower severity class.

GE, gross efficiency; SV, stroke volume; VT, ventilatory threshold; Heart Rate (HR), Rating of perceived exertion (RPE).

5.4.2.3. Aerobic and strength training in GSD 2

5.4.2.3.1 Characteristics and quality

A combination of aerobic and resistance exercises was investigated in 4 studies consisting of 29 of adults with GSD 2 (Favejee et al., 2015; Leutholtz & Ripoll, 1996; Terzis et al., 2011; van den Berg et al., 2015). The basic characteristics of these studies are shown in **Table 5.3**. These were a mixture of poor (Leutholtz & Ripoll, 1996), fair (Terzis et al., 2011) and good quality studies (Favejee et al., 2015; van den Berg et al., 2015). Participants were reported to be receiving ERT in three studies (Favejee et al., 2015; Terzis et al., 2011; van den Berg et al., 2015) and hormone replacement therapy in one study (Leutholtz & Ripoll, 1996). Two studies included patients supported by walking aids (Favejee et al., 2015; van den Berg et al., 2015) and others included patients supported with NIV (Leutholtz & Ripoll, 1996). All of these studies were non-randomised uncontrolled intervention studies, with van den Berg et al. (2015) and Favejee et al. (2015) reporting on different outcomes from the same study population. Interventions included aerobic and strength (Leutholtz & Ripoll, 1996; Terzis et al., 2011) and aerobic, strength and core stability exercise (Favejee et al., 2015; van den Berg et al., 2015). The frequency of training was 3 times per week with a varied duration between 12 and 20 weeks. Aerobic training consisted of 30 min cycling (Favejee et al., 2015; Leutholtz & Ripoll, 1996; Terzi et al., 2011; van den Berg et al., 2015). Strength training included major muscle groups, using either body weight or weights (Leutholtz & Ripoll, 1996; Terzis et al., 2011) or exercise machines (van den Berg et al., 2015; Favejee et al., 2015). In addition, core stability exercises were included in two studies (van den Berg et al., 2015; Favejee et al., 2015).

Table 5.3 GSD 2: Population Characteristics and Study Design.

Author (year)	Quality Rating	Participants (age)	Study design
Leutholtz & Ripoll (1996)	Poor	*n*=1 (24 years)	Nonrandomised uncontrolled intervention trial
Terzis, et al. (2011)	Fair	*n*=5 (36 years to 71 years)	Nonrandomised uncontrolled intervention trial
van den Berg et al. (2015)	Good	*n*=23 patients (46 years (19.6-70.5)	Nonrandomised uncontrolled intervention trial with staggered starts.
Favejee et al. (2015)	Good	*n*=23 patients (46 years (19.6-70.5)	Nonrandomised uncontrolled intervention trial
Sechi et al. (2020)	Good	*n*=13 (49±11.0 years)	Partially blinded, randomised, crossover study
Slonim et al. (2007)	Fair	*n*=34 (44 ±11yrs)	Uncontrolled prospective study.
Montagnese et al. (2016)	Poor	*n*=2 (52 and 74 years)	Nonrandomised uncontrolled Intervention trial
Khan et al. (2009)	Poor	*n*=1 (34 years)	Nonrandomised uncontrolled intervention trial

5.4.2.3.2 Outcomes

5.4.2.3.2.1 Cardiorespiratory fitness

$\dot{V}O_{2peak}$ increased after aerobic and strength training and was broadly consistent with aerobic training alone (**Table 5.4**; van den Berg et al. (2015) 22.1 ± 7.0 to 24.1 ± 7.1 ml/min/kg). Increases were also found in VT (16.7 ± 4.3 to 18.5 ± 4.7 ml/min/kg) and maximum work rate (110 ± 52 W to 122 ±53 W) (van den Berg et al., 2015).

5.4.2.3.2.2 Ventilatory function

VC was only found to increase by Leutholtz and Ripoll (1996) (1.2 to 1.5 L).

5.4.2.3.2.3 Muscular strength

Improvements in muscular strength were shown in three studies (Leutholtz & Ripoll, 1996; Terzis et al., 2011; van den Berg et al., 2015) with increases in maximum isometric strength found by Terzis et al.(2011) (Hip extension: 4.6 ± 3.3 kg to 6.9 ±3.7 kg; Bench press: 12.2 ± 5.3 kg to 15.2 ± 7.8 kg, Rowing: 16.7 ± 9.0 kg to 19.8 ± 5.9 kg) using a load transducer and van den Berg et al. (2015) (Hip flexors: 156.4 ± 61.9 N to 180.7 ± 57.7 N, Shoulder abductors: 143.1 ± 29.1 N to 150.7 ± 35.4 N) using hand-held dynamometry of individual muscle groups. An increase in resistance training repetitions (Curls: 10 to 15; Leg extensions: 7 to 10; Pullovers: 10 to 20; Chest presses: 10 to 20) using a 10-lb weight was observed by Leutholtz and Ripoll (1996).

5.4.2.3.2.4 Functional capacity and well-being

Functional capacity was shown to improve in two studies (van den Berg et al., 2015; Terzis et al., 2011) with improvements found by Terzis et al. (2011) (6MWT: 204 ±177 m to 248 ± 184 m) and van den Berg et al.(2015) (6MWT: 492 ±89 to 508 ± 97m; Time to climb four steps −0.54 to−0.04 s and supine-stand time: −2.0 to 0.01 s), in contrast to others (Leutholtz & Ripoll,

1996). Well-being outcomes included reduced fatigue (median scores: 5.33 to 4.78) and the numbers of patients reporting pain (13/23 versus 5/23) (Favejee et al., 2015).

5.4.2.3.2.5 Adherence

Adherence was only reported in 1 of 3 studies, which found high (89%) rates of session completion (van den Berg et al., 2015).

5.4.2.4 Aerobic, strength and nutrition interventions in GSD 2

5.4.2.4.1 Characteristics and quality

Aerobic, strength and nutrition interventions were described by 2 studies, consisting of 47 adults with LOPD, which were deemed of good (Sechi et al., 2020) or fair quality (Slonim et al., 2007) (**Table 5.3**). Participants were receiving ERT in the study by Sechi et al. (2020) with some patients supported by NIV in the study by Slonim et al. (2007). These studies were a partially blinded, randomised crossover study (Sechi et al., 2020) and an uncontrolled prospective study (Slonim et al., 2007). There was a large variation in duration from 26 weeks to 10 years, at a frequency of training between 4 and 7 times per week. Aerobic training consisted of 30–40 min cycling (at 11–13 Borg Scale or 60% $\dot{V}O_2$ or 60% max HR) or 45–50 min (at 60–65% max HR) on a treadmill, with strength training including 10–15 min using exercise machines or resistance bands. All patients were recommended to consume a caloric distribution of 25–30% protein, 30–35% carbohydrate and 35–40% fat, with the ingestion of l-alanine, 1.5 g, 4 times/day by Slonim et al. (2007). In contrast, patients were randomly assigned to exercise alone or exercise + diet by Sechi et al. (2020) in which the dietary intervention was a personalised high protein diet (25–30% protein, 30–35% carbohydrate, 35–40% fat).

5.4.2.4.2 Outcomes

5.4.2.4.2.1 Cardiorespiratory fitness

Significant improvements were reported in peak work rate after aerobic exercise alone **(Table 5.4)** (although no difference in median was found 75 ± 80 to 75 ± 70 W). With aerobic exercise and diet there were improvements in peak work rate (median 63 ± 55 to 73 ± 55 W) and $\dot{V}O_{2peak}$ (median: 22.2 ± 7.3 ml/min/kg to 22.2 ± 4.6 ml/min/kg) (Sechi et al., 2020).

5.4.2.4.2.2 Ventilatory function

VC did not change (Sechi et al., 2020; Slonim et al., 2007).

5.4.2.4.2.3 Muscular strength

No differences were found by Sechi et al. (2020) however, there was a significant improvement in muscle function deterioration after nutrition, aerobic and resistance exercise by Slonim et al. (2007) [−0.29 (95% CI −0.36, −0.19)].

5.4.2.4.2.4 Functional capacity and well-being

Significant improvements in general health and vitality after aerobic, resistance exercise and nutrition were also found (Sechi et al., 2020).

5.4.2.4.2.5 Adherence

Twenty-six of the thirty-four patients were considered to have moderate to good compliance to the combined exercise and nutrition intervention (Slonim et al., 2007). Similarly, Sechi et al. (2020) found reasonable adherence to exercise (69% for warm up, 61% for strength training, 74% for cycling, 69% for stretching) with no significant difference between arms. Within the dietary intervention, the percentage of calories introduced with proteins was 96% (median value) of those prescribed and significantly increased from habitual diet.

5.4.2.5 Strength training in GSD 2

5.4.2.5.1 Characteristics and quality

Whole body vibration training (WBVT) and side alternating vibration training (SAVT) were described by two nonrandomised uncontrolled intervention studies which were deemed of poor quality (Khan et al., 2009; Montagnese et al., 2016) and included three adults with LOPD **(Table 5.3)**. Both studies included patients supported by walking aids, with some receiving ERT and additional regular physiotherapy (Montagnese et al., 2016). Training was carried out 3 times per week; however, there was a large variation in duration of training ranging from 15 to 104 weeks (Khan et al., 2009; Montagnese et al., 2016).

5.4.2.5.2 Outcomes

5.4.2.5.2.1 Muscular Strength

Improvements in muscular strength included increases in MRCss (41.5 to 47.5), knee extension (70.8 to 106.3 Nm), arm flexion (38.3 to 67.9 Nm) (Montagnese et al., 2016) and peak power using jumping mechanography (83 to 136 W) (Khan et al., 2009). Improvements in functional capacity were also found (6MWT: 166 to 282 m) (Khan et al., 2009) **(Table 5.4)**.

5.4.2.5.2.2 Adherence

This was not reported in either study.

5.4.2.6 Respiratory interventions in GSD 2 disease

5.4.2.6.1 Characteristics and quality

Respiratory muscle training was described in a total of 7 studies consisting of 60 adults with LOPD **(Table 5.5)** (Aslan et al., 2014; Jones et al., 2011; Jones et al., 2016; Jones et al., 2020; Martin et al., 1983; Mitja et al., 2015; Wenninger et al., 2019). Most of the studies were deemed fair quality (Aslan et al., 2014; Jones et al., 2016; Mitja et al., 2015; Wenninger et al., 2019) with only Jones et al. (2020) deemed fair to good quality. The population characteristics and

study design are shown in **Table 5.5.** All included patients had respiratory muscle weakness, with five papers including a subset of patients receiving non-invasive nocturnal ventilation (including between 1 and 13 patients) (Aslan et al., 2014; Jones et al., 2016; Jones et al.,2020; Martin et al., 1983; Wenninger et al., 2019). Adjuvant ERT treatment was used in all but one study (Martin et al., 1983). Three studies were nonrandomised uncontrolled trials (Aslan et al., 2014; Jones et al., 2011; Martin et al., 1983). Jones et al. (2020) was the only double-blind RCT. Others included an A-B-A single subject trial (Jones et al., 2016), a single-arm pilot study A-B-C design (Wenninger et al., 2019) and a longitudinal observational study (Mitja et al., 2015). A summary of the interventions and outcomes are shown in **Table 5.6**. All of the papers included RMT, with both Inspiratory Muscle Training (IMT) and Expiratory Muscle Training (EMT) used in three studies (Jones et al., 2011; Jones et al., 2016; Jones et al., 2020) and IMT used alone in four studies (Aslan et al., 2014; Martin et al., 1983; Mitja et al., 2015, Wenninger et al., 2019).

The majority of the studies had a training period of 15 weeks or less, with two papers of longer training duration of up to 96 weeks (Jones et al., 2011; Mitja et al., 2015). The interventions used pressure threshold RMT which consisted of multiple repetitions of RMT against fixed resistance (threshold) at either a relatively fixed intensity (Jones et al., 2011, Jones et al., 2016, Jones et al., 2020, Mitja et al., 2015) or progressive intensities over the duration of the training (Aslan et al., 2014; Martin et al., 1983; Wenninger et al., 2019). Patients were prescribed between 30 and 45 min training per day, between 5 and 7 times per week.

5.4.2.6.2 *Outcomes*

5.4.2.6.2.1 Respiratory muscle strength

Improvements in markers of muscular strength were found in six of the seven studies after IMT alone or with both IMT and EMT **(Table 5.6)**. Significant improvements in MIP were observed in three studies, specifically after IMT (Mitja et al.(2015) 31.6 ±17.7 to 37.2 ± 19.3 cmH_2O;

Aslan et al. (2014) median 30 cmH_2O (21.5–48.0) to 39 cmH_2O (31.2–56.5); Wenninger et al. (2019) 48.6 ± 18.0 to 56.2 ± 19.9 cmH_2O after initial 6-week training period and 48.6 ± 18.0 to 61.4 ± 28.7 cmH_2O over the total duration of study including an additional training period). Improvements in MEP were observed in three studies; however, in contrast, these were predominantly observed after inspiratory and expiratory training combined and values showing statistical significance were not presented (Jones et al., 2011; Jones et al., 2016; Martin et al., 1983).

5.4.2.6.2.2 Ventilatory function

Improvements in ventilatory function were only found by Jones et al. (2016) with increases in PCF (7.5 ± 0.6 to 8.5 ± 1.4 L/s). No differences were found in other ventilatory markers.

5.4.2.6.2.3 Functional capacity and well-being

Improvements in markers of functional capacity were found after IMT and EMT [Jones et al. (2016) 6MWT: Increased 2.2% (+6.9 m); Supine-stand: Decreased 13.4% (−1.6 s), climb 4 stairs: Decreased 15% (−0.6 s), walk 10 m: Decreased 3.4% (−0.3 s) Jones et al. (2020) Climb 4 steps −0.9 s treatment versus −0.1 s control, p = 0.03]. Well-being including social isolation scores significantly improved [Aslan et al. (2014) Median 22.5 (22.1–69.8) to 0.0 (0.0–16.9)] and daytime sleepiness significantly decreased compared to controls [Jones et al. (2020) ESS score −1.2 treatment versus +1.1 controls].

5.4.2.6.2.4 Adherence

Adherence was excellent, in which Wenninger et al. (2019) found 107% of the training sessions were completed. Similarly, Jones et al. (2016) found a mean of 99% prescribed IMT repetitions and 101% of prescribed EMT repetitions were completed and Jones et al. (2020) found mean adherence to be 98% in the treatment arm and 97% in the control arm.

Table 5.4. Aerobic and Muscular Interventions in GSD 2

Author (year)	Duration (weeks)	Frequency (days/week)	Protocol of sessions	Outcomes			
				Cardiorespiratory fitness	Muscular strength	Ventilatory function	Functional Capacity and Wellbeing
Aerobic and Strength Training							
Leutholtz & Ripoll (1996)	12	3	**Aerobic exercise:** 30 min Cycle RPE 11 to 13 of Borg scale. 30 min **Strength training:** 30% of 1RM, 12-15 reps using "Pyramid" CAM assisted circuit machines.	-	**Repetitions: (at wt. 10lbs)** **Curls:** Increased 50% (10 to 15) **Leg ext.:** Increased 42% (7 to 10) **Pullovers:** Increased 100% (10 to 20) **Chest press:** Increased 100**%** (10 to 20)	**VC:** Increased 31% (1.2-1.5 L)	**Sit to stand:** Unable to complete
Terzis et al. (2011)	20	3	1) 30 min cycling 2)10 min stretching of major muscle groups. 3) Resistance exercises of major muscle groups (1-3 sets of 10 reps, resistance 50% 10 reps max.	-	**Knee extension:** (MVC) Increased 46% (+2.3 kg) ($p>0.05$) **Hip extension:** (MVC) Increased 51% (+2.3 kg) ($p<0.05$). **Bench press:** (MVC) Increased 25% (+3.0 kg) ($p<0.05$). **Rowing:** (MVC) Increased 19% (+3.1 kg) ($p<0.05$)	-	**6MWT:** Increased 22% (+44 m) ($p<0.01$)
Van den Berg, et al. (2015)	12	3	1)5 min Warm-up, intensity 100-110 BPM. 2)15 min Cycling (Intensity 60% $\dot{V}O_{2max}$) 3) Strength training (Weight 70% of 4 RM, 3 sets 15-20 reps) 4) 15 min Cycling 5) Core stability (3 sets of 30 secs) 6) 5 min Cool down	**Peak Work rate:** Increased 11% (+12 watts) ($p<0.01$) $\dot{V}O_{2peak}$**:** Increased 9% (2.0 ml/min/kg) ($p<0.01$) **VT:** Increased 11% (+1.8 ml/min/kg) ($p<0.01$)	**Hip flexors:** (MVC) Increased 15% (+24 N) ($p<0.01$) **Shoulder abductors: (**MVC) Increased 5% (+7.6 N) ($p=0.02$) **Others:** No differences	**VC:** No differences	**6MWT:** Increased 3% (+16 m) ($p=0.01$) **Time to climb 4 steps:** Decrease 12% (-0.3 s) ($p=0.02$) **Rise to standin**g: Decrease 17% (-1.0 s) ($p=0.05$) **Others:** No difference

Favejee et al. (2015)	12	3	As Van den Berg *et al*, 2015	-	-	-	**Fatigue:** Decreased 10% (Medians: 5.33 to 4.78) (p=0.007) **Pain:** Decreased 35% (p=0.040). **Mental Health:** No differences

				Outcomes			
Author (year)	**Duration (weeks)**	**Frequency (days/week)**	**Protocol of sessions**	**Cardiorespiratory fitness**	**Muscular strength**	**Ventilatory function**	**Functional Capacity and Wellbeing**
Aerobic and Strength Training plus Dietary Intervention							
Sechi et al. (2020)	26	4	**Aerobic exercise:** 1) Warm up 2) 10-15 min Stretching and balance 3) 15 min Strength, moderate loads of main muscle groups using elastic bands. 3 x 10 reps. 4) 30-40 min Cycling (intensity 60% max HR) **Diet:** 25-30% protein, 30-35% carbohydrate, 35-40% fat.	**Peak Work rate:** Increased after exercise (medians 75±80 to 75±70 watts (p=0.023) and 16% (+10 watts) after exercise and diet (Medians:63±55 to 73±55) (p=0.093) **$\dot{V}O_{2peak}$:** Increased 10%, (+2.0ml/min/kg) (Medians:20.2±7.3 to 22.2±4.6 ml/min/kg (p=0.009). after exercise and diet **VT:** No differences	**Arms extensors, Arm flexors, Leg extensors, Legs flexors:** No differences (MVC)	**VC:** No differences	**6MWT:** No differences **Walton score:** No differences. **General health:** Increased (p=0.03) after exercise and diet **Vitality**: Increased (p=0.03) after exercise and diet. **Other components:** No differences
Slonim et al. (2007)	104-520 (234±130)	7	**Aerobic exercise:** 1) 45-50 min treadmill (or cycle) Intensity 60-65% max HR 2)10-15 min upper body exercise. **Nutrition:** 25-30% protein, 30-35% Carbohydrate 35-40% fat + L-alanine 1.5g/day 4x/day.	-	-	**VC:** No differences	Difference between pre-NET slope of muscle function deterioration to that of post-NET slope was (-0.29 (95% CI, 0.19, 0.39) (p<0.0001).

Vibration Training							
Montagnese et al. (2016)	104	3	2 x 3 min standing 2 x 30 secs semi push up position.	-	**MRCss**: Increased 14% (+6 N) **Knee extension**: (MVC) Increased 44% (+35.5 bil. Nma) **Arm flection:** (MVC) Increased 77% (+29.6 bil. Nma)	**VC**: No differences	**6MWT**: Decreased 13% (-19 m) **TFTs and WGMS:** No differences
Khan, et al. (2009)	15	3	Cycle: 60 secs vibration on then 60 secs vibration off. 2 cycles initially then progressing to 4. Standing.	-	**Peak power:** increased 64% (+53 watts). **Knee extensors:** (MVC) Increased 17% (+6 Nm) **Flexors:** (MVC) Decreased 13% (-2 Nm)	**VC:** No differences	**6MWT:** Increased 70% (+116 m) **Mean grip:** No differences

CI, confidence interval; VC, vital capacity; VT, ventilatory threshold; WGMS, well-being markers included functional status; HR, Heart Rate; RPE, Rating of perceived exertion; MVC, Maximal Voluntary Muscle Contraction; RM, Repetition Maximum; 6MWT, Six Minute Walk Test; CAM, Computer aided manufacturing.

Table 5.5 GSD 2: Population Characteristics and Study Design.

Author (year)	Quality Rating	Participants with LOPD (age)	Study design
Martin et al. (1983)	Poor	*n*=1 (42 years)	Nonrandomised uncontrolled intervention trial
Mitja et al. (2015)	Fair	*n*=8 (13-58 years)	Longitudinal observational study
Aslan et al. (2014)	Fair	*n*=8 (23-64years)	Nonrandomised uncontrolled intervention trial
Wenninger et al. (2019)	Fair	*n*=11 (50±15.6 years)	Prospective monocentric unblinded single-arm pilot study A-B-C design
Jones et al. (2011)	Poor	*n*=2 (55 and 64 years)	Nonrandomised uncontrolled intervention trial
Jones et al. (2016)	Fair	*n*=8 (49.3±8.4 years)	A-B-A single subject experimental design
Jones et al. (2020)	Fair to Good	*n*=22 RMT: 12 patients (53.2±12.7 years) Sham-RMT:10 patients (46.6±13.9 years)	Double-blind randomised control trial

LOPD, late-onset Pompe disease; RMT, respiratory muscle training.

Table 5.6 Respiratory Muscle Training in GSD 2

					Outcomes		
Author (year)	**Duration (weeks)**	**Frequency (days/week)**	**Intensity (% MIP or MEP)**	**Protocol of sessions**	**Muscular Strength**	**Ventilatory function**	**Functional Capacity and Wellbeing**
Inspiratory Muscle Training							
Martin et al. (1983)	15	7	6-46 cmH_2O L/sec	15 min x 2/day.	**MIP:** Increased 45% (+27.0 cmH_2O) **MEP:** Increased 70% (+42.0 cmH_2O)	**FEV_1**: No differences **FVC:** Decreased 7% (-0.32)	
Mitja et al. (2015)	96	7	30	**Cycle:** 1′ at 30% MIP then 2′ deep slow breathing. 15 cycles per day for 45 min (15′ at 30% MIP and 30′ at rest with deep slow breathing)	**MIP:** Increased 18% (+5.6 cmH_2O). (p=0008). Improvements stable over the course of the study (p<0.05). **MEP:** No differences	**FVC:** No differences	**Gardner-Medwin-Walton scale:** No differences
Aslan et al. (2014)	8	≥5	30 initially, increased weekly by 2cmH_2O	15 min, twice/ day 80 sessions per patient	**MIP:** Increased 30% (+9.0 cmH_2O) (p=0.01) **MEP:** No differences	**FVC, FEV1, PCF:** No differences	**QoL:** **Social isolation scores:** Improved (Medians: 22.5 (22.1-69.8) to 0.0 (0.0-16.9) (p=0.02) **Other Subscores**: No differences **Sleep Quality:** No differences
Wenninger et al. (2019)	6 (+6 detraining + 40 optional training period)	5	30-40 initially then optional increase by 10-15.	30 min daily 7 x 15 inhalations each 525 IMT reps per week.	**MIP:** Increased 16% (+7.6 cmH_2O) (*p* =0.024) Increased 26% (+13.4 cmH_2O) ** (*p* =0.001) **MEP:** No differences.	**FVC, FEV1, Capillary capnometry:** No Differences	**6MWT, quality of life (SGRQ, MMRC-Dysnea scale):** No differences

Inspiratory and Expiratory Muscle Training							
Jones et al. (2011)	16-32	6	≥60	2 x 25 reps of IMT or EMT daily for 4 -10 weeks then both IMT and EMT	**MIP:** Increased 65% (+18.0 cmH_2O) **MEP:** Increased 39% (+17.0 cmH_20)	**FVC:** No differences*	
Jones et al. (2016)	12	5	60-70	3 x 25 reps of IMT and EMT daily. **Overall:** 4,500 reps IMT 4,500 reps EMT.	**MIP: I**ncreased 20% (+8.6 cmH_2O) **MEP:** Increased 16% (+11.6 cmH_2O)	**PCF:** Increased 12% (+1.0L/s)***	**6MWT:** Increased 2.2% (+7 m) **Supine to stand:** Decreased 13% (-1.6 s) **Stair climbing:** Decreased 15% (-0.6 s) **10m walk:** Decreased 3% (-0.3 s)
Author (year)	**Duration (weeks)**	**Frequency (days/week)**	**Intensity (% MIP or MEP)**	**Protocol of sessions**	**Muscular Strength**	**Ventilatory function**	**Functional Capacity and Wellbeing**
Jones et al. (2020)	12	5	**RMT:** 50-70 **Sham-RMT**: 15	3 x 25 reps of IMT and EMT daily. **Overall:** 4,500 reps IMT 4,500 reps EMT.	**MIP:** No differences (between groups) **MEP:** No differences (between groups) **Diaphragm Thickness:** No differences.	**PCF:** No differences **Polysomnography:** no differences	**Time to climb 4 steps:** Decreased 0.9s in RMT group Decreased 0.1s in Sham-RMT group (p=0.0346) **Daytime sleepiness (ESS):** Decreased 1.2 in RMT group Increased 1.1 in sham-RMT (p=0.0160)**.** (no raw data available) **Other gross motor function and patient reported outcomes:** No differences (between groups)

EMT, expiratory muscle training; ESS, daytime sleepiness; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IMT, inspiratory muscle training; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; PCF, peak cough flow; RMT, respiratory muscle training; 6MWT, Six Minute Walk Test; SGRQ, St. Georges Respiratory Questionnaire; - Not included;* Obtained 10 weeks after discontinuation of RMT in 1 patient and after approximately 6 months of RMT in the second patient; **After 6 weeks of training; ***Over the total study period of 52 weeks including 6 weeks of training, 6 weeks detraining and a 40 week optional training period.

5.5 Discussion

The aim of this review was to investigate the effectiveness of exercise training in adults with GSDs. Of the recognised 16 forms of GSDs (Heller et al., 2008) no data were available for 14, with exercise interventions only assessed in adults with GSD 5 or GSD 2. In GSD 5, aerobic exercise in five of the seven studies improved aerobic performance (Haller et al., 2006; Lucia et al., 2007; Mate-Munoz et al., 2007; Perez et al., 2007; Porcelli et al., 2016) with further benefits on functional capacity and well-being found by Lucia et al.(2007) and Perez et al.(2007) Strength training increased muscular strength and reduced disease severity (Santalla et al., 2014) **(Table 5.2)** and these improvements were found to be retained in all but one patient after a period of 2 months detraining (Santalla et al., 2014). In GSD 2, the literature shows that a combination of aerobic and strength training improves aerobic capacity, muscular strength, functional capacity and well-being **(Table 5.4)**. Furthermore, RMT improved respiratory muscular strength in all of the studies of GSD 2, with additional benefits in aerobic capacity, functional capacity and well-being shown by some **(Table 5.6)**. In the current literature, exercise training appears to be safe and beneficial to health in adults with GSD 5 and GSD 2 and thus there appears to be a growing body of evidence which suggests that supervised exercise training is safe and effective in improving aerobic capacity and muscle function in adults with GSD 5 or GSD 2. The literature base is limited, however, in both quality and quantity with a dearth of literature regarding exercise training in other GSD subtypes. Further research of robust design would be beneficial across the spectrum of GSDs.

5.5.1 Aerobic and strength training in GSD 5

Glycogen Storage Disease 5 is caused by a deficiency of myophosphorylase (PYGM), which impairs glycogenolysis specifically in skeletal muscle (Kanungo et al., 2018; Santalla et al., 2014; Scalco et al., 2020). This block in glycogenolysis limits glucose availability (via glycogen) and places greater reliance on blood glucose and non-esterified fatty acids to meet

the metabolic needs of skeletal muscle. During exercise, when the metabolic rate is elevated, the impairment in substrate availability can result in an acute energy crisis and result in pain, fatigue and contractures (Preisler et al., 2015; Scalco et al., 2020). In acute exercise of moderate intensity, these symptoms can subside as exercise duration persists beyond 10 min due to greater uptake of blood-borne glucose derived from the liver and fat oxidation in contracting muscles (Santalla et al., 2014; Scalco et al., 2020; Ørngreen et al., 2009; Vissing & Haller, 2003b). However, despite some improvement in exercise capacity during moderate intensity, during longer duration exercise people with GSD 5 still exhibit impaired exercise performance and aerobic capacity compared to a healthy population (Preisler et al., 2015; Santalla et al., 2014; Scalco et al., 2020). Due to this, the majority of studies in GSD 5 investigated the effect of aerobic training, which is hypothesised to increase exercise tolerance primarily through an improvement in aerobic capacity that is driven by a training-induced improvement in free fatty acid oxidation (the 'second wind' effect). In addition, aerobic training may also counteract the effects of a sedentary lifestyle, which can include an increased dependence of glycogen as a fuel, skeletal muscle atrophy and weakness, and poor cardiovascular fitness (Preisler et al., 2015).

The current literature supports the hypothesis that aerobic training improves exercise capacity in GSD 5 and provides evidence for the mechanisms involved in the improvement. Exercise capacity improved after aerobic training in adults with GSD 5 with increases in peak work rates reported in all studies that measured this outcome (n=5) (Haller et al., 2006; Lucia et al., 2006; Mate-Munoz et al., 2007; Perez et al., 2007; Porcelli et al., 2016). The magnitude of exercise performance gains was not only consistent but appeared substantial, with intervention studies reporting mean improvements in maximal cycling work rates ranging between 22% and 38% (Haller et al., 2006; Mate-Munoz et al., 2007; Porcelli et al., 2016) while case studies reported improvements between 61% and 103% (Lucia et al., 2007; Perez et al., 2007). Although the

improvements documented above are promising, the limited study quality hinders our ability to form strong conclusions and the effect of exercise training on exercise capacity is yet to be fully elucidated. It is likely that the greater exercise capacity following training is partly attributable to improvements in oxidative metabolism, with studies finding concurrent increases in $\dot{V}O_{2peak}$, indicative of an increase in cardiac output (Haller et al., 2006; Lucia et al., 2007; Mate-Munoz et al., 2007; Perez et al., 2007; Porcelli et al., 2016) and increased VT (Lucia et al., 2007). Improvements were even found in an individual with severe clinical features and the presence of two neuromuscular diseases (Lucia et al., 2007).

The magnitude of this training-induced change is in line with those found in a healthy population, indicating a similar relative capability to improve exercise performance and aerobic capacity, albeit from lower baseline values (Debusk et al., 1990).

The literature indicates that exercise training in GSD 5 elicits physiological adaptations at several steps of the oxygen cascade, which underpin the improvement in exercise and aerobic capacity, most notably improved cardiovascular function, and muscle oxidative metabolism. Cardiovascular function was markedly improved by training, with 15–24% increases in peak cardiac output (Haller et al., 2006; Porcelli et al, 2016) achieved via improvements in both peak HR (Lucia et al., 2007; Mate-Munoz et al., 2007; Perez et al., 2007) and peak stroke volume (SV) (Porcelli et al., 2016). Furthermore, lower heart rates were recorded during submaximal exercise, also indicating improved SV (Olivier et al., 2005; Porcelli et al., 2016). Although the changes in cardiovascular function are considerable and certainly beneficial to overall health (Laukkanen et al., 2001), they are likely to facilitate the training-induced improvements in aerobic and exercise capacity, rather than drive them. The primary training adaptation in GSD 5 patients is most likely related to improvements in skeletal muscle oxidative metabolism. In the most in-depth study, Porcelli et al. (2016) found that 12 weeks of cycling training at 65–70% max HR resulted in a reduction in the O_2 cost of submaximal exercise (15.8 ± 1.3 to 13.6

± 1.2 ml/ min/W, p = 0.03), faster pulmonary $\dot{V}O_2$ kinetics in those with slow $\dot{V}O_2$ kinetics before training and lower submaximal RER. These results indicate that skeletal oxidative metabolism is more efficient following training and that substrate utilisation during submaximal exercise is shifted towards greater free fatty acid utilisation. This is further supported by evidence of an increase in the mitochondrial enzymes citrate synthase and B-hydroxyacyl coenzyme A dehydrogenase (Haller et al., 2006; Mate-Munoz et al., 2007). However, these metabolic adaptations to exercise training were not uniform across studies, with Olivier et al. (2005) reporting no difference in sub max $\dot{V}O_2$ which is likely attributable to less total training sessions (24 sessions *versus* ⩾60 sessions by others) and Mate-Munoz et al. (2007) reporting no differences in GE, potentially due to exercising at a lower intensity compared to others **(Table 5.2)**. Due to the improvements in cardiorespiratory fitness shown, it is unsurprising that there were improvements in functional capacity (Quinlivan et al., 2011) and the ability to perform activities of daily living (Lucia et al., 2007; Perez et al., 2007) and QoL (Cakir et al., 2017). Surprisingly, despite improvements in outcomes of cardiorespiratory fitness (Peak work rate, $\dot{V}O_{2peak}$, GE, Peak SV and Peak cardiac output), Porcelli et al. (2016) found no improvements in habitual levels of physical activity or QoL. However, the post training measurements of physical activity and QoL were taken up to 3 months after the termination of training, thus if any improvements were made, they were not found to be sustained.

Strength training improved strength due, in part, to increases in total and lower body lean mass; these improvements appeared to reduce disease severity. However, these results are from just one small study, thus limiting the validity of findings to the wider population (Santalla et al., 2014). Overall, based on the literature reviewed, exercise may be an effective method of reducing symptoms in GSD 5 through improvements in aerobic and physical capacity.

5.5.2 Aerobic and strength training in GSD 2

Glycogen Storage Disease 2 is a GSD that also affects skeletal muscle; however, in contrast to GSD 5, the heterozygous mutation in the GAA gene is within the lysosomes and lysosomal glycogenolysis is blocked. As there is minimal contribution from lysosomal glycogen breakdown to ATP production, it is therefore not a deficiency in ATP resynthesis (Preisler et al., 2012). Instead, the deficiency of alpha-1,4-glucosidase causes an accumulation of lysosomal glycogen in skeletal, respiratory and cardiac muscle which leads to exercise intolerance and skeletal muscle weakness and wasting (Kanungo et al., 2018). A sedentary lifestyle further impacts exercise intolerance, with immobility causing skeletal muscle atrophy, weakness with a low $\dot{V}O_2$ and increased dependence of glycogen as fuel (Preisler et al., 2015). As GSD 2 primarily impacts muscle weakness, wasting and physical activity, all studies in adults with GSD 2 focussed on muscular interventions alone or in combination with aerobic training.

The literature shows that a combination of aerobic and strength training increased muscular strength, with improvements observed in three of the four studies which measured this (Leutholtz & Ripoll, 1996; Terzi et al., 2011; van den Berg et al., 2015). The studies that employed formal weight training protocols with clearly defined levels of resistance were able to increase strength by 5–100% **(Table 5.4)**; however, these were nonrandomised uncontrolled studies including 23 patients or less who exercised between 12 and 20 weeks (Leutholtz & Ripoll, 1996; Terzi et al., 2011; van den Berg et al., 2015). The trial which showed no improvement in strength employed resistance band training and a subjective marker of intensity, which may account for the lack of improvement (Sechi et al., 2020). Following improvements in muscle strength, subsequent increases in functional capacity were found, with increases in 6MWT (Terzi et al., 2011; van den Berg et al., 2015), time to climb 4 steps and rise to standing (van den Berg et al., 2015). The mechanisms underpinning the strength gains were not investigated in depth; however, increased lean body mass (LBM) accompanied strength gains

(Terzis et al., 2011), indicating participants may have undergone training-induced muscle hypertrophy. Indeed, the magnitude of the change in LBM found by Terzis et al.(2011) (+8.4%) is similar to that observed in a healthy population undergoing a similar strength training programme (+8.5%) (Narici et al., 1989). These results are encouraging, particularly as the quality of evidence appears greater compared to that of GSD 5 due to the inclusion of large sample sizes and inferential statistics.

Despite only two studies reporting on aerobic performance, significant improvements in maximum work rate (Sechi et al., 2020; van den Berg et al., 2015), $\dot{V}O_{2peak}$ and VT (van den Berg et al., 2015) were found indicating that exercise training in GSD 2 elicits physiological adaptations along the oxygen cascade as observed in GSD 5. Furthermore, the addition of a high protein diet appeared to elicit greater improvements in maximum work rate and an increase in $\dot{V}O_{2peak}$ (Sechi et al., 2020). Further to these improvements, reductions in fatigue and pain were also found (Favejee et al., 2015). Where aerobic, resistance exercise and diet were combined in an intervention lasting 2–10 years, a reduction in muscle function deterioration was observed, most likely being due to a reduction of glycogen and a reduction in proteolysis, autophagy and muscle damage (Marek et al., 1983; Slonim et al., 2007;). Furthermore, Sechi et al. (2020) found improvements in general health and vitality, which is unsurprising following the improvements in aerobic capacity.

Vibration training was shown to improve muscular strength (Khan et al., 2009; Montagnese et al., 2016), which could be due to muscle adaptations including type two myofiber hypertrophy and an increased muscle cross-sectional area (Schoser, 2015; Lochynski et al., 2013) and may explain improvements in 6MWT by Khan et al. (2009). Vibration training could therefore offer a time efficient and easily adopted mode of exercise (Khan et al., 2009; Montagnese et al., 2016); however, as results were derived from poor-quality case reports (Khan et al., 2009;

Montagnese et al., 2016), larger studies of enhanced quality are necessary before recommendations can be made.

In summary, all training modalities appear to benefit muscular strength and functional capacity, with improvements in aerobic performance where aerobic exercise is included.

5.5.3 Respiratory interventions in GSD 2

Progressive respiratory weakness is prevalent in LOPD (Wenninger et al., 2019) with symptoms such as nocturnal hypoventilation, diaphragm weakness or sleep apnoea becoming apparent before other muscle weakness (Margolis et al., 1994; Mellies et al., 2005; Mellies et al., 2011). Despite ERT, respiratory weakness persists in approximately one third of patients, in which respiratory muscle weakness can decline by approximately 3.2% MIP per year (Regnery et al., 2012; van der Beek et al., 2011). This leads to reduced airway clearance (Pitts et al., 2019) sleep disordered breathing and the requirement of ventilatory support towards the latter stages. In 70% of patients, this can even progress to premature death (Boentert et al., 2015). RMT was conducted in adults with LOPD as it offers a therapeutic option using pressure threshold respiratory trainers calibrated to provide inspiratory or expiratory resistance for forced voluntary inspiration/expiration muscle contractions (Jones et al., 2011). As inspiratory muscles are similar to skeletal muscle, they should respond to training and enhance ventilation with increased coordination, endurance and strength (Wenninger et al., 2019). IMT protocols were therefore conducted in all studies, aiming to target specific inspiratory muscle weakness (Jung et al., 2014). The literature shows that IMT increased inspiratory muscle strength, with MIP improving in six of seven studies (Aslan et al., 2014; Jones et al., 2011; Jones et al., 2016; Martin et al., 1983; Mitja et al., 2015). Improvements were observed after just 6 weeks (+15.7% MIP) (Wenninger et al., 2019), increased over the duration of training (Jones et al., 2011) and improvements were found to be maintained following training cessation (Jones et al., 2020; Jones et al., 2016; Wenninger et al., 2019). The addition of EMT to IMT also led to increased

expiratory muscle strength in the form of MEP (Jones et al., 2011; Jones et al., 2016). In the only randomised double-blind controlled trial by Jones et al. (2020) despite the magnitude of improvements in MIP and MEP being similar to others (Jones et al., 2011; Jones et al., 2016), no statistical differences were found between RMT and Sham-RMT arms due to the control arm appearing to elicit an active response. This study was also underpowered and despite randomisation there were differences in baseline characteristics between groups, with those assigned the treatment being older, on ERT for longer, and with increased respiratory muscle involvement. Interestingly, it appears EMT is necessary to elicit improvements in functional capacity (Jones et al., 2016; Jones et al., 2020) which may be due to the role of respiratory muscles in aiding truncal mobility and stabilisation (Alejaldre et al., 2012; Jung et al., 2014; Lee et al., 2013). The evidence appears to be of fair to good quality due to well-defined participant selection, repeat outcome measures and the inclusion of statistics. Isolating the effect of RMT on the outcomes reported is difficult as all studies included patients receiving ERT which is known to stabilise or even reduce respiratory decline (Bebi et al., 2010). However, improvements from ERT largely occur 12–26 weeks after treatment and are usually modest (3–4% for MIP and MEP) (Bembi et al., 2010; van der Ploeg et al., 2010). Patients had been receiving ERT for at least 10 months in the majority of studies prior to RMT; thus, the improvements shown were likely attributable to RMT alone (Jones et al., 2011; Jones et al., 2016; Jones et al., 2020; Mitja et al., 2015; Wenninger et al., 2019).

5.5.4 Safety and adherence

Aerobic exercise in GSD 5 was shown to be well tolerated in the two studies that reported this (Haller et al., 2006; Olivier et al., 2005), with no adverse effects such as muscle injury, contractures, rhabdomyolysis or myoglobinuria. Furthermore, aerobic exercise appeared safe in five studies in which the muscle damage marker creatine kinase (CK) remained stable (Haller et al., 2006; Olivier et al., 2005), or even decreased throughout the trial (Lucia et al.,

2007; Mate-Munoz et al., 2007; Perez et al., 2007). Adherence was only measured in one of the seven studies but was reported to be very good with 96% of training sessions completed, which was most likely due to the high levels of support provided, with weekly phone calls and encouragement given (Porcelli et al., 2016). Similarly, strength training in GSD 5 was well tolerated, with no adverse effects reported and CK remaining stable. In addition, patients were very complaint, with 100% of sessions completed in five of the seven participants (Santalla et al., 2014).

Aerobic and strength training in GSD 2 was reported to be well tolerated in the only study that reported on this, with no adverse events observed (Terzis et al., 2011) and safe with CK levels shown to decrease over the duration of the trial in the only other study that reported on this (van den Berg et al., 2015). Adherence was reported in four of the six studies (Favejee et al., 2015; Sechi et al., 2020; Slonim et al., 2007; van den Berg et al., 2015); however, only two studies provided data (Sechi et al., 2020; Slonim et al., 2007). Sechi et al. (2020) found adherence to exercise was good (61–74%) and Slonim et al. (2007) found 26 out of 34 patients were consistently compliant with the nutrition and exercise protocol. Similarly, both studies, including vibration training in GSD 2, found it to be well tolerated, with no adverse events reported and CK remaining stable. However, no measures of adherence were reported (Khan et al., 2009; Montagnese et al., 2016).

Respiratory interventions for GSD 2 were well tolerated with no adverse effects reported in three of the seven studies that reported this (Aslan et al., 2014; Jones et al., 2016; Wenninger et al., 2019). Where side effects were reported, the majority were mild and almost half were unrelated (Jones et al., 2020). Adherence was reported by three of the seven studies and of these it was reported to be excellent, with 107% (Wenninger et al., 2019), 99% (IMT sessions) and 101% (EMT sessions) (Jones et al., 2016) and 98% (treatment arm) and 97% (control arm) completion rates (Jones et al., 2020). Wenninger et al. (2019) found adherence to decrease over

the full duration of the study, with a drop of 13% (107 to 94%) training sessions completed over the total duration which included 6 weeks of detraining and then a 40-week optional training period.

Overall, aerobic, strength and respiratory muscle training appears to be safe and well tolerated with good adherence in GSD 2 and GSD 5 patients. However, this was only reported on in a limited number of studies and should be important factors to include in future studies.

5.5.5 Strengths and limitations

The major strength of this review is it is the first to systematically investigate the effectiveness of exercise training across the full spectrum of GSDs, using detailed and reproducible methodology with strict inclusion and exclusion criteria. Considering the full spectrum of GSDs allowed us to identify that exercise training interventions have only been studied in GSD 5 and GSD 2 disease, leaving 14 of the 16 GSD types unstudied. We also considered the effectiveness of several exercise training modalities, allowing us to consider the relative benefits of each for both GSD types.

The major limitation of this review was a lack of research into other GSDs, particularly others with skeletal muscle involvement (GSD 7, 9d, 10) and those with skeletal muscle and liver involvement (GSD 3, GSD 14), in which the effects of exercise on the skeletal and hepatic presentation could have been investigated (Kanungo et al., 2018; Preisler et al., 2013; Tegtmeyer et al., 2014). Furthermore, the potential impact of exercise on overall general health, fitness and QoL could have been investigated in non-muscular forms of GSDs (GSD 0a, GSD 1a, GSD 1b, GSD 6, GSD 9A1, GSD 9A2, GSD 9c) (Blair et al., 1995; Pedersen & Saltin, 2006). The majority of the studies included were deemed poor to fair quality, largely due to being uncontrolled, of small sample sizes including several case studies and of short duration. This deficit in study quality impacts interpretation; however, some limitations are to be

expected given the rarity of these diseases and the impact this has on recruitment. Regarding study design, it is important to acknowledge that there could have been a learning effect of the pre and post intervention tasks which may have impacted on the results reported. In addition, interpretation of the literature was also impaired by the heterogeneity of training interventions, which varied substantially in regard to modality, duration, intensity and the inclusion of other treatment strategies (e.g. ERT). In those receiving ERT, they had been on this for at least 1 year; therefore, the initial benefits of ERT would have stabilised and thus improvements observed were likely due to the interventions alone (Favejee et al., 2015; Montagnese et al., 2016; Sechi et al., 2007; van den Berg et al., 2015). Furthermore, staggered starts of studies showed patients remained relatively stable and exercise training and nutrition still reduced muscle deterioration in those not receiving ERT (Slonim et al., 2007).

5.5.6 Further research

Further RCTs and intervention studies should include adults with other GSDs particularly those with skeletal muscle involvement as part of larger multicentre randomised studies to clarify the effectiveness, safety and adherence of exercise training across the broad spectrum of GSDs. However, it is acknowledged this would be difficult given the rarity of these diseases. Comparison between individual exercise components within studies would offer greater insights into the most effective methods of training, with further research into vibration training and RMT warranted given the success in GSD 2. Further studies of longer duration with multiple follow-up periods would allow us to see if beneficial effects would be maintained long term and if exercise training has wider implications on preventing chronic diseases such as diabetes and cardiorespiratory disease (Olivier et al., 2005).

5.6 Conclusion

In conclusion, the current evidence shows exercise training appears to be safe and effective in adults with GSD 5 or GSD 2, with improvements observed in aerobic capacity, muscular strength and functional capacity. The effect of RMT in GSD 2, where sufficiently intense, was also found to be beneficial, with these improvements appearing to be maintained several months after training stopped. However, these findings are largely based on the limited quality of evidence available, largely derived from small uncontrolled intervention studies of short duration that included highly varied exercise protocols which limits the generalisation of findings. Further research of increased quality is required, particularly focussing on how exercise may benefit the clinical course of the disease across the broad spectrum of GSD types.

Chapter 6 - Barriers and Facilitators to Physical Activity in Glycogen Storage Disease: A Cross-Sectional Survey

6.1 Links with previous chapters

In **Chapter 5**, we highlighted the benefits of exercise as an intervention for those with GSDs, specifically GSD 2 and GSD 5. However, despite the benefits of exercise being acknowledged, the extent of exercise participation among the spectrum of GSD is unknown. To address this, **Chapter 6** aims to investigate physical activity levels, behaviours, barriers, facilitators, and preferences within the GSD population.

6.2 Introduction

We have previously demonstrated that a common feature across almost all GSDs is exercise intolerance, which tends to progress over time (**Chapter 3**; Decostre et al., 2017; Hijazi et al., 2021; Lucia et al, 2008). In addition, to progressive physical impairments, individuals frequently report high levels of mental fatigue and reduced motivation, further compounding their overall condition (Slipsager et al, 2024). These combined physical and mental health challenges are likely to increase sedentary behaviours, further elevating the risk of additional chronic health problems and metabolic complications (Stein & Wade, 2005).

Physical activity offers several potential benefits for those with GSDs, with growing evidence underscoring the positive impact of physical activity to alleviate symptoms and enhance QoL rather than worsening the condition (Preisler et al., 2015). For several years, researchers and clinicians have advocated for the therapeutic potential of physical activity for individuals with GSDs, with supervised training programs even included in clinical guidelines for GSD 2, GSD 3, GSD 5 and GSD 7 (Cupler et al., 2012; Kishnani et al., 2006; Kishnani et al., 2010; Lucia et

al, 2021). Certainly, physical activity has been found to be both safe and effective in adults with GSD 2 and GSD 5 in a systematic review, with benefits of supervised aerobic and/or resistance training leading to improvements in aerobic capacity ($\dot{V}O_{2peak}$), muscle strength, functional ability, disease severity, and overall well-being (**Chapter 5**). Furthermore, as with the general population, physical activity may further improve general health, fitness and QoL (Blair et al., 1995; Pedersen & Saltin, 2006).

Despite the widespread recognition of poor tolerance of physical activity and the acknowledged benefits of physical activity, no studies have thoroughly explored the extent of physical activity impairment, physical activity behaviours, or the perceived barriers and facilitators in this population. Furthermore, associated factors such as fatigue and motivation have yet to be explored. A wide variety of factors are known to influence participation in physical activity programs in the general population (Mbabazi et al., 2022), and individuals with GSDs face additional, unique challenges that warrant further exploration. Obtaining quantitative information on physical activity levels and identifying factors influencing physical activity participation are crucial for researchers and healthcare professionals to provide tailored support that fits patients' specific needs and lifestyles.

To address this gap in the literature, we conducted a cross-sectional survey which aims to take a comprehensive approach towards describing the current physical activity levels, behaviours, barriers and facilitators and physical activity preferences within those with GSDs. Furthermore, we aim to explore the association of contributing factors including dimensions of fatigue and motivation. It was anticipated that this would provide extensive and valuable information on physical activity levels and associated factors within and between different GSD subtypes, which may serve as a basis for designing physical activity interventions tailored to the specific needs of those with GSDs.

6.3 Methodology

6.3.1 Study Design

This cross-sectional study involved the distribution of an online survey to collect quantitative data on participants health, physical activity behaviours, barriers and facilitators and physical activity preferences. Ethical approval was obtained from Nottingham Trent University Non-Invasive Ethics Committee (Application 1565310).

6.3.2 Participants

Participants were included in the study if they met the following criteria: Adult patients (>=18 years) with a diagnosis of any type of GSD. Participants were excluded from the study if they did not have the capacity to consent.

6.3.3 Recruitment

Recruitment was conducted via advertisements on the Association for Glycogen Storage Community UK (AGSD UK) social media platforms. Interested participants were provided with an email link to the online survey with study information and contact details of researchers in order to ask any questions. All participants provided written informed consent to participate.

6.3.4 Data collection

The content of the online survey was based on the study aims and previous research of physical activity within various other comparable clinical populations (Blaney et al, 2013; Davergne et al, 2020; Karlsson et al, 2018; McPhail et al, 2014; Rodrigues et al, 2017; Slipsager et al, 2024). Patient members of AGSD UK (GSD 2, GSD 3a, GSD 5) and a metabolic consultant were involved in the development of the survey questions, with consideration to the burden of the study from a patient perspective and contributed to the dissemination plan.

6.3.4.1 Online Survey

An internet-based survey (Jisc Online Surveys: www.onlinesurveys.ac.uk) was opened on the 5th July 2023 for a period of 3 months. The survey was circulated in English via the AGSD UK Chief Executive, Chair and patient advocates and was designed to achieve the objectives of the study. The online survey was split into two parts. Part one comprised of four sections and obtained information on participants 1) Sociodemographic characteristics 2) Clinical characteristics including weight, height, diagnosed GSD, treatment, symptoms and comorbidities; 3) QoL (Short Form Health Survey, SF-36) (Ware & Sherbourne, 1992) 4) Physical activity (International Physical Activity Questionnaire Short Form, IPAQ-SF) (Craig et al., 2003; Lee et al., 2011), Behavioural regulation in exercise (BREQ-3 SF) (Markland & Tobin, 2004; Wilson et al., 2006) and Fatigue (Multi-Dimensional Fatigue Symptom Inventory, MFSI-SF) (Smets et al., 1995) **(Appendix I)**. Part two obtained information on 5) Physical activity behaviours; 6) Facilitators and Barriers to physical activity (IFAB Questionnaire, Davergne et al., 2020) and Section 7) covered information on activity programme preferences (Blaney et al., 2013, Personalised Exercise Questionnaire, Rodrigues et al., 2017) **(Appendix J)**.

6.3.4.1.1 Measurement tools

6.3.4.1.1.1 Quality of life

Quality of Life was assessed via the SF-36 v1.0 questionnaire as previously detailed in **Chapter 3**. Comparisons were made with normative values derived from the Office for National Statistics (ONS) omnibus survey of Britain (Burholt & Nash, 2011; Bowling et al., 1999). The SF-36 was chosen due to its reliability and validity in assessing health related QoL in the general population (Jenkinson et al., 1994) and within those with musculoskeletal disorders (Beaton et al., 1997).

6.3.4.1.1.2 Physical activity

Self-reported levels of physical activity were investigated using the International Physical Activity Questionnaire Short Form (IPAQ-SF; Craig et al., 2003; Lee et al., 2011) and included three questions about days and time of walking, moderate and vigorous activity and one question covering daily sedentary time over the last 7 days. The metabolic equivalent of task (MET) minutes per week (energy expended while performing various activities throughout the whole week) were calculated by multiplying weekly active time by intensity specific metabolic values as per IPAQ scoring instructions (Craig et al., 2003). The IPAQ-SF has consistently shown high reliability for assessing physical activity in in health (Craig et al., 2003; Deng et al., 2008; Dinger, Behrens & Han, 2006) and appears valid for use in clinical populations such as COPD (Flora et al., 2023).

6.3.4.1.1.3 Behavioural regulation in physical activity

The BREQ-3 SF (Markland & Tobin, 2004; Wilson et al., 2006) was used to assess behavioural regulation in exercise and thus different types of motivation and comprises of 5 subscales which include Identified regulation (2 items), Introjected regulation (2 items), Amotivation (2 items), Intrinsic regulation (2 items) and External regulation (2 items). Responses were provided on a 5-point Likert- type scale, ranging from 0 ("*not true for me")* to 5 ("*very true for me"*). The means of each subscale were calculated to provide multidimensional scores (Banger University, 2021). Each subscale score represents the level of that particular type of motivation, with higher scores indicating a greater presence of that motivational style. For example, a high score on Intrinsic regulation indicates that the individual activities for the enjoyment of the activity itself, while a high score on External regulation suggests they are motivated primarily by external factors, such as rewards or pressures (Banger University, 2021). The BREQ-3 was selected because it is a validated and reliable instrument for assessing behavioural regulations based on self-determination theory within the physical activity context (Wilson et al., 2006).

6.3.4.1.1.4 Fatigue

The validated Multidimensional Fatigue Inventory-Short Form (MFSI-SF; Smets et al., 1995) assessed participants levels of fatigue over the last 4 weeks. It consists of 30 items with 5 subscales including general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigour (Stein et al., 2004). Responses from a 5-point Likert-type scale ranging from 0 (*not at all*) to 4 (*extremely*) are summed to obtain subscale scores. A total fatigue score is calculated by summing the 4 fatigue subscales (general, physical, emotional, mental), then subtracting the vigour subscale. Higher scores indicate a higher level of fatigue. The MFSI-SF was selected due to its broad coverage of fatigue domains and as it been widely used within various chronic conditions, demonstrating strong reliability and validity particularly within cancer patients (Stein et al., 2004; Donovan et al., 2015).

6.3.4.1.1.5 Facilitators and Barriers to physical activity

Barriers and facilitators to physical activity were measured using the IFAB questionnaire which includes 10 items, with 4 assessing barriers or facilitators (scored from -10 to 10), 3 assessing barriers (scored -10 to 0) and 3 assessing facilitators (scored 0 to 10) with items related to psychological status (n=6) social support (n=2) disease (n=1) and environmental factors (n = 1). The total score ranges from -70 to 70, with higher scores indicative of an increased level of facilitators and/or a lower level of barriers (Davergne et al., 2020). This questionnaire has previously been shown to be a reliable and valid tool for assessing factors influencing physical activity in patients with rheumatoid arthritis (Davergne et al., 2020).

6.3.4.1.1.6 Physical activity preferences

The Personalised exercise questionnaire (PEQ) was utilised to assess physical activity preferences and consists of 38 questions across 6 domains including 1) support network; 2) access; 3) goals; 4) preferences; 5) feedback and tracking; and 6) barriers (Modified from Rodrigues et al., 2017). Section one has three questions and can have a maximum score of 3,

where “no”, “not sure”, and “not applicable” receive a score of 0 for each item, and “yes” a score of 1. A score of 3 indicates a strong support network and suggests an individual is more likely to participate in physical activity. Section two can have a maximum score of 6 and uses the same scale as section one. A higher score suggests participants have access to a sports facility, a good indication of activity participation. Section three can have a maximum score of 14. Higher scores indicate participants do not have a specific activity goal and may be exercising for overall health benefits. Lower scores should be individually studied to determine the respondents most important physical activity goal. Section five can have a maximum score of 3 with a higher score indicates participants would like to participate in feedback and tracking methods, while a lower score, less feedback. Sections four (“my exercise preferences”) and six (“my exercise barriers”) do not have an overall score and facilitators and barriers in the PEQ were examined by studying each item (Rodrigues et al., 2017). The PEQ has been found to be a strong and reliable tool for assessing physical activity-related perceptions, barriers and facilitators in those with low bone mass and osteoporosis (Rodrigues et al., 2019).

6.3.5 Data Analysis

Quantitative data was entered into Microsoft Excel, checked for accuracy and analysed using descriptive statistics (mean, median, standard deviation and percentage). The data analysis was conducted using SPSS statistical software version 28.0 (IBM Corporation, Armonk, NY, USA). As a preliminary analytical step, and all data were checked for normality. The Kolmogorov–Smirnov test was used to check the distribution of data. The data showed a not normal distribution, consequently Spearman correlation analysis was conducted to determine the correlation between weekly physical activity, the multidimensional nature of fatigue (MFSI-SF) and behavioural regulation in exercise (BREQ-3 SF).

6.4 Results

6.4.1 Participant Characteristics

A total of 55 participants completed part one of the survey, and a total of 18 participants completed part two. Demographic and clinical characteristics of all respondents are shown in **Table 6.1**. Overall, the mean age of respondents was 56 years (±15), in which the majority were male (*n*=28, 51%), of white-English/Welsh/Scottish/Northern Irish/British ethnicity (n=47, 85%), with a mean body weight and BMI of 79kg (±18) and 27kg/m^2 (±5). On the whole, a variety of GSD types and clinically established methods of diagnosis were reported, with the type 5 being the most common (*n*=28, 51%) and most frequently diagnosed via biopsy (n=20, 71%) and/or genetic testing (n=14, 50%). Thirty-three percent (*n*=18) of all respondents were reported to be on dietary treatment, in which all of the GSD 5 respondents reported to be on either a low carbohydrate diet (*n*=5, 83%) or specifically a ketogenic diet (*n*=1, 17%). In contrast, in those with GSDs with solely liver involvement, including GSD 1a and GSD 1b who were on dietary treatment, carbohydrates were important, with a combination of uncooked cornstarch, carbohydrate feeds and small frequent carbohydrate meals used in all participants (*n*=5, 100%). In addition, over half of all respondents (*n*=28, 51%) regularly consumed dietary supplements, particularly vitamin D (*n*=20, 36%) and/ or a multivitamin (*n*=13, 24%). Long term health conditions were reported in almost half of all respondents (*n*=26, 47%), which reportedly impacted daily activities to a variable degree in the majority (*n*=22, 85%).

6.4.2 Symptoms, QoL and Fatigue

6.4.2.1 Symptoms

Table 6.2 reports on the symptoms associated to GSD and the QoL and Fatigue of respondents (*n*=55). The vast majority (*n*=52, 95%) reported that GSD impacted daily activities, with all but one reporting to experience symptoms associated to GSD (*n*=54, 98%). Muscle weakness

(*n*=42, 89%), tiredness (*n*=36, 67%) and muscle cramps (*n*=27, 50%) were particularly common; however, symptoms were variable between individuals and GSD subtypes. As expected, GSDs with muscle involvement (GSD 2, GSD 3a, GSD 4, GSD 5, GSD 9d, *n*=47) reported to suffer from muscular symptoms, with muscular weakness (*n*=42, 89%) and high levels of muscle pain, aches and cramps (*n*=29, 62%) reported. Fixed contractures were particularly common in GSD 5 (*n*=25, 89%), with 29% (*n*=8) reported to have visited hospital due to the effects of contractures/rhabdomyolysis, whereas muscle weakness was a prominent feature of GSD 2 (*n*=9, 69%). Across all GSDs, 51% (*n*=24) of respondents felt they were unable to engage in physical activity due to muscle weakness and 40% (*n*=19) reported to avoid physical activity for fear of muscle pain or contractures. In addition to muscular symptoms, breathing problems were common in GSD 2 (*n*=9, 69%), and low blood sugar (*n*=4, 100%) in GSD 3a, where there is additional liver involvement. Moreover, low blood sugars (*n*=4, 57%) and tiredness (*n*=6, 86%) were predominant symptoms those GSDs with solely liver involvement.

6.4.2.2. Quality of Life

Overall, self-reported QoL was lower across all of the SF-36 domains compared to normative values (**Tabe 6.2**; Bowling et al., 1999; Burholt & Nash, 2011), particularly in the domains of physical functioning (43±34 vs. 90±19) and role limitation (physical) (37±100 vs. 84±33), whereas mental health variables were less affected with emotional wellbeing only minimally impaired (70±20 vs. 77±18). Within GSD 2, the physical function (13±17 vs. 90±19), role limitation (physical) (31±50 vs 84±33) and social functioning domains (40±28 vs 89±21) were particularly reduced, in contrast to emotional wellbeing (63±21 vs. 77±18) and role limitation (emotional) (54±100 vs. 88±29). GSD 5 showed a similar pattern, with reductions in physical functioning and role limitations but to a much lesser extent, and emotional wellbeing (76±17 vs. 77±18) and social functioning only minimally impaired (73±25 vs. 89±21). In contrast,

those with GSDs with solely liver involvement, such as GSD 9a reported minimal reductions compared to normative values in physical functioning (88±20 vs. 90±19) and role limitation (physical) (83±25 vs. 84±33).

6.4.2.3 Fatigue

With regards to fatigue, across all respondents, scores were highest in the domain of general fatigue (12±7), followed by vigour (11±5), with the mean intensity of total fatigue score 22±22. Total fatigue was reported to be particularly high (32±19) in those with GSD 2, with increased scores in the domains of physical (13±5) and general fatigue (15±6) compared to mental fatigue (4±3) and emotional fatigue (6±7) **(Table 6.2)**.

6.4.3 Physical activity levels and behaviours

6.4.3.1 Physical Activity

Physical activity and behavioural regulation in exercise of respondents is displayed in **Table 6.3.** The results of the survey showed that the majority of respondents (*n*=27, 49%) had low physical activity levels according to IPAQ categories (<600 MET-minutes per week in total), particularly those with GSD 4 (*n*=1, 100%), GSD 2 (*n*=11, 85%) and GSD 3a (*n*=3, 75%). In contrast, just over half of GSD 5 (*n*=15, 54%) respondents reported to be moderately physically active, with 11% (*n*=3) reporting high activity levels. The respondent's physical activity was also expressed as MET minutes/week. Overall, the mean total MET minutes/week was 1561±2603, with the majority of MET minutes spent walking (762 ± 1126). Distinctly reduced total weekly MET minutes in GSD 2 was evident (303 ± 563 min) compared to GSD 3a, GSD 5 and GSD 9d; with the majority of physical activity in GSD 2 being walking (256 ± 420 min) and no vigorous activity reported. Conversely, those with GSD 5 reported much higher total weekly MET minutes compared to GSD 2, GSD 3a and GSD 4, with notably increased walking (1020 ± 1322 min), moderate (439 ± 986 min) and vigorous activity (467 ± 1336 min). With

regards to behavioural regulation in exercise, the majority of respondents showed higher intrinsic motivation (1.64 (1.30)), which refers to motivation driven by the inherent enjoyment and satisfaction from the activity itself, without any external incentives, such as exercising because it is fun or fulfilling (Havnen et al., 2023). In contrast, lower external regulation (0.38 (0.73)) was observed across the majority of respondents, which is defined as motivation driven by external rewards or pressures (e.g., exercising to receive praise or avoid punishment) (Havnen et al., 2023).

6.4.3.2 Associations between Physical activity, Fatigue and Behavioural Regulation in Exercise

The correlation analysis of physical activity and dimensions of fatigue is presented in **Table 6.4.** The results showed that participants physical activity levels were negatively correlated to general fatigue (r_s (53)= -0.41, p=0.002); physical fatigue (r_s (53)= -0.46, p<0.001) and total fatigue (r_s (53)= -0.47, p<0.001). Whereas, participants physical activity levels were positively correlated with vigour fatigue, r_s (53)= 0.54, p<0.001). The correlation analysis of physical activity and dimensions of behavioural regulation in exercise is presented in **Table 6.5.** A positive correlation between participants physical activity levels and identified regulation (r_s (53)= 0.36, p=0.006) and intrinsic regulation (r_s (53)=0.555, p<0.001) was observed. In contrast, a negative correlation was found between participant physical activity levels and Amotivation (r_s (53)=- 0.46, p<0.001).

6.4.3.3 Physical activity Behaviours

Eighty-nine percent of all respondents (*n*=16) reported to engage in a variety of physical activity, with cardiovascular/aerobic activity (e.g. running, walking, cycling, swimming) (n=13, 81%), resistance training (*n*=5, 31%), yoga/pilates (*n*=6, 38%) and/or "other" activities (*n*=6, 38%) most frequently reported **(Table 6.6)**. Eighty-one percent of all respondents (*n*=13) engaged in physical activity at least 4 times per week, either at home (*n*=9, 56%) and/or in

public outdoor spaces (*n*=7, 44%), usually alone (*n*=10, 63%) and/or with friends/family members (*n*=4, 25%). The majority of all respondents reported that they engage in physical activity to improve or maintain physical heath (*n*=11, 69%) and mental health (*n*=9, 56%) but this was highly variable between individuals and GSD types. In GSD 5, the majority engaged in cardiovascular/aerobic activities (*n*=4, 100%) and resistance training with free weights/machines (*n*=3, 75%) 4 or more times per week (*n*=3, 75%) to improve physical (*n*=4, 100%) and/or mental health (*n*=3, 75%). GSD 2 respondents also reported to engage in physical activity 4 or more times per week (*n*=3, 100%), however compared to GSD 5 respondents, only 67% (*n*=2) engaged in cardiovascular/aerobic activities, with the majority reporting to engage in physical activity alone (*n*=2, 67%) and all at home (*n*=3, 100%) reportedly to improve or maintain physical health (*n*=3, 100%). Of those respondents that did not engage in physical activity (*n*=2, 14%), a lack of motivation, other health problems and a lengthy recovery time were detailed as reasons.

6.4.4 Barriers and Facilitators of Physical Activity

The personalised exercise questionnaire (PEQ) **(Table 6.8)** showed 83% (*n*=15) of all respondents reported to have barriers to physical activity which included not wanting to injure themselves (*n*=6, 35%) (particularly in GSD 3a, *n*=3, 60%), not wanting to fall (*n*=3, 18%), feeling bored when physically active (*n*=4, 24%) feeling pain when physically active (*n*=3, 18%) and not liking physical activity (*n*=2, 12%). Furthermore, not having time (*n*=8, 47%) and mobility (*n*=5, 29%) were prominent barriers. Notably, almost all (*n*=15, 83%) reported that they would spend more time being physically active if they had fewer barriers. The influence of perceived barriers and facilitators for physical activity in all respondents (*n*=18) is displayed in **Table 6.7**. The overall total IFAB score was -0.9 (+18.8), median -2.0, with the main barriers including the level of symptoms (-3.9 (5.7), a belief that physical activity will make symptoms worse (-2.7 (3.8) and a lack of motivation (-2.7 (3.3). In contrast, the

knowledge of the benefits of physical activity to mood (4.8 (3.8) and the knowledge of the benefit of physical activity to health (4.5 (3.7) were the main facilitators. GSDs with solely liver involvement had positive IFAB scores, indicating more facilitators in comparison to those with muscle involvement, in which the level of symptoms was the primary barrier.

6.4.5 Physical activity programme preferences

The survey showed that 86% (*n*=12) of all respondents would be interested in taking part in a physical activity programme, with 56% (*n*=10) reported as able to take part and 39% (*n*=7) unsure **(Table 6.9)**. Overall, there was interest in a wide variety of activities **(Figure 6.1a)** with strengthening activities (*n*=13, 81%), flexibility (*n*=8, 50%), walking (*n*=7, 44%) and swimming (*n*=7, 44%), of preference, particularly among those with GSD 2. There was a particular preference for strengthening activities among those with GSD 3a (*n*=3, 75%), GSD 5 (*n*=3, 75%) and GSD 9a (*n*=2, 100%). Overall, the preferred intensity of activity was variable, with the majority of respondents preferring either light or light to moderate activity (*n*=9, 56%), particularly in GSD 2 and 3a. **(Figure 6.1b)**, whereas 50% (*n*=2) of those with GSD 5 had a preference for vigorous activity. The majority of all respondents preferred to be physically active for at least 20 minutes (*n*=11, 69%), at least twice per week (n=10, 66%) at variable times of day **(Figure 6.1c, 6.1d)**. Of all respondents, 50% (n=8) had no preference on who they would prefer to be physically active with, where there was a preference, the majority reported a preference towards engaging in physical activity alone (*n*=4, 25%) or with other GSD patients (*n*=3, 19%). Similarly, fifty percent of respondents (*n*=8) had no preference on where the activity should take place, but those with a preference preferred home-based activity (*n*=4, 25%). Overall, 47% (*n*=7) reported a preference for the physical activity to be delivered by a professional, including a physiotherapist, healthcare/fitness instructor or clinical exercise physiologist. Almost all of the total respondents preferred to receive information on available

physical activity programmes by email (*n*=14, 88%) but had no preference of whom they would like to receive this information from (*n*=11, 69%).

Table 6.1 Demographic and Clinical Information of respondents (*n*=55)

Variables	**All (*n*=55)**	**1a (*n*=2)**	**1b (*n*=3)**	**2 (*n*=13)**	**3a (*n*=4)**	**4 (*n*=1)**	**5 (*n*=28)**	**9a (*n*=3)**	**9d (*n*=1)**
Age (years): Mean (SD)	56 (15)	39 (28)	34 (1)	58 (15)	42 (12)	35 (0)	62 (14)	43 (7)	60 (0)
Sex									
Male	28 (51%)	1 (50%)		11 (85%)	3 (75%)		9 (32%)	3 (100%)	1 (100%)
Female	26 (47%)	1 (50%)	3 (100%)	2 (15%)	1 (25%)	1 (100%)	18 (64%)		
Prefer not to say	1 (2%)						1 (4%)		
Ethnicity									
White-English/Welsh/Scottish/Northern Irish/British	47 (85%)	1 (50%)	2 (67%)	11 (85%)	4 (100%)	1 (100%)	25 (89%)	3 (100%)	
White- Irish	2 (4%)						1 (4%)		1 (100%)
White-Any other white background	1 (2%)			1 (8%)					
Asia/Asian British Pakistani	4 (7%)	1 (50%)	1 (33%)	1 (8%)			1 (4%)		
Prefer not to say	1 (2%)						1 (4%)		
Anthropometry	**(*n*=49)**	**(*n*=1)**		**(*n*=10)**			**(*n*=25)**		
Body weight (kg): Mean (SD)	79 (18)	85 (0)	67 (6)	88 (17)	76 (10)	75 (0)	77 (20)	87 (24)	69 (0)
Body Mass Index (kg/m^2): Mean (SD)	27 (5)	30 (0)	27 (1)	27 (4)	24.54 (6)	29 (0)	27 (5)	27 (7)	22 (0)
Treatment									
Number reported to be on dietary treatment	18 (33%)	2 (100%)	2 (100%)	2 (15%)	4 (100%)	1 (100%)	6 (21%)	0 (%)	1 (100%)
Type of dietary treatment	**(*n*=19)**			**(*n*=2)**	**(*n*=4)**	**(*n*=1)**	**(*n*=6)**		**(*n*=1)**
Uncooked Cornstarch	3 (16%)	1 (50%)	1 (33%)		1 (25%)				
Uncooked cornstarch & Carbohydrate tube feed during the night	1 (5%)		1 (33%)						
Uncooked cornstarch, Carbohydrate tube feed during the night & small frequent carbohydrate meals	1 (5%)		1 (33%)						
Complex Carbohydrate & high protein	4 (21%)			1 (50%)	2 (50%)				1 (100%)
Carbohydrate feed during the night	1 (5%)	1 (50%)							
High protein	1 (5%)			1 (50%)					
Low carbohydrate diet	5 (26%)						5 (83%)		
Ketogenic diet	2 (11%)				1 (25%)		1 (17%)		

Ketogenic & low GI diet	1 (5%)					1 (100%)			
Dietary supplements consumed (>3 times/week)	**(*n*=55)**	**(*n*=2)**	**(*n*=3)**	**(*n*=13)**	**(*n*=4)**	**(*n*=1)**	**(*n*=28)**	**(*n*=3)**	**(*n*=1)**
None	27 (49%)			4 (31%)			19 (68%)	3 (100%)	1 (100%)
Calcium	3 (5%)		1 (33%)	1 (8%)	1 (25%)				
Iron	2 (4%)						2 (7%)		
Vitamin D	20 (36%)	2 (100%)	2 (67%)	8 (62%)	2 (50%)	1 (100%)	5 (18%)		
Multivitamin	13 (24%)	1 (50%)	1 (33%)	4 (31%)	3 (75%)		4 (14%)		
Multivitamin & Mineral	3 (5%)		1 (33%)	1 (8%)		1 (100%)			
Omega-3 fish oil	9 (16%)		1 (33%)	2 (15%)	3 (75%)		3 (11%)		
Other	7 (13%)	1 (50%)	1 (33%)	2 (15%)	1 (25%)		2 (7%)		
Suffering from other long term health condition(s)?									
Yes	26 (47%)		1 (67%)	7 (54%)	1 (25%)	1 (100%)	15 (54%)	1 (33%)	
No	28 (51%)	1 (50%)	2 (33%)	6 (46%)	3 (75%)		13 (46%)	2 (67%)	1 (100%)
Prefer not to say	1 (2%)	1 (50%)							
How much other long term health condition(s) impacts daily activities	**(*n*=26)**		**(*n*=1)**	**(*n*=7)**	**(*n*=1)**	**(*n*=1)**	**(*n*=15)**	**(*n*=1)**	
Not at all	4 (15%)			1 (14%)			3 (20%)		
A little	7 (27%)			2 (28%)	1 (100%)		4 (27%)		
Somewhat	5 (19%)			2 (28%)			3 (20%)		
Quite a bit	7 (27%)		1 (100%)	2 (28%)		1 (100%)	3 (20%)		
A lot	3 (12%)						2 (13%)	1 (100%)	

Table 6.2 Symptoms, QoL and Fatigue of respondents (*n*=55)

	All (*n*=55)	**1a (*n*=2)**	**1b (*n*=3)**	**2 (*n*=13)**	**3a (*n*=4)**	**4 (*n*=1)**	**5 (*n*=28)**	**9a (*n*=3)**	**9d (*n*=1)**
Impact of GSD on daily activities									
Not at all	3 (5%)						1 (4%)	2 (67%)	
A little	9 (16%)	2 (100%)					7 (25%)		
Somewhat	14 (25%)		1 (33%)		2 (50%)	1 (100%)	9 (32%)	1 (33%)	
Quite a bit	12 (22%)		2 (67%)	2 (15%)			7 (25%)		1 (100%)
A lot	17 (31%)			11 (85%)	2 (50%)		4 (14%)		
Number reported to experience symptoms associated to GSD	54 (98%)	2 (100%)	3 (100%)	13 (100%)	4 (100%)	1 (100%)	28 (100%)	2 (67%)	1 (100%)
Current symptoms associated to GSD*	**(*n*=54)**	**(*n*=2)**	**(*n*=3)**	**(*n*=13)**	**(*n*=4)**	**(*n*=1)**	**(*n*=28)**	**(*n*=2)**	**(*n*=1)**
Low blood sugar	12 (22%)	1 (50%)	3 (100%)		4 (100%)		4 (14%)		
Muscle weakness	42 (89%)			12 (92%)	3 (75%)	1 (100%)	25 (89%)		1 (100%)
Muscle Cramps	27 (50%)		1 (33%)	7 (54%)	2 (50%)	1 (100%)	15 (54%)		1 (100%)
Tiredness	36 (67%)	2 (100%)	3 (100%)	9 (69%)	4 (100%)	1 (100%)	15 (54%)	1 (50%)	1 (100%)
Obesity	9 (17%)		1 (33%)	2 (15%)	1 (25%)		4 (14%)	1 (50%)	
Problems with bleeding and blood clotting	3 (6%)	1 (50%)		1 (8%)			1 (4%)		
Kidney problems	2 (4%)	1 (50%)					1 (4%)		
Low resistance to infections	7 (13%)	1 (50%)	1 (33%)	3 (23%)			2 (7%)		
Breathing problems	15 (28%)		1 (33%)	9 (69%)		1 (100%)	4 (14%)		
Heart problems	6 (13%)			1 (8%)	2 (50%)		3 (11%)		
Mouth Sores	3 (6%)					1 (100%)	1 (4%)	1 (50%)	
Gout	5 (9%)	1 (50%)		1 (8%)	1 (25%)		2 (7%)		
Other	8 (15%)		1	4 (31%)	1 (25%)		1 (4%)	1 (50%)	
Muscular Symptoms	**(*n*=47)**	**(*n*=2)**	**(*n*=3)**	**(*n*=13)**	**(*n*=4)**	**(*n*=1)**	**(*n*=28)**	**(*n*=3)**	**(*n*=1)**
Suffer from muscular symptoms	47 (100%)	2 (100%)	1 (33%)	13 (100%)	4 (100%)	1 (100%)	28 (100%)	0 (100%)	1 (100%)
Experience high levels of muscle pain, aches and cramps	29 (62%)	1 (50%)	1 (33%)	8 (62%)	2 (50%)	1 (100%)	18 (64%)		0 (0%)
Experienced fixed contractures	30 (64%)	1 (50%)	0 (0%)	2 (15%)	2 (50%)	0 (0%)	25 (89%)		1 (100%)
Visited hospital due to the effects of contractures/rhabdomyolysis	9 (19%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	8 (29%)		0 (0%)
Unable to exercise due to muscle weakness?	24 (51%)	0 (0%)	0 (0%)	9 (69%)	1 (25%)	1 (100%)	13 (46%)		0 (0%)
Avoid exercise for fear of muscle pain or fixed contractures	19 (40%)	0 (0%)	0 (0%)	2 (15%)	1 (25%)	1 (100%)	15 (54%)		0 (0%)

QoL Scores (SF-36)	**Normative values (*n*=2051)**	**All (*n*=55)**	**1a (*n*=2)**	**1b (*n*=3)**	**2 (*n*=13)**	**3a (*n*=4)**	**4 (*n*=1)**	**5 (*n*=28)**	**9a (*n*=3)**	**9d (*n*=1)**
Physical Functioning: Mean (SD)	90 (19)	43 (34)	78 (18)	72 (24)	13 (17)	33 (25)	15 (0)	47 (31)	88 (20)	90 (0)
Role Limitation (physical) Mean (IQ range)	84 (33)	37 (100)	38 (38)	33 (50)	31 (50)	13 (25)	25 (0)	41 (100)	83 (25)	0 (0)
Role Limitation (emotional) Mean (IQ range)	88 (29)	58 (100)	50 (50)	33 (50(	54 (100)	42 (25)	100 (0)	64 (75)	67 (50)	0 (0)
Energy/Fatigue: Mean (SD)	65 (21)	37 (23)	35 (14)	52 (18)	25 (18)	36 (13)	5 (0)	42 (25)	42 (38)	25 (0)
Emotional Wellbeing: Mean (SD)	77 (18)	70 (20)	76 (23)	57 (17)	63 (21)	63 (19)	64 (0)	76 (17)	61 (37)	60 (0)
Social Functioning: Mean (SD)	89 (21)	62 (30)	81 (27)	54 (44)	40 (28)	47 (28)	63 (0)	73 (25)	71 (31)	38 (0)
Pain: Mean (SD)	83 (35)	54 (25)	84 (23)	53 (13)	44 (24)	69 (25)	13 (0)	53 (25)	97 (6)	45 (0)
General Health: Mean (SD)	74 (22)	44 (26)	60 (35)	30 (25)	28 (21)	31 (11)	10 (0)	54 (24)	55 (35)	45 (0)
Fatigue Intensity (MFSI-SF)										
Physical Fatigue: Mean (SD)		9 (6)	6 (1)	4 (4)	13 (5)	8 (1)	20 (0)	8 (6)	2 (4)	8 (0)
Mental Fatigue: Mean (SD)		6 (5)	8 (4)	10 (6)	4 (3)	5 (4)	16 (0)	6 (5)	6 (6)	6 (0)
Emotional Fatigue: Mean (SD)		6 (5)	6 (0)	7 (5)	6 (7)	5 (5)	9 (0)	4 (4)	10 (10)	6 (0)
Vigour: Mean (SD)		11 (5)	13 (1)	10 (7)	7 (4)	10 (3)	7 (0)	12 (5)	12 (7)	13 (0)
General Fatigue: Mean (SD)		12 (7)	9 (2)	11 (3)	15 (6)	11 (3)	24 (0)	10 (7)	11 (12)	18 (0)
Total fatigue: Mean (SD)		22 (22)	16 (8)	22 (15)	32 (19)	20 (12)	62 (0)	17 (23)	17 (39)	25 (0)

Table 6.3 Physical Activity and Behavioural Regulation in Exercise of respondents (*n*=55)

Physical Activity (IPAQ-SF) **Self-reported Physical Activity levels (MET/week)**	**All (*n*=55)**	**1a (*n*=2)**	**1b (*n*=3)**	**2 (*n*=13)**	**3a (*n*=4)**	**4 (*n*=1)**	**5 (*n*=28)**	**9a (*n*=3)**	**9d (*n*=1)**
MET-Walking: Mean (SD)	762 (1126)	1518 (2503)	198 (280)	256 (420)	693 (1386)	264 (0)	1020 (1322)	253 (382)	1386 (0)
MET-Moderate: Mean (SD)	371 (876)	840 (1188)	400 (302)	46 (166)	900 (1800)	0 (0)	439 (986)	267 (395)	240 (0)
MET-Vigorous: Mean (SD)	428 (1256)	3000 (4243)	560 (771)	0 (0)	0 (0)	0 (0)	467 (1336)	507 (441)	1280 (0)
MET-Total: Mean (SD)	1561 (2603)	5358 (7484)	1092 (751)	303 (563)	1593 (3186)	264 (0)	1925 (2818)	1026 (1069)	2906 (0)
Low (%)	27 (49%)	1 (50%)		11 (85%)	3 (75%)	1 (100%)	10 (36%)	1 (33%)	
Moderate (%)	21(38%)		2 (67%)	2 (15%)	0 (0%)		15 (54%)	2 (67%)	

High (%)	7 (13%)	1 (50%)	1 (33%)		1 (25%)		3 (11%)		1 (100%)
Behavioural Regulation in Exercise (BREQ-3 SF)									
Identified regulation	1.42 (0.86)	2.00 (0.00)	2.00 (0.50)	1.19 (0.99)	1.13 (0.25)	2.00 (0.00)	1.43 (0.89)	1.33 (1.15)	2.00 (0.00)
Introjected regulation	1.41 (1.11)	1.25 (1.77)	2.17 (1.04)	1.38 (1.08)	1.38 (0.48)	3.00 (0.00)	1.38 (1.18)	0.50 (0.87)	2.00 (0.00)
Amotivation	0.90 (1.30)	2.00 (2.83)	0.00 (0.00)	1.27 (1.44)	1.13 (0.85)	0.00 (0.00)	0.79 (1.26)	0.83 (1.44)	0.00 (0.00)
Intrinsic regulation	1.64 (1.30)	2.50 (2.12)	2.83 (0.58)	1.0 (1.22)	1.63 (0.75)	0.00 (0.00)	1.64 (1.25)	2.67 (1.53)	3.00 (0.00)
External regulation	0.38 (0.73)	0.00 (0.00)	0.17 (0.29)	0.31 (0.52)	0.0 (0.0)	0.00 (0.00)	0.59 (0.90)	0.00 (0.00)	0.00 (0.00)

Table 6.4 Spearman Rank-Order Correlations between Weekly Physical Activity and dimensions of Fatigue (MFSI-SF)

	Physical Activity (MET min/week)
Physical Fatigue	-0.463***
Mental Fatigue	-0.090
Emotional Fatigue	-0.221
Vigor Fatigue	0.544***
General Fatigue	-0.413**
Total Fatigue	-0.467***

**Indicates p=0.002 ***Indicates p<0.001

Table 6.5 Spearman Rank-Order Correlations Between Weekly Physical Activity and dimensions of Behavioural Regulation in Exercise (BREQ-3)

	Physical Activity (MET min/week)
Identified Regulation	0.364**
Introjected Regulation	0.195
Amotivation	-0.460***
Intrinsic Regulation	0.555***
External Regulation	0.074

**Indicates p=0.006 ***Indicates p<0.001

Table 6.6 Physical Activity Behaviours of respondents (*n*=18)

	All (*n*=18)	**1b (*n*=2)**	**2 (*n*=4)**	**3a (*n*=4)**	**5 (*n*=5)**	**9a (*n*=2)**	**9d (*n*=1)**
Do you engage in exercise?							
Yes	16 (89%)	2 (100%)	3 (75%)	4 (100%)	4 (80%)	2 (100%)	1 (100%)
No	2 (14%)		1 (25%)		1 (20%)		
Exercise behaviours in Exercisers	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
What types of exercise do you typically engage in? *							
Cardiovascular/aerobic exercise (*e.g.,* running, walking, cycling, swimming)	13 (81%)	2 (100%)	2 (67%)	2 (50%)	4 (100%)	2 (100%)	1 (100%)
Resistance training with free-weights/machines	5 (31%)	1 (50%)		1 (25%)	3 (75%)		
Bodyweight exercises (*e.g.,* push-ups, pull-ups, sit-ups)	4 (25%)	1 (50%)		1 (25%)		2 (100%)	
Yoga/Pilates (or similar mobility-based exercise)	6 (38%)	1 (50%)	1 (33%)	1 (25%)	1 (25%)	1 (50%)	1 (100%)
Competitive sport (*e.g.,* tennis, football, golf, netball)	4 (25%)	1 (50%)		1 (25%)		2 (100%)	
Other	6 (38%)	2 (100%)	2 (67%)	1 (25%)	1 (25%)		
During a typical 7-day week, how many times do you exercise?	**(*n*=16)**		**(*n*=3)**	**(*n*=4)**	**(*n*=4)**		**(*n*=1)**
1 time per week	1 (6%)			1 (25%)			
2-3 times per week	2 (13%)				1 (25%)	1 (50%)	
4-5 times per week	9 (56%)	1 (50%)	1 (33%)	3 (75%)	2 (50%)	1 (50%)	1 (100%)
6-7 times per week	4 (25%)	1 (50%)	2 (66%)		1 (25%)		
Where does your exercise typically take place? *	**(*n*=16)**		**(*n*=3)**	**(*n*=4)**	**(*n*=4)**		**(*n*=1)**
Gym/leisure centre	2 (13%)	1 (50%)	1 (33%)		1 (25%)	1 (50%)	
Home	9 (56%)	1 (50%)	3 (100%)	3 (75%)	2 (50%)	1 (50%)	1 (100%)
Public outdoor spaces	7 (44%)	1 (50%)	2 (67%)	2 (50%)	2 (50%)	2 (100%)	1 (100%)
Sports specific facilities						2 (100%)	
Other	3 (19%)	1 (50%)			3 (75%)		
How do you usually exercise? *	**(*n*=16)**		**(*n*=3)**	**(*n*=4)**	**(*n*=4)**		**(*n*=1)**

Alone	10 (63%)	1 (50%)	2 (67%)	3 (75%)	4 (100%)	2 (100%)	1 (100%)
With a friend(s)/family member(s)	4 (25%)	2 (100%)	1 (33%)	1 (33%)	2 (50%)	2 (100%)	
As part of a larger class/team	1 (6%)	1 (50%)			1 (25%)	1 (50%)	
Supervised in person by a trainer	2 (13%)	1 (50%)	1 (33%)		1 (25%)		
Supervised virtually/online by a personal trainer		1 (50%)					
Other	1 (6%)		1 (33%)				
What are your main reasons for engaging in exercise? *	**(*n*=16)**		**(*n*=3)**	**(*n*=4)**	**(*n*=4)**		**(*n*=1)**
To have fun	3 (19%)	2 (100%)		1 (25%)	2 (50%)	2 (100%)	
To improve or maintain my physical health	11 (69%)	2 (100%)	3 (100%)	3 (75%)	4 (100%)	2 (100%)	1 (100%)
To improve or maintain my mental health	9 (56%)	2 (100%)	2 (67%)	3 (75%)	3 (75%)	2 (100%)	1 (100%)
To increase my physical strength	4 (25%)	2 (100%)		2 (50%)	2 (50%)		
To build muscle	1 (6%)	2 (100%)			1 (25%)		
To control or lose weight	5 (31%)	2 (100%)	1 (33%)	1 (25%)	3 (75%)	1 (50%)	
To look good		2 (100%)				1 (50%)	
To feel good	6 (38%)	2 (100%)	1 (33%)	1 (25%)	3 (75%)	2 (100%)	1 (100%)
To reduce stress	6 (38%)	2 (100%)	2 (67%)	1 (25%)	2 (50%)	2 (100%)	1 (100%)
To increase self-esteem	2 (13%)	2 (100%)		1 (25%)		1 (50%)	1 (100%)
To socialise and meet new people		1 (50%)				1 (50%)	
To feel a sense of achievement	3 (19%)	1 (50%)			2 (50%)	1 (50%)	1 (100%)
To train for and compete in sport		1 (50%)					

Table 6.7 Influence of perceived Barriers and Facilitators for Physical Activity in all respondents (*n*=18)

	All (*n*=18)	**1b (*n*=2)**	**2 (*n*=4)**	**3a (*n*=4)**	**5 (*n*=5)**	**9a (*n*=2)**	**9b (*n*=1)**
Items	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]
1) Level of Symptoms	-3.9 (5.7) [-6.0]	3.0 (4.2) [3.0]	-5.0 (9.3) [-9.5]	-6.3 (1.7) [-6.5]	-4.8 (4.6) [-6.0]	0.0 (0.0) [0.0]	-8.0 (0.0) [0.0]
2) Weather conditions	-2.2 (3.0) [0.0]	-3.5 (4.9) [-3.5]	-1.75 (3.5) [0.0]	-5.0 (2.94) [-5.0]	-0.4 (0.89) [0.0]	-2.0 (2.8) [-2.0]	0.0 (0.0) [0.0]
3) Presence or absence from support from others	0.4 (3.1) [0.0]	3.5 (4.9) [3.5]	-1.25 (5.5) [-2.5]	0.0 (0.0) [0.0]	1.0 (2.24) [0.0]	0.0 (0.0) [0.0]	0.0 (0.0) [0.0]
4) Presence of absence from support &/or advice from HCPs	-0.7 (3.6) [0.0]	0.0 (0.0) [0.0]	0.25 (6.2) [1.0]	-1.5 (1.91) [-1.0]	-0.2 (3.19) [0.0]	0.0 (0.0) [0.0]	-7.0 (0.0) [-7.0]
5) A belief that PA will make symptoms worse	-2.7 (3.8) [0.0]	0.0 (0.0) [0.0]	-1.75 (3.5) [0.00]	-3.5 (2.65) [-4.0]	-4.0 (5.48) [0.0]	0.0 (0.0) [0.0]	-7.0 (0.0) [-7.0]
6) Lack of motivation	-2.7 (3.3) [-1.0]	0.0 (0.0) [0.0]	-3.5 (4.4) [-2.5]	-3.5 (3.0) [-2.0]	-2.6 (3.58) [0.0]	0.0 (0.0) [0.0]	-7.0 (0.0) [-7.0]
7) Lack of knowledge on which exercises to do & how much	-1.0 (2.4) [0.0]	0.0 (0.0) [0.0]	0.0 (0.0) [0.0]	-1.0 (2.0) [0.0]	-1.4 (3.13) [0.0]	0.0 (0.0) [0.0]	-7.0 (0.0) [-7.0]
8) Knowledge of benefits of PA to health	4.5 (3.7) [5.0]	4.5 (6.4) [4.5]	4.5 (3.7) [5.0]	4.0 (3.3) [4.0]	3.4 (4.7) [0.0]	7.5 (0.7) [7.5]	6.0 (0.0) [6.0]
9) Knowledge of benefits of PA to mood	4.8 (3.8) [6.0]	4.5 (6.4) [4.5]	3.0 (3.8) [2.0]	5.3 (3.9) [6.0]	(4.0) (4.3) [3.0]	8.0 (0.0) [8.0]	8.0 (0.0) [8.0]
10) Confidence on how to exercise safely	2.7 (3.4) [0.0]	1.5 (2.1) [1.5]	0.0 (0.0) [0.0]	0.5 (1.0) [0.0]	4.4 (4.1) [6.0]	7.5(0.7) [7.5]	6.0(0.0) [6.0]
Total IFAB Score	**-0.9 (18.8) [-3.0]**	**13.5 (14.8) [13.5]**	**-5.5 (24.2) [-4.0]**	**-11.0 (4.97) [-12.5]**	**-0.6 (21.5) [-2.0]**	**21 (1.4) [21]**	**-16 (0.0) [-16.0]**

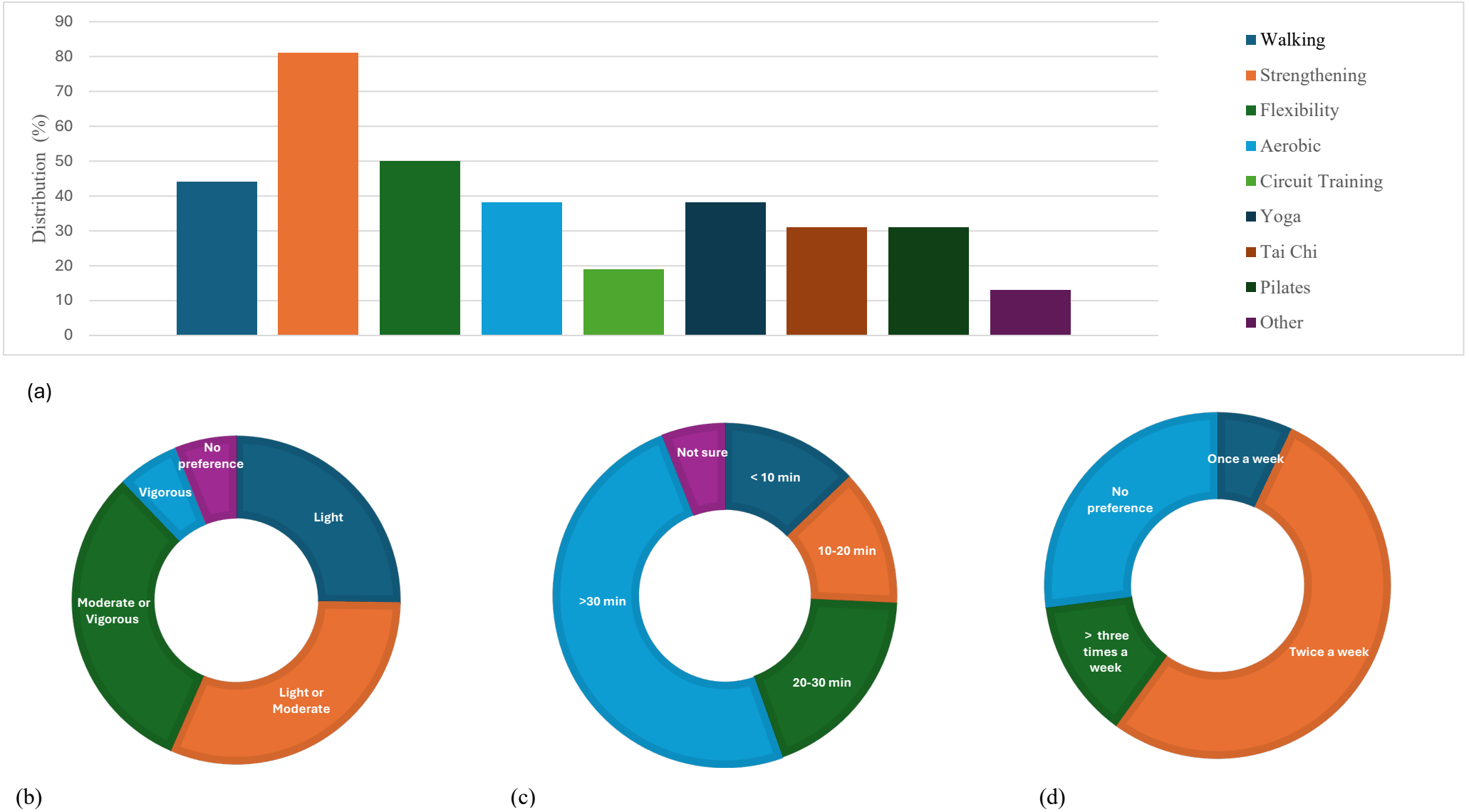


Figure 6.1 (a) Distribution of responses for preferred form of physical activity (*n*=16), (b) Preferred physical activity intensity (*n*=16) (c) Preferred physical activity duration (*n*=16), (d) Preferred attendance of respondents (*n*=15).

Table 6.8 Facilitators, Barriers and Preferences (*n*=18)

	All (*n*=18)	**1b (*n*=2)**	**2 (*n*=4)**	**3a (*n*=4)**	**5 (*n*=5)**	**9a (*n*=2)**	**9d (*n*=1)**
Domains	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]	Mean (SD) [median]
1) My social support network	1.9 (1.1) [2.0]	3.0 (0.00) [3.0]	2.5 (0.58) [2.5]	0.75 (0.96) [0.5]	2.0 (1.22) [2.0]	1.5 (0.71) [1.5]	3.0 (0.0) [3.0]
2) My access to exercise	4.6 (1.9) [5.0]	3.0 (2.83) [3.0]	3.75 (1.26) [4.0]	5.25 (1.5) [6.0]	4.4 (2.51) [5.0]	6.0 (0.00) [6.0]	6.0 (0.0) [6.0]
3) My exercise goals	9.4 (3.5) [10.0]	13 (1.41) [13.0]	10.0 (4.24) [11.0]	11.0 (2.16) [10.5]	9.2 (1.92) [9.0]	3.0 (0.00) [3.0]	8.0 (0.0) [8.0]
5) My feedback and training	2.6 (0.8) [3.0]	3.0 (0.00) [3.0]	2.75 (0.50) [3.0]	2.5 (1.0) [3.0]	0.0 (0.0) [0.0]	0.0 (0.00) [0.0]	0.0 (0.0) [0.0]
Section 4) Exercise Preferences	**(*n*=18)**	**(*n*=2)**	**(*n*=4)**	**(*n*=4)**	**(*n*=5)**	**(*n*=2)**	**(*n*=1)**
What is your preferred exercise schedule? *							
Fixed time	11 (61%)	2 (100%)	2 (50%)	1 (25%)	3 (60%)	2 (100%)	1 (50%)
Multiple drop-in times	5 (28%)	2 (100%)			1 (20%)	1 (50%)	1 (50%)
On my own time	10 (56%)	2 (100%)	2 (50%)	3 (75%)	1 (20%)	2 (100%)	
Section 6) My Exercise Barriers	**(*n*=18)**	**(*n*=2)**	**(*n*=4)**	**(*n*=4)**	**(*n*=5)**	**(*n*=2)**	**(*n*=1)**
Do you have things that STOP you from exercising?							
Yes	15 (83%)	2 (100%)	4 (10%)	4 (100%)	4 (80%)		1 (100%)
No	3 (17%)				1 (20%)	2 (100%)	
I do not exercise as often as I like because: *	**(*n*=17)**	**(*n*=2)**				**(*n*=1)**	
I do not like exercise	2 (12%)		2 (50%)				
I do not want to fall	3 (18%)		1 (25%)	2 (50%)			
I do not want to injure myself	6 (35%)	1 (50%)		3 (60%)	1 (20%)		1 (50%)
I feel pain when I exercise	3 (18%)	1 (50%)	1 (25%)		1 (20%)		
I feel bored when exercising	4 (24%)	1 (50%)	1 (25%)	2 (50%)			
Other	5 (29%)		1 (25%)	1 (25%)	1 (20%)	1 (100%)	1 (50%)
None of the above	5 (29%)		1 (25%)	1 (25%)	3 (60%)		
I do not exercise as often as I like because I have difficulty: *	**(*n*=17)**	**(*n*=2)**	**2 (*n*=4)**	**3a (*n*=4)**	**5 (*n*=5)**	**(*n*=1)**	**9d (*n*=1)**
Understanding the exercise	1 (6%)	1 (50%)					
Performing the exercise (i.e., I do not know how to exercise safely)	4 (24%)			2 (50%)	1 (20%)		1 (100%)

Other	2 (12%)		1 (25%)				
None of the above	11 (65%)	1 (50%)	3 (75%)	2 (50%)	4 (80%)	1 (100%)	
I do not exercise as often as I like because I do not have: *	**(*n*=17)**					**(*n*=1)**	
A place to exercise	1 (6%)		1 (25%)				
Confidence (e.g., I feel self-conscious about my body)	3 (18%)	1 (50%)		2 (50%)			
Finances	4 (24%)	1 (50%)		1 (25%)		1 (100%)	1 (100%)
Mobility (e.g., limited movements due to pain)	5 (29%)	1 (50%)	1 (25%)	2 (50%)	1 (20%)		
Proper quality of sleep	4 (24%)		1 (25%)		2 (40%)		1 (100%)
Time (e.g., family priorities, work, etc.)	8 (47%)		1 (25%)	2 (50%)	3 (60%)	1 (100%)	1 (100%)
Willpower/motivation	4 (24%)	1 (50%)	1 (25%)	1 (25%)	1 (20%)		
Other	2 (12%)		1 (25%)		1 (20%)		
None of the above	1 (6%)		1 (25%)				
Do weather conditions stop you from exercising as often as you like?	**(*n*=18)**					**(*n*=2)**	
Sometimes	7 (39%)	1 (50%)	1 (25%)	3 (75%)	1 (20%)	1 (50%)	
Rarely	10 (56%)	1 (50%)	2 (50%)	1 (25%)	4 (80%)	1 (50%)	1 (100%)
Never	1 (6%)		1 (25%)				
If you had fewer barriers, would you spend more time exercising?	**(*n*=18)**						
Yes	15 (83%)	2 (100%)	4 (100%)	3 (75%)	4 (80%)	1 (50%)	1 (100%)
No	2 (11%)				1 (20%)	1 (50%)	
Not sure	1 (6%)			1 (25%)			
Please check any mobility aids that you normally use:	**(*n*=18)**		**(*n*=4)**	**(*n*=4)**	**(*n*=5)**		**(*n*=1)**
Cane/Walking stick/ Hiking pole	3 (17%)		1 (25%)	1 (25%)	1 (20%)		
Wheelchair	1 (6%)		1 (25%)				
Other	2 (11%)			1 (25%)	1 (20%)		
None	12 (67%)	2 (100%)	2 (50%)	2 (50%)	3 (60%)	2 (100%)	1 (100%)

*Multiple options selected: Number and percentage of respondents who selected each answer option e.g. 100% represents that all respondents chose that option

Table 6.9 Physical Activity Programme Preferences of respondents (*n*=18)

	All (*n*=18)	**1b (*n*=2)**	**2 (*n*=4)**	**3a (*n*=4)**	**5 (*n*=5)**	**9a (*n*=2)**	**9d (*n*=1)**
Are you interested in taking part in an exercise programme							
Yes	12 (86%)	2 (100%)	2 (50%)	3 (75%)	3 (60%)	1 (50%)	1 (100%)
No	2 (14%)		1 (25%)		1 (20%)		
Not sure	4 (29%)		1 (25%)	1 (25%)	1 (20%)	1 (50%)	
Do you feel you could take part in an exercise programme	**(*n*=18)**	**(*n*=2)**	**(*n*=4)**	**(*n*=4)**	**(*n*=5)**	**(*n*=2)**	**(*n*=1)**
Yes	10 (56%)	2 (100%)	1 (%)	1 (25%)	3 (%)	2 (100%)	1 (100%)
No	1 (6%)				1 (%)		
Not sure	7 (39%)		3 (%)	3 (75%)	1 (%)		
What type of exercise would you be most interested in*	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
Walking	7 (44%)	2 (100%)	1 (33%)	1 (25%)	2 (50%)	1 (50%)	
Strengthening	13 (81%)	2 (100%)	2 (67%)	3 (75%)	3 (75%)	2 (100%)	1 (100%)
Flexibility	8 (50%)	1 (50%)	2 (67%)	1 (25%)	2 (50%)	1 (50%)	1 (100%)
Aerobic	6 (38%)		1 (33%)	1 (25%)	2 (50%)	2 (100%)	
Swimming	7 (44%)	2 (100%)	2 (67%)	2 (50%)			1 (100%)
Circuit training	3 (19%)	1 (50%)				2 (100%)	
Yoga	6 (38%)	2 (100%)	1 (33%)	1 (25%)	1 (25%)	1 (50%)	
Tai Chi	5 (31%)	2 (100%)	1 (33%)		1 (25%)	1 (50%)	
Pilates	5 (31%)	1 (50%)	2 (67%)			1 (50%)	1 (100%)
Other	2 (13%)	1 (50%)	1 (33%)				
What intensity would you like to exercise at?	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
Light	4 (25%)		2 (66%)	1 (25%)	1 (25%)		
Light or moderate	5 (31%)	1 (50%)	1 (33%)	2 (50%)	1 (25%)		
Moderate or vigorous	5 (31%)	1 (50%)			2 (50%)	1 (50%)	1 (100%)
Vigorous	1 (6%)					1 (50%)	
No preference	1 (6%)			1 (25%)			
How long do you think you would be able to exercise for?	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
Less than 10min	2 (13%)			1 (25%)	1 (25%)		
10-20 min	2 (13%)			2 (50%)			
20-30 min	3 (19%)	1 (50%)	2 (66%)				

Over 30 min	8 (50%)	1 (50%)	1 (33%)		3 (75%)	2 (100%)	1 (100%)
Not sure	1 (6%)			1(25%)			
How often would you be interested in attending	**(*n*=15)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=3)**	**(*n*=2)**	**(*n*=1)**
Once a week	1 (7%)				1 (33%)		
Twice a week	8 (53%)	1 (50%)	2 (66%)	2 (50%)	2 (67%)	1 (50%)	
More than three times a week	2 (13%)			1 (25%)			1 (100%)
No preference	4 (27%)	1 (50%)	1 (33%)	1 (25%)		1 (50%)	
What time of day would you prefer to exercise	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
Morning	5 (31%)	1 (50%)		1 (25%)	3 (75%)		
Morning of afternoon	1 (6%)	1 (50%)					
Afternoon	3 (19%)		1 (33%)	1 (25%)	1 (25%)		
Afternoon or Evening	4 (25%)		2 (66%)	1 (25%)		1 (50%)	
No preference	3 (19%)			1 (25%)		1 (50%)	1 (100%)
Who would you prefer to exercise with?	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
Alone	4 (25%)	1 (50%)	1 (33%)	2 (50%)			
Other GSD	3 (19%)		1 (33%)		2 (50%)		
General public	1 (6%)				1 (25%)		
No preference	8 (50%)	1 (50%)	1 (33%)	2 (50%)	1 (25%)	2 (100%)	1 (100%)
Who would you prefer your exercise was delivered by?	**(*n*=15)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=3)**	**(*n*=2)**	**(*n*=1)**
Physiotherapist	1 (7%)		1 (33%)				
Other Healthcare professional /Fitness Instructor	1 (7%)			1 (25%)			
Clinical Exercise Physiologist	5 (33%)		1 (33%)		3 (100%)		1 (100%)
Not sure	6 (40%)	2 (100%)	1 (33%)	3 (75%)		2 (%)	
Where would you prefer an exercise programme to take place?	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
Home	4 (25%)		1 (33%)	1 (25%)	2 (50%)		
Community centre	1 (6%)		1 (33%)				
Leisure centre	1 (6%)				1 (25%)		
No preference	8 (50%)	1 (50%)	1 (33%)	2 (50%)	1 (25%)	2 (100%)	1 (100%)
Not sure	2 (13%)	1 (50%)		1 (25%)			
How would you like to receive information on available exercise programmes?	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**

Telephone	1 (6%)	1 (50%)					
Email	14 (88%)	1 (50%)	3 (100%)	3 (75%)	4 (100%)	2 (100%)	1 (100%)
No preference	1 (6%)			1 (25%)			
Who would you like to receive this information from?	**(*n*=16)**	**(*n*=2)**	**(*n*=3)**	**(*n*=4)**	**(*n*=4)**	**(*n*=2)**	**(*n*=1)**
Specialist nurse	1 (6%)		1 (33%)				
Physiotherapist	4 (25%)		1 (33%)		2 (50%)		1 (100%)
No preference	11 (69%)	2 (100%)	1 (33%)	4 (100%)	2 (50%)	2 (100%)	

6.5 Discussion

To our knowledge, this is the first quantitative study to explore physical activity levels, barriers, facilitators, and preferences in individuals with GSDs. Our results reveal that GSD significantly affects daily physical activity for the majority of respondents. Individuals with a GSD that has muscular involvement commonly reported symptoms such as weakness, pain, aches, and cramps, which appeared to negatively impact their QoL. Specifically, these individuals experienced lower overall well-being, particularly in areas related to physical health, when compared to typical norms. Increased fatigue, especially physical and general fatigue, was also a prominent issue in this subgroup. As anticipated, physical activity levels were generally low across the cohort, with fatigue and motivation being associated to these reduced levels. The main barriers to physical activity reported by participants included symptom severity, concerns that physical activity might worsen their condition, and a lack of motivation. However, many participants indicated a willingness to increase their physical activity if these barriers could be addressed, and most expressed interest in engaging in a physical activity program. Among those interested in physical activity, there was a clear preference for light to moderate intensity activities, including strengthening and cardiovascular activities, which could be performed at home or in outdoor settings with regular professional support. Overall, this study emphasises the significant limitations to physical activity participation among individuals with GSD and highlights the need for tailored physical activity interventions to address these barriers. Future research should focus on developing personalised physical activity programs that effectively mitigate these challenges and promote increased physical activity in this population.

Our results highlight that muscular symptoms, such as weakness, pain, cramps, and fatigue are prominent, especially in individuals with muscular involvement. These symptoms not only contribute to physical discomfort but also appear to affect QoL, by increasing fatigue and limiting engagement in daily physical activities. Previous research has established that the

physical manifestations of GSDs impair functional capacity and daily activities, consequently impacting QoL (**Chapter 3**; Chen et al., 2021; Derks et al., 2021; Gungor et al., 2016). Within the current study QoL overall was found to be lower across all domains compared to normative values, particularly in the physical functioning and role limitation (physical) domains, which aligns with previous research (**Chapter 3**). Furthermore, mental health domains across all GSD subtypes were relatively less impacted, with physical health, especially in those with muscular involvement, experiencing more noticeable declines. Individuals with GSD 2 had considerably lower QoL in the physical functioning domain, which concurs with previous research in which there were notable reductions in physical health domains, with less of a reduction in mental health domains compared to the general population (Hagemans et al., 2004). Moreover, reductions in QoL and physical health within this GSD subtype were found to be worse compared with other rare diseases (Martinez et al., 2017) suggesting that the main challenges for these patients and other muscular GSDs, are the physical symptoms. Certainly, in GSD 3a, reductions in physical functioning, role limitation due to physical health and energy and fatigue were found, which is in agreement with previous research **(Chapter 3)**, with a similar pattern, although not as marked found in GSD 5, which again appears to align with others (Karazi et al., 2023). Furthermore, fatigue, specifically physical fatigue appeared to be a notable issue, particularly in those who reported increased muscular symptoms. Previous research has found fatigue to be associated with symptom severity, with increased physical fatigue, general fatigue, mental fatigue with increased symptom severity in GSD 5 (Slipsager et al., 2024).

Considering the impact of GSD symptoms, including their effects on QoL and fatigue, it is not surprising that nearly half of GSD respondents were classified as having low levels of physical activity and fail to meet the recommended health guidelines for the general population (at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity activity

per week (Bull et al., 2020). This aligns with previous research showing low levels of physical activity in GSD 5 (Karazi et al., 2023; Slipsager et al., 2024), classifying those individuals as more sedentary compared to the general population (Munguia-Izquierdo et al., 2015; Scalco et al., 2020). Additionally, prior research on GSD 3a found that most participants exhibited sedentary behaviour, exceeding 8 hours (480 minutes) per day, with those classified as ambulatory primarily engaging in light to moderate-intensity activity, consistent with our findings. It is important to consider that the actual physical activity levels in this study may be even lower than reported, as the IPAQ-SF is known to overestimate activity compared to objective measures (Lee et al., 2011), and the reported levels of moderate and vigorous activity may reflect an increased perception of difficulty due to the symptoms of disease (Slipsager et al., 2024).

Individuals with GSDs generally exhibited lower levels of physical activity, but within-group analysis revealed interesting associations between physical activity, fatigue, and motivation. Physical activity levels were found to negatively correlate with general, physical, and total fatigue, meaning higher fatigue was linked to lower activity. This finding aligns with previous research in GSD 5, where increased fatigue was also associated with reduced physical activity (Slipsager et al., 2024). Moreover, motivation played a significant role, with physical activity levels showing a negative correlation with amotivation, defined as a lack of intention to act (Havnen et al., 2023). In contrast, positive correlations were observed with identified regulation, where activities are seen as valuable and important, and intrinsic motivation, driven by enjoyment and satisfaction (Havnen et al., 2023). These two types of motivation, known as self-determined motivation, have been documented as critical for both short- and long-term adherence to physical activity and may be essential factors when planning future interventions (Teixeira et al., 2012). In addition to the influences of fatigue and motivation, participants reported a variety of perceived barriers to physical activity. Many indicated they would increase

their physical activity if these barriers were addressed. Commonly reported barriers included the severity of symptoms, concerns that physical activity might worsen their condition, and lack of motivation. Similar barriers, such as fatigue, discomfort, and pain, have been noted in individuals with musculoskeletal disorders (McPhail et al., 2014) and rheumatoid arthritis (Wilcox et al., 2006), and these symptoms often influence motivation (Whipple et al., 2019; Wilcox et al., 2006). A lack of time was also frequently cited, consistent with reports from the general population (Cavallini et al., 2020).

Despite the barriers to physical activity, the vast majority of respondents were actively engaging in various physical activities and expressed a strong interest in participating in a structured physical activity program. This is particularly significant, as physical activity has long been recommended for individuals with GSDs due to its substantial health benefits, including improved cardiovascular fitness, increased muscular strength, and enhanced overall well-being (**Chapter 5**; Cupler et al., 2012; Kishnani et al., 2006). Among individuals with GSD in this study, most were already participating in cardiovascular activities—such as walking, running, cycling, or swimming—at least four times per week. Reflecting these habits, respondents preferred physical activity programs consisting of at least 20-minute sessions, twice weekly, incorporating similar activities. Strengthening activities were particularly favoured by 81% (*n*=13) of participants, with flexibility (*n*=8, 50%), swimming (*n*=7, 44%), and walking (*n*=7, 44%) also popular choices, suggesting that interventions building on familiar and appealing activities may be more effective. Strengthening activities are especially beneficial for individuals with GSD 2 and GSD 5, with evidence showing improvements in functional capacity and disease severity (**Chapter 5**). While walking has not been specifically studied in GSD populations, it is well known as a safe, effective, and accessible form of physical activity that requires no special skills or expensive equipment (Hanson & Jones, 2015; Lee & Buchner, 2008; Lee et al., 2010; Magistro et al., 2014; Siegel, Brackbill & Health,

1995). Its appeal across various clinical populations, coupled with its flexibility and ease of implementation, supports its inclusion in physical activity programs for GSD. The intensity of preferred activities varied by GSD subtype, with individuals with GSD 2 and GSD 3a favouring light or light-to-moderate activity, while those with GSD 5 preferred more vigorous activity. These differences likely reflect variations in disease severity and physical activity tolerance, as noted by others (Preisler et al., 2015). Most respondents reported engaging in physical activity alone, either at home or in public spaces, rather than in sport facilities, indicating a preference for home-based activity programs. However, adherence to such programs can be challenging, with non-adherence rates as high as 50% in individuals with musculoskeletal disorders, which negatively affects clinical outcomes and increases the burden on healthcare systems (Bassett, 2003; Sluijs et al., 1993). Connected health technologies, such as mobile devices, wearable sensors, and telehealth platforms, may offer a solution to improve adherence by providing real-time feedback and virtual coaching, aligning with respondents' preference for regular professional support (Argent et al., 2018). Nevertheless, further research is needed to determine the specific components of a physical activity program that would be most effective for individuals with GSDs.

6.5.1 Strengths and Limitations

A key strength of the study is the use of an online survey which ensured that we were not excluding potential participants with this rare disease due to geographical or functional barriers, thus capturing a relatively large and diverse range of people with various GSD subtypes from across the UK. It is important to acknowledge, however, that internet-based strategies can also present challenges, as they may exclude those with more severe mobility impairments or limited digital access, potentially underrepresenting the least active members of the GSD population. Another strength is the use of comprehensive measurement tools, many of which have been validated for use within other clinical populations. This allowed for a wide range of

valuable quantitative data to be collected efficiently and allowed for comparisons to be easily made between different GSD subtypes. Despite the strengths of this research, there are several limitations. The study specifically included participants perceptions, which whilst this addressed the research aims, it is possible that participants may have under-estimated their sedentary behaviour and over-estimated the amount or type of physical activity they currently do or are capable of doing. The use of objective activity monitors, such as accelerometers or wearable devices, would have provided more accurate measures of activity levels and sedentary time. Moreover, the patient population may represent the most engaged and active patients and as such may not be truly representative of the population. Furthermore, due to this study being cross-sectional in nature, we were unable to examine changes over time, which given the known progression of GSDs may be particularly insightful.

6.6 Conclusion

In conclusion, this study highlights the complex relationship between GSDs and physical activity, with significant barriers including fatigue, symptom severity, and low motivation contributing to reduced activity levels. Despite these challenges, individuals with GSDs express strong interest in participating in a physical activity program, creating a valuable opportunity for targeted interventions. The study's findings can guide the development of personalised physical activity interventions that align with patient preferences for light to moderate cardiovascular and strengthening activities, which can be performed at home or in public spaces with professional support. Given the variability between GSD subtypes, qualitative exploration of the facilitators and barriers to physical activity specific to each subtype is required, employing methods such as interviews and focus groups. This approach would provide deeper, context-specific insights at an individual level. Understanding these unique challenges will help in designing personalised physical activity programs that accommodate individual needs, promoting long-term adherence and better QoL.

Chapter 7 - Understanding the Barriers and Facilitators to Physical Activity in Glycogen Storage Disease: A Qualitative Study

7.1 Links to previous chapters

Findings from **Chapter 6** revealed low physical activity levels among individuals with GSD, influenced by factors such as fatigue, lack of motivation, and numerous barriers. Notably, there was a strong interest in participating in physical activity programs. Building on this foundation, **Chapter 7** aims to provide a deeper exploration of the barriers and facilitators to physical activity, offering insights that could inform the optimal design of future physical activity interventions.

7.2 Introduction

Glycogen Storage Diseases primarily affect the liver and skeletal muscle (Di Mauro et al., 2004; Laforet et al., 2012). In cases where the liver is involved, symptoms typically include fasting hypoglycaemia ± hepatomegaly (Kanungo et al., 2018). Whereas, muscle involvement is associated with profound muscle weakness, reduced aerobic capacity, and significant exercise limitations (**Chapter 3**), with these impairments known to progress throughout adulthood (Decostre et al., 2017; Hijazi et al., 2021). These physical symptoms may lead to increased sedentary behaviour, which subsequently heightens the risk of additional chronic health conditions and metabolic complications (Stein & Wade, 2005). Consequently, current therapeutic strategies aim to alleviate these physical manifestations and improve QoL (Stone et al., 2025).

Growing evidence has highlighted the therapeutic benefits of exercise, particularly in reducing symptoms and increasing QoL, rather than accentuating the disease (Preisler et al., 2015).

Researchers and clinicians have promoted the potential therapeutic benefits of exercise training for people with GSDs for many years and supervised training programmes have even been included in consensus guidelines for those with GSD 2 (Cupler at al., 2012; Kishnani et al., 2006; Kishnani et al., 2010). A previous systematic review investigated the effectiveness of exercise in this clinical population and found supervised exercise training including aerobic and/or resistance training to be safe and effective in adults with GSD 5 and GSD 2; with improvements in aerobic capacity ($\dot{V}O_{2peak}$), muscle strength, functional capacity, disease severity and well-being (**Chapter 5**). Furthermore, similar to trends observed in the general population, exercise could also enhance general health, fitness, and overall QoL (Blair et al., 1995; Pedersen et al., 2006).

Despite poor exercise tolerance and the benefits of physical activity being acknowledged, to date no research has been conducted to document the impairment of physical activity levels and current exercise behaviours, barriers and facilitators to exercise within the GSD population. Furthermore, there is a lack of investigation into the optimal design and implementation of exercise interventions tailored to the specific needs and preferences of various GSD types. Given the variable onset and progression of symptoms, individuals with GSD are likely to face unique challenges compared to those without the disorder, meriting further study. Understanding physical activity levels and recognising factors that influence exercise participation from patients own perspective and lived experiences is essential for researchers and health professionals. This knowledge allows them to effectively tailor their support and develop interventions that align with the needs and lifestyles of their patients, ultimately aiming to enhance long-term health outcomes.

To address this gap in the literature, we conducted this qualitative study which aims to explore the barriers and facilitators to physical activity in individuals with GSDs. It was anticipated that gaining in-depth perspectives on the barriers and facilitators to activity at an individual

level, in participants own words, may uncover specific nuances, that may not otherwise have been identified. The knowledge gained can then be utilised within future interventions focussed towards increasing activity in this population.

7.3 Methodology

7.3.1 Study Design

To explore barriers and facilitators to physical activity in those with GSDs, a qualitative approach was adopted, in which participants took part in a semi structured interview (*n*=3) or focus group (*n*=5). Ethical approval was obtained from Nottingham Trent University Non-Invasive Ethics Committee (Reference 1565310).

7.3.2 Participants

Participants were included in the study if they met the following criteria: Adult patients (>=18 years) with a diagnosis of any type of GSD. Participants were excluded from the study if they did not have the capacity to consent.

7.3.3 Recruitment

Recruitment was conducted via advertisements on the Association for Glycogen Storage Community UK (AGSD UK) social media platforms. Interested participants provided researchers with their contact details to participate in an online semi-structured interview or focus group. All participants provided verbal consent to participate.

7.3.4 Data collection

The content of the semi-structured interview and focus group guides were based on the study aims and previous research of physical activity within various other comparable clinical populations (Bakaa, et al. 2021; Baxter et al. 2016; Blaney et al. 2013; Booth et al. 2013; Karlsson et al. 2018; Kehn & Kroll, 2009; Meade et al., 2021; McPhail, et al. 2014; Simpson

et al., 2011; Tierney et al. 2011; Vader et al., 2021; Wang, et al. 2015; Wilcox et al. 2006). Patient members of AGSD UK (GSD 3a, GSD 5, GSD 2) and a metabolic consultant were involved in the development of the interview and focus group guide **(Appendix K)**, with consideration to the burden of the study from a patient perspective and contributed to the dissemination plan.

7.3.4.1 Online Focus groups and semi-structured Interviews

Participants that consented to take part were contacted to participate in a semi-structured interview or focus group at a time that was convenient for them. All semi structured interviews or focus groups were led by FK, an Exercise Psychologist, who has extensive experience of qualitative research methods. At the start, participants were reminded that they did not have to take part if they no longer wished to do so and were informed that the data collected would only be shared within the immediate research team, with all final data being fully anonymised. Consent was obtained from participants for their involvement and for the recording and transcription. All semi-structured interviews and focus groups were conducted over Microsoft Teams and utilised a range of open-ended questions in order to generate discussion. Topic areas and sample questions included Exercise Behaviours: Tell me about your experience with exercise? Have you received any advice regarding exercise an GSD?; Facilitators and Barriers to exercise: Tell me about the factors that you feel make it easier to exercise? Tell me about the factors you feel make it harder to exercise? and Exercise programme preferences: If you were designing an exercise programme for those with GSD, what would the ideal exercise programme look like to you? Where further information was required, questions were followed up with sub questions. Where some participants did not respond to specific topics discussed, the facilitator (FK) asked if these participants had any further comments to ensure the entire sample was represented. Field notes were taken throughout to provide context for the transcription process. All interviews and focus groups were audio recorded and transcribed

using Microsoft Teams. Interviews and transcripts were reviewed, with any transcription errors corrected and data anonymised for analysis.

7.3.5 Data Analysis

Data was analysed thematically using a Framework approach (Ritchie & Lewis, 2003). This approach is best suited to research with specific research questions and a priori ideas, while equally encouraging an inductive, data driven approach (Srivastava & Thomson, 2009). This approach involved: 1) familiarisation with the data; 2) development of a thematic framework; 3) indexing data; 4) devising a series of thematic charts 5) mapping and interpreting the data. The focus group and one to one interview transcripts were reviewed by the lead author to ensure accuracy of transcription. Following familiarisation of the transcripts, initial themes were discussed with members of the research team to create an indexing scheme. The indexing scheme was organised by the most pertinent topics uncovered from the analysis of the qualitative data. The lead author indexed all transcripts and produced an Excel matrix, summarising the data. The matrix was discussed with the research team and final themes were developed, refined and are presented within this paper. The qualitative data was used to give context and elaborate on the quantitative data, to provide a more robust understanding of the facilitators and barriers of physical activity to better inform future intervention strategies.

7.4 Results

A total of 8 participants took part in an online one-to-one interview or focus group (*n*=5 participants with GSDs with muscle ± liver involvement, including *n*= 2 GSD 2, *n*= 1 GSD 3a, *n*= 1 GSD 5, and *n*=3 participants with GSDs with liver involvement, including *n*=1 GSD1b, *n*=2 GSD 9a, *n*=1 GSD 9d). A total of 145 minutes of qualitative data was collected and a variety of barriers and facilitators to physical activity were captured in four framework

categories as follows **(Figure 7.1)**; 1) Physical Factors, 2) Psychological Factors, 3) Social Factors and 4) Environmental Factors.

1) Physical Factors

The physical factors category included themes pertaining to participants physical health and nutrition. Barriers related to physical health were commonly identified across all GSD subtypes and included the following themes: Fatigue**,** difficulty at the start of exercise, muscular symptoms (weakness, pain, cramping), low blood sugar and unrelated health problems. Across GSDs with muscle ± liver and solely liver involvement fatigue was a common barrier, with multiple reports of participants having less energy and less stamina compared to others (GSD 2 participant: " *when you're fatigued you definitely feel like you don't want to do the exercise*."). Furthermore, those with muscular involvement commonly reported physical health factors as barriers to physical activity. Experiencing difficulties at the start of exercise was isolated to those with GSD 5 (GSD 5 participant: "*I think listening to the others….the type 5 is a bit different to most of these in the group today, in that exercise is difficult from the onset straight away. You know it doesn't matter what the exercise is, whether it's gentle walking or going up a few flights of stairs or, you know, diving in the pool and starting to swim some lengths…physically you grind to a halt after a short period of time*."). Whereas muscular symptoms including muscular pain and weakness in particular were predominant barriers in GSD 2 and GSD 3a (GSD 3a participant: "*It's hardly any hypoglycaemia type of symptoms…It's just my muscles don't work… or don't respond or I don't have the strength*.") with muscular cramping reported in GSD 9d. Furthermore, muscular weakness and cramping were reported to have become more evident throughout adulthood, with a notable decline in participants physical capabilities reported (GSD 3a participant: *"I guess the myopathy… started kicking in mid 30s…. it's just got harder and harder to do anything. So, it's gone from clifftop walks to, a clifftop walk with a stick, to no clifftop walk, to a stick just to get down the road to hardly going*

out." The decline in physical capabilities, specifically muscle weakness appeared further exacerbated where participants had not continued physical activity (GSD 2 participant: *"I used to play golf and in my late, even till early 40s, my golfing partners moved away and I didn't play for about 18 months…just 18 months. Then I went back to it... , went out into the garden, tried swinging a club and fell over")*. In contrast, those with GSDs with liver involvement reported low blood sugar as a barrier to physical activity (GSD 1b participant: "*It goes really low… and I can have a fit if it goes too low. Sometimes it does go low, really low, like one, two and I can look normal").* Moreover, multiple unrelated health problems were reported as barriers in an individual with GSD 9a.

Facilitators related to physical health were only reported in those with GSDs with muscular involvement and included themes: Ensuring adequate warm up and physical ease of exercise. Ensuring adequate warmup was isolated to GSD 5 (GSD 5 participant: "*Once you're warmed up with McArdles disease, then you're fine and there isn't a fatigue issue. Once you're into second wind, I mean, that's clear to me, you know, you can do two or three hours of sport, quite hard sport once you're warmed up*."). Whereas the physical ease of performing specific activities, including the modality and duration was an important facilitator in GSD 2 and 3a (GSD 2 participant on swimming: *"I'm quite fortunate because a lot of people with Pompe suffer with the diaphragm problems and they can't breathe and they have to have BiPAPs. I don't need that. I've just got the speech problem. So I'd go into the water, no problem. I'd go under water and it's no real problem. So, it's quite handy from that point*"; GSD 3a participant: "*It's probably better if I do it more often, but short bursts*.").

With regards to nutrition, a lack of carbohydrate, specifically prior to exercise, was the only theme identified as a barrier to physical activity, specifically reported by those with muscle involvement. Across all GSD subtypes nutrition appeared to be a key facilitator, with themes including regular carbohydrate, high protein or low carbohydrate diet. The consumption of

simple carbohydrates before exercise was key facilitator across GSDs (GSD *5* participant: *"I suppose, taking glucose before you exercise. If you know you're going to do exercise with McArdles….some glucose beforehand does help you get through to second wind more easily for sure."* ; GSD1b participant: "*I aways got advice like to make sure my sugars don't go low, so to eat, have a meal, then have cornstarch and then always have like dextrose or a snack with you.")*. High protein was also cited as a key facilitator *(*GSD 2 participant: *"I always try to have some protein before exercise, like if there's a high protein meal or protein supplement. I don't always get to do it and I think one of the theories er that it's about how the muscle gets degraded in type 2").* In contrast a low carbohydrate diet was reportedly of benefit in GSD3a (GSD3a participant*: I think a diet's helped. Well, it seems to have slowed and possibly very slightly reversed in some ways…some of the sort of muscle loss…muscle myopathy…weakness…it's very slightly improved it, maybe*.").

2) Psychological Factors

Themes identified as barriers within psychological factors included a lack of motivation, lack of interest, fear of physical injury and fear of low blood sugar. A lack of motivation and a lack of interest were reported across GSD subtypes. This was particularly associated to the physical difficulties experienced in those with GSDs with muscle involvement (GSD 3a participant: " *anything from the weather to lack of motivation to…and yeah, it's just not very interesting, really, the exercise I can do*.") and lead to a fear of physical injury in an individual with GSD 2. In contrast, a fear of low blood sugars was isolated to individuals with GSDs with liver involvement alone (GSD 9a participant: "*I still worry about my blood sugar".*

Among psychological facilitators, themes included knowledge of physical health benefits, mental health benefits and motivation. The knowledge of the physical benefits of exercise was important across the vast majority of GSD subtypes, with participants reporting to exercise to improve GSD symptoms and general health and wellbeing (GSD 9d participant: *"These days*

I've always got plenty of exercise. I've more consciously realised that it, it helps my symptoms and these days I'm, I'm more of a runner than anything else"; GSD 9d participant: "*It's not always been properly explained as being part of this GSD, but I'm convinced it (fatigue) is [is what] and what I realise is that even when I feel fatigued on a day like this morning for example, I'll still go out for a run, for about 5 miles this morning…..fairly quickly and whilst it's hard to begin with, I do feel the benefits later on and being generally as fit as possible… I notice it does give me more stamina really…I get more out of the day.").* The knowledge of the role activity plays in maintaining participants physical capabilities to avoid decline were particular facilitators across individuals with GSDs with muscle involvement (GSD 2 participant: *"The one problem with… with the state like I'm in, is that you're going to hit a very low ceiling, but you've got to maintain that ceiling. Otherwise, if you don't, you will come down and come down and come down."*; GSD 2 participant "*I'd be feeling that if I didn't do the exercise, I wouldn't be where I am today. I mean, I'm pretty sure, right?* 'Whereas the experience of mental health benefits and self-motivation were important across GSD subtypes (GSD 2 participant: "*I don't know why other people wouldn't exercise; I mean….. I get a buzz out of exercising really.";* GSD1b participant*:* "*it's good for your mental health….like after I exercise, I feel really good…..you know, I feel more positive*."; GSD 9a: "*Self-motivation is obviously key*").

3) Social Factors

A wide range of social barriers were highlighted, with themes including time constraints, lack of professional input (including lack of exercise advice and difficulty in understanding and performing exercise advised), concern from others and a lack of awareness of their needs from others. Time constraints, including difficulty scheduling exercise was the only social barrier reported across all GSD subtypes (GSD 2 participant: "*If I have a day where I've got a lot of meetings and things and deadlines, I might not exercise*."). A lack of professional input was a predominant barrier, particularly highlighted in those with muscle involvement and with

increased physical barriers such as GSD 2 and GSD 3a. Where there was professional input, there were several reports of difficulties understanding the advice (GSD 9d participant: "*Some of the advice, I don't understand so find it difficult to work out what the methodology of the… approach is. For example, no isometric exercise. I don't understand why that is. I follow the advice as much as possible, but it's a bit, I find it a bit odd. I don't know, I don't understand it*."; GSD 3a participant " *It's just felt very unclear the advice or the reasoning behind it, and that might just be because of the lack of research or theories are not quite in place. I don't know. I can figure lots of reasons, but it's a bit frustrating*."). Difficulties performing the exercise, including judging how much exercise to do proved further barriers in individuals with GSD 2 and GSD 3a. Additionally, those with muscular involvement, reported concern from family members and a lack of awareness of their needs from others as barriers (GSD 9d participant: *"One factor I can think of is …. I don't know what can be done about it, but it's the attitude of others, really. They don't always understand your restrictions, about whether it be eating or needing a very long warm up. I remember, being on a swimming team one time and I used to go running because I knew I needed to warm up and that the coach wasn't very happy with this, didn't want me expending so much energy before the race starts, but for me it was a logical thing to do, but it's difficult for people….people often don't say anything..they're too polite, but you can tell from the look that they think it's a bit odd. Why has he suddenly stopped at 50 minutes? What's going on? He's nearly finished? What's up with him?"*).

Social facilitators included themes: incorporating exercise into personal routine, regular professional input and an increased awareness and understanding from others. Incorporating exercise into personal routine was important across GSD subtypes (GSD 1b participant: "*So I would say like for me, exercise classes help a lot with routine and stuff because sometimes I do feel fatigued quite a lot and then when I when I know I have to go to exercise class, I'll push myself. If I'm at home, I will like be, OK, let me just rest …. Also, I have friends who are into*

fitness and health and well-being, so that helps your environment. Also, my family, I live with my brothers and they're all into fitness"). Regular professional input including personalised exercise advice with regular monitoring and feedback was specifically important to those with muscle involvement, where increased physical barriers presented (GSD 3 participant: *"A better idea about… just about myself…..about what exercise actually helps or the question about … can I overexercise?…it's still slightly bare sometimes.";* GSD 2 participant: *"I think follow up and feedback would be good. That's in tailoring, so that you know if a physical therapist or whoever recommends a programme….I know that that takes resources of course, so I don't know how practical that is for everyone's situation, but I think that would be important";* GSD 2 participant*: "Yeah, I think..At the back of a lot of people's mind is they won't do things just so they think we're not sure whether it'd be good for (indicating Pompe disease) but you might do more damage than good. So, I think it would be good to have some someone that you could go to, I suppose your consultant, but I haven't seen my consultant for 2 years…it's always somebody standing in for him ….. I suppose if I wanted to and I was thinking about doing something, I could contact him by e-mail ……We used to have… somebody who was dedicated to go round all the Pompe patients and talk to them and try and encourage them to do the things, I think that made a lot of difference. So, I know a lot of people that have mentioned that that was it a good thing*"). Moreover, the social environment with the support and encouragement of others was an important facilitator across GSD subtypes (GSD 1b participant: "*Like everyone around me if they encourage me, they encourage me. It helps me. But if I'm alone and I'm just like busy with other things and you know it's not good*"; GSD 9a participant "*Yeah, empathy is key in life generally as well, though, isn't it? So, we all have good days and bad days, so if there's someone that to support you, they have to understand that. Yeah, whether you're afflicted with a condition that actually some days you just don't feel like it and other days are the days you're bouncing off the walls*." GSD 9a participant: "*I used to do five aside*

football after work and it was the camaraderie and the actual…I mean obviously it was a pub afterwards but it sort of negates the exercise but it's ….You know, if you've got people").

4) Environmental Factors

Themes identified as environmental barriers included accessibility and weather conditions and were exclusively reported in those with increased muscular impairments (GSD 2, GSD 3a). Accessibility was a predominant barrier, with difficulties getting to the exercise location and accessing equipment (GSD 2 participant: "*The only downside in swimming is, I've got to get there, I'll walk into the gym and I know they've got an escalator going up, so it's not a problem going up there, but I've got to get undressed, get in the pool, get out the pool and because I can't get up steps, I've got to get out the side.*") with certain individuals with GSD 2 specifically requiring the assistance from others to set up exercise equipment (GSD 2 participant: "So I've got a little foot pedal that I put on my lap and pedal with my arms just so I can get some kind of exercise….I mean I require the help of someone to kind of set up the pedals usually, so one thing is needing assistance from someone else").

Themes identified as environmental facilitators included accessibility (i.e. proximity to exercise, personal exercise equipment, assistance from others) and fitness monitoring. Accessibility to activity including the proximity to exercise was important across GSD subtypes, with a clear preference for activity to be conducted at home and/or online, particularly in those with increased physical health barriers (GSD 3a participant: "*If I'm being realistic, probably if it was home based it'd be easier just cause it's such an effort to get out and it's I'm not saying I'd rule out anything else, but I just…where I am now, the additional effort to going to the gym to do something I could probably do at home… in some format... yeah just don't seem worth it.").* Moreover, the use of personal exercise equipment was particularly important in individuals with GSDs with muscular involvement (GSD 2 participant: "*I go up to my room…my rower is there…I just need to change my footwear into trainers and*

put my heart rate monitor on, put music on, and then, I'm away sort of thing and again that is brilliant …I mean that's even better than going walking. I mean even walking; I've got to put my walking boots on and get the dog harnessed up and all the rest of it."). In addition, fitness monitoring, particularly the use of fitness devices were cited as a facilitator across GSD subtypes (GSD 5 participant: *"I've enjoyed tracking improvement for sure. I mean, I'm on about my 4th Fitbit…and you know, I don't have many years of data. I've got on my phone and, you know, watching, watching your resting heart rate gradually fall as you as you, you know, continue to do more aerobic. It's quite a nice thing to see.";* GSD 9a participant: *"For me personally, I actually get great pleasure in seeing improvement, whether that's getting faster, changing shape a little bit or* $\dot{V}O_{2max}$ *or whatever. Actually, just playing with the stats, I find quite entertaining and I get a buzz out of trying to hit some improvements I suppose.").*

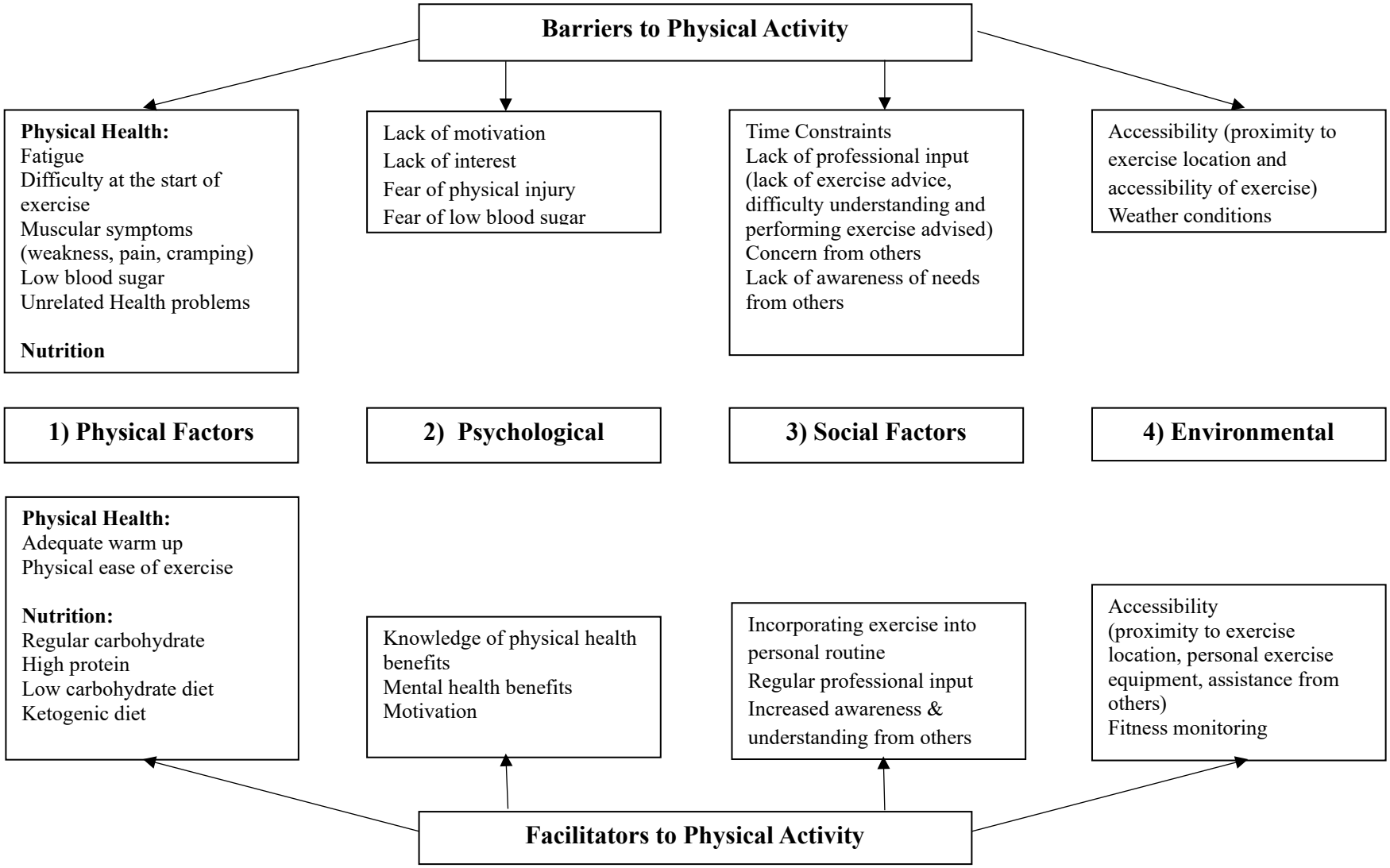


Figure 7.1 Themes and subthemes related to the barriers and facilitators of physical activity in GSD

7.5 Discussion

To our knowledge, this is the first qualitative study investigating barriers and facilitators to exercise among individuals with GSDs. The study identified a broad spectrum of barriers and facilitators, categorized into four main categories: 1) Physical, 2) Psychological, 3) Social, and 4) Environmental factors. As might be anticipated in this context, within the category of physical factors, physical health emerged as a significant theme to engaging with physical activity, particularly due to disease-specific symptoms. Fatigue was commonly reported across subtypes, while muscle-related symptoms and hypoglycaemia were particularly noted in subtypes involving muscle and/or liver. Moreover, barriers stemming from physical health challenges often influenced psychological factors, including motivation, interest, and fears related to symptoms and potential injury. Within the category of environmental factors, accessibility to exercise facilities and the proximity of these facilities were crucial, especially for those with prominent muscular symptoms who require specialised equipment. Within the social factor's category, the support of others including family, friends and professional input played dual roles, acting as both barriers and facilitators, depending on the presence of support or lack of. Support, particularly from professionals, including tailored exercise advice, monitoring, and feedback, was deemed crucial, particularly for those with significant muscular involvement in GSDs.

7.5.1 Physical Factor: Physical Health & Psychological Factors: Motivation & Interest

Participants emphasised the challenge of participating in physical activity, with physical symptoms including fatigue, muscle weakness and pain particularly prevalent in those with GSDs with muscular involvement. The experience of fatigue (specifically low energy), discomfort and pain have commonly been described as barriers to physical activity within those with chronic pain (Karlsson et al, 2018; Vader et al., 2021), musculoskeletal disorders (Mcphail et al, 2014), peripheral neuropathy (Anens et al., 2015) and rheumatoid arthritis (Wilcox et al,

2006). Within the current study, this had notable implications on psychological factors such as motivation and interest in physical activity. This is consistent with research in those with rheumatoid arthritis, in which the occurrence of physical symptoms such as pain not only prevented participants from engaging in exercise, but also affected their motivation to exercise and decreased willingness to participate in exercise in the future (Wilcox et al, 2006). Moreover, these findings are also consistent in those with peripheral artery disease and diabetes in which there was a close relationship was found between pain and motivation (Whipple et al, 2019). In contrast, to the predominant muscular pain and weakness in those with GSDs with muscular involvement, participants with solely liver involvement detailed concerns regarding low blood sugar, specifically being conscious of their blood sugar dropping during activity. This has also been reported in adults with type 1 diabetes, who have reported the burden of thinking about their blood sugars throughout exercise and altering their physical activity in response to low blood sugar (Oser et al, 2019). It is therefore essential for health professionals to continue to monitor and manage the physical health of patients with GSDs where possible, even if some of the reported barriers, such as fatigue, muscle weakness, and pain, may be considered non-modifiable or, at the very least, difficult to modify. Pain, particularly in those with muscle involvement, should be managed effectively as improvements in pain has been associated with exercise participation in those with arthritis (Minor & Brown, 1993). On the whole, the acknowledgement and impact of patients existing symptoms and their progression is crucial when designing and implementing interventions which are appropriately tailored towards mitigating these barriers. Given the physical barriers in this population, a graded exercise approach may be an appropriate strategy to consider (Booth et al, 2017).

7.5.2 Environmental Factor: Accessibility

Our findings also highlight accessibility as a key factor in physical activity participation, including the proximity to the exercise location and the accessibility of the exercise given the participants reported symptoms. This is similar to previous work, which cited the proximately to exercise, including being close to home as a facilitator in the general population (Bartholomew et al, 2011; Yeo et al, 2014) and in older adults with chronic diseases, those with chronic pain, peripheral artery disease and diabetes, Musculoskeletal disorders and survivors of stroke (Bearne & Godfrey, 2021; Bethancourt et al, 2014; Blonski et al, 2014; Dnes et al., 2021; Li et al, 2017; Meade,; Whipple et al, 2019). Those with GSDs with muscular involvement, with increased physical barriers specifically reported difficulties getting into and out of a pool as a barrier to physical activity. This concurs with previous research in those with disabilities, who report difficulty accessing hot tubs and whirlpools, with ramps seldom available (Rimmer et al, 2004). Home based exercise was of particular preference in those with increased physical difficulties, and in other research has been found to be safe and beneficial in frail older adults (Matsuda et al., 2010). It may therefore be important for health professionals to consider delivering physical activity interventions that can be performed in the home environment, without the need for specialised equipment, potentially utilising equipment already available in the patient's home. This approach may make physical activity feel less daunting, more appealing, manageable, and achievable (Booth et al, 2012). Additionally, accessibility should be a key consideration for exercise outside the home, with leisure centres ensuring ramp access to pools and incorporating zero-depth entry pools, which allow entry without the need for a ramp or pool lift (Rimmer et al, 2004).

7.5.3 Social Factor: Support from others

Social factors including the support from others such as family and friends and professional input appeared integral to participation in physical activity. Across GSD subtypes, the support and encouragement of others was commonly cited as an important facilitator to physical activity, with several individuals citing the benefit of having the support of family and friends, which can further impact motivation. The importance of having social support, including the support of family and friends as a facilitator to engage in physical activity has been shown in a variety of populations including those living with chronic pain (Vader et al., 2021), rheumatoid arthritis (Baxter et al, 2016), diabetes (Oser et al, 2019; Whipple et al, 2019) and Charcot-Marie Tooth disease (Anens et al., 2015). Indeed, in an exploratory study by Anens et al (2019) qualitative and quantative analysis showed that social support, particularly family as an important facilitator, which has been shown to correlate to physical activity by others (Bauman et al, 2012). Furthermore, the benefits of exercising with others, particularly as an aid to motivation aligns with previous research showing a preference for group-based formats providing social support and motivation (Dnes et al, 2021, Vader et al., 2021; Wilcox et al, 2006). Professional support was particularly important in those with GSDs with muscular involvement, with many participants reporting a lack of professional input as a predominant barrier to participating in activity. Furthermore, where professional input was provided (by healthcare and/or fitness professionals) it was evident that participants struggled to understand and perform the advice given, with concerns over how much activity to do given their physical symptoms. This is in agreement with previous research highlighting the need for a feeling of safety when participating in activity (Dnes et al, 2021; Slade et al., 2009). Indeed, in previous research in those with chronic lower back pain, there was a preference for exercise instructors who were knowledgeable on their condition, who could demonstrate exercise, provide corrections and offer supervision and reassurance (Slade et al., 2009). This approach has further

been found to increase confidence and encourage exercise adherence among those living with HIV (Lia et al, 2017) and fibromyalgia (Jones et al, 2006). Health professionals therefore need to acknowledge their fundamental role in the safe prescription of physical activity to those with GSDs, including delivering detailed tailored information on exercise targets, intensity, frequency and duration, while offering ongoing guidance and monitoring. Social connections could be utilised positively, by integrating patients' family and friends through group activities, in which patients can discuss and share experiences, as has been utilised effectively in other populations (Petter et al 2009; Schutzer & Graves 2004).

7.5.4 Clinical implications and future research

This research contributes to our understanding of factors important for physical activity engagement within those with GSDs, which appear largely interrelated in nature and should be considered as a whole to inform future interventions. These results specifically highlight the importance of considering the physical impact of GSD on individuals when designing and implementing interventions to encourage physical activity. It is important that future interventions include a range of potential physical activity types with a graded approach and which patients can integrate easily within their daily lives. This should include physical activities that are easily accessible, offering options that can be done within the patient's home. The importance of professional input was specifically emphasised, in which opportunities where patients can interact with health professionals that have in depth knowledge of their condition are essential in future interventions. Specific detailed information should be given on exercise targets, intensity, frequency and duration for the safe initiation of activity interventions, with ongoing monitoring of physical symptoms and support. Moreover, given social support was highlighted as an important component to physical activity engagement, targeting the involvement of patient's family and peers within group-based activity could be of benefit. Future research should include longitudinal studies, to identify which barriers and

facilitators have the strongest association with participation in physical activity as GSDs progress. These would be of value in the development of effective long-term physical activity interventions in this population.

7.5.5 Strengths and Limitations

One of the key strengths of this study lies in its qualitative design, which enabled an in-depth exploration of the barriers and facilitators to physical activity among individuals with GSDs. The use of both focus groups and one-to-one interviews was largely pragmatic, reflecting participant availability and preference, and enabled the inclusion of individuals who might otherwise have been excluded. Conducting these sessions online via Microsoft Teams provided further advantages, enabling participation from individuals across the UK, including those with mobility or health limitations and therefore ensured that diverse perspectives were captured. Another notable strength is the application of Framework Analysis (Ritchie & Lewis, 2003), which facilitated a systematic comparison within and between GSD subtypes, including those with muscular (± liver) involvement and those with solely liver involvement.

Despite these strengths, there are some limitations to consider. The small sample size (n=8) in the interviews and focus groups, while fostering in-depth discussion and reflection, may not fully represent the views of the broader population. While the pragmatic use of both focus groups and interviews enhanced inclusivity, it may have affected the data, as group dynamics in focus groups can differ from the individualised insights generated through interviews (Lambert & Loiselle, 2008). Similarly, the use of an online format, although enhancing convenience, also may have introduced potential drawbacks. Technical issues such as unstable internet connections or software incompatibility could disrupt the flow of discussion and affect data quality (Thunberg & Arnell, 2021). Subtle nonverbal cues, such as body language and facial expressions, may not have been fully captured (Opdenakker, 2006), and building rapport was sometimes more challenging without the immediacy of physical presence (Moussavou,

2022). These issues were mitigated as far as possible by using a consistent semi-structured guide across formats, allowing additional time for technical difficulties, and incorporating informal conversation and active listening to foster rapport. Furthermore, this study focused on participants' perceptions, which, while aligning with the research objectives, could have led to potential under- or over-estimation of the amount or type of physical activity they currently engage in or are capable of performing. Furthermore, due to the cross-sectional nature, we were unable to examine changes over time, which given the known progression of GSDs may be particularly insightful.

7.6 Conclusion

These results show a myriad of barriers and facilitators to physical activity within those with GSDs. Important factors highlighted, include the influence of physical health, accessibility and social interactions on physical activity engagement, which may be useful to inform future person-oriented physical activity and exercise interventions for adults with GSDs. Given the diverse range of barriers and facilitators to activity, it is evident that future interventions would need to take a tailored approach, whereby an individual's unique barriers and facilitators are explored and an individual goal setting approach is utilised to successfully promote exercise engagement in those with GSDs. Based on these results, adults with GSDs, particularly those with physical difficulties may benefit from physical activity advice that includes physical activities that are easily accessible, offering options that can be done at home and with others. This advice should be provided by those with expertise in physical activity and GSD, who can monitor symptoms and offer continued support and feedback.

Chapter 8 - Effects of Oral Lactate Supplementation on Acid–Base Balance and Prolonged High-Intensity Interval Cycling Performance

8.1 Links to previous chapters

In addition to investigating exercise as a therapeutic intervention for individuals with GSDs in **Chapter 5**, **Chapter 6**, and **Chapter 7**; **Chapter 8** aims to explore the potential of lactate supplementation as a novel treatment strategy. This chapter specifically explores the feasibility, safety, and efficacy of oral lactate supplementation in glycogen-depleted healthy participants, aiming to mimic those with glycogenolytic or glycolytic deficiencies.

8.1.1 Preface

The growing recognition of lactate as an alternative energy source and metabolic buffer has generated significant interest in its potential role in the therapeutic management of GSDs (Bertocci et al., 1993; Ørngreen et al., 2015; Vissing et al., 2005). Lactate supplementation offers distinct advantages over other dietary targets, such as amino acids which require slower gluconeogenic processing and generate nitrogen waste, or glucose polymers, which still depend on glycolysis and glycogenolysis for utilisation (Brooks, 2023; Melkonian et al., 2022; Patino & Orrick, 2024). In contrast lactate can bypass the metabolic blockages characteristic of glycogenolytic and glycolytic deficiencies, such as those seen in GSD 3, GSD 5, GSD 7, and GSD 10. By directly entering oxidative metabolism (Ørngreen et al., 2015), lactate supplementation can potentially increase energy availability and act as a metabolic buffer, particularly during physical activity. These effects hold promise for improving exercise tolerance, physical function, and ultimately the QoL in affected individuals.

Although research of lactate in GSD is limited, early studies have highlighted the importance of lactate uptake and oxidation within active muscles (Ørngreen et al., 2015), as well as the potential benefits of exogenous lactate supplementation (Bertocci et al., 1993; Lewis et al., 1991). Consequently, lactate supplementation could serve as an important ergogenic aid for GSD patients, especially those with glycogenolytic or glycolytic deficiencies. However, existing research focuses on short-term intravenous lactate supplementation, which, while effective, is neither practical nor sustainable in everyday contexts. This raises critical questions about the feasibility, tolerability, and effectiveness of alternative administration methods, such as oral lactate supplementation.

Currently, it remains unexplored if oral lactate supplementation is safe, tolerable, and beneficial for improving physical performance; therefore, it is essential to establish its effects in healthy individuals before considering its application within GSD. This Chapter therefore aimed to address the feasibility, tolerability, safety, and efficacy of oral lactate in healthy participants who became glycogen-depleted during prolonged exercise; thus mimicking conditions similar to those with glycogenolytic/glycolytic deficiencies such as GSD 3a, GSD 5, and GSD 7. The findings from this study aim to provide fundamental data on the potential of oral lactate supplementation in healthy individuals and offer critical insights into its viability as a novel therapeutic strategy for managing GSDs with glycogenolytic and/or glycolytic deficiencies.

8.2 Introduction

Lactate is no longer deemed a harmful waste product of glycolysis that causes muscle fatigue through associated muscle acidosis (Gladden, 2016; Hall et al., 2016; Rabinowitz & Enerbäck., 2020). Rather, lactate is an important energy intermediate, signalling molecule, and metabolic buffer (Morris, 2016). When lactate is consumed orally, it is readily absorbed into the bloodstream (Morris et al., 2016) and various tissues, including the skeletal muscle, where it can fuel oxidative metabolism (Jacobs et al., 2013). Lactate can also be absorbed by hepatocytes and converted into glucose through gluconeogenesis, which can then be stored as glycogen (Hostetler et al., 1969). Moreover, these reactions consume hydrogen ions, which may potentially preserve the blood bicarbonate levels and enhance the ability to buffer the extracellular pH (Brooks, 1986; Brooks et al., 2021; van Montfoort et al., 2004). Therefore, lactate potentially plays a multifaceted role as an ergogenic aid by supporting both energy production and the maintenance of the acid–base balance during exercise.

While lactate's roles as an energy intermediate and metabolic buffer are well-established, its practical application as an ergogenic aid presents a more complex picture, appearing to vary with the intensity and duration of exercise. Prolonged moderate-intensity (86% max heart rate or 70% $\dot{V}O_{2max}$) exercise tolerance is not improved with oral lactate supplementation (Bryner et al., 1998; Swensen et al., 1994). Conversely, during high-intensity exercise such as sprint running or at 100% $\dot{V}O_{2max}$, lactate supplementation has been shown to extend time to task failure by 4–26% (Morris et al., 2011; Morris et al., 2016; van Montfoort et al., 2004), although other studies report no ergogenic effects (Northgraves et al., 2013; Oliveira et al., 2016; Peveler & Palmer., 2012; Russ et al., 2019; de Salles Painelli et al., 2014).

Lactate's ergogenic potential appears to be most significant when high-intensity exercise follows prolonged moderate-intensity activity. For example, Azevedo et al. (2007) used a two-stage exercise test which consisted of participants cycling at 62% $\dot{V}O_{2max}$ for 90 min, then at

86% $\dot{V}O_{2max}$ until reaching their limit of tolerance. The consumption of lactate (alongside fructose, glucose, and a glucose polymer) increased time to task failure by 25% compared to consuming only fructose and glucose. Exercise tests that include long-duration, moderate-intensity exercise combined with short-duration high-intensity bouts may be most amenable to improvements through lactate supplementation, as they provide challenges to the energy metabolic pathways and buffering systems, both of which may be improved by lactates' proposed mechanisms of action.

Road cycling is predominantly characterised by steady-state and non-steady-state exercise, in line with competitive cyclists breaking away from the pack or completing hill climbs (Sanders & Heijboer., 2018; Vogt et al., 2006). The prolonged nature of road race cycling leads to the gradual depletion of muscle glycogen (Jacobs et al., 1981; Ortenblad et al., 2013) thus affecting the availability of the substrates required for ATP synthesis. Additionally, high-intensity interval exercise will induce a transient metabolic acidosis, which can contribute to peripheral muscle fatigue and also central fatigue by acting on group III/IV muscle afferents and impairing overall performance (Amann et al., 2020). Due to its mechanisms of action as an energy substrate and potential mediator of acid–base balance, lactate supplementation may offer a promising solution to mitigate the effects of these co-existing metabolic challenges on race cycling exercise performance. Thus far, no studies have investigated the efficacy of oral lactate during a prolonged performance test that includes repeated bouts of high-intensity exercise interspersed with moderate-intensity exercise, as the nature of road race cycling can be (Sanders & Heijboer., 2018; Vogt et al., 2006). Furthermore, the literature presents conflicting reports on gastro-intestinal disturbances associated with lactate supplementation (Azevedo et al., 2007; Morris et al., 2011; Péronnet et al., 1997; de Salles Painelli et al., 2014), raising concerns about its suitability for prolonged exercise such as competitive cycling events. The aim of this study was to examine the effects of oral lactate supplementation on the time taken

to complete a cycling exercise protocol comprising repeated bouts of high-intensity exercise interspersed with moderate intensity exercise. Additionally, we evaluated the gastro-intestinal tolerance of oral lactate supplementation throughout the exercise protocol. It was hypothesised that the use of calcium lactate supplementation would induce significant metabolic alkalosis, leading to an enhanced cycling time trial performance.

8.3 Methods

8.3.1 Participants

Approval for the study procedures was obtained from the Nottingham Trent University Human Invasive Ethics Committee (Reference: 709) before participant recruitment. Sixteen healthy male (trained) road cyclists with at least 1 year of training history, including in prolonged (3–4 h) riding, were recruited through various means, including email circulars, posters, word of mouth, and the local cycling community. The flow of participants through the study is detailed as a CONSORT flow diagram **(Figure 8.1)**. All participants provided written informed consent and the research was performed in accordance with the principles stated in the Declaration of Helsinki **(Appendix N; Appendix O)**. The participants had an average age of 26 ± 6 years, body mass of 72.2 ± 6.8 kg, height of 179 ± 5 cm, body fat of 11 ± 4%, and a $\dot{V}O_{2max}$ of 4.3 L · min−1 (59 ± 7 mL · kg^{-1} · min−1).

The G*Power software version 3.1.9.7 (Faul et al., 2007) was used to calculate the necessary sample size to ensure that our study was sufficiently powered to identify differences in the time trial performance. We estimated an effect size of 0.68, using prior research that evaluated the effects of 120 mg/kg body weight calcium lactate on exercise performance (Morris et al., 2016). With this effect size, an alpha of 0.05, and a power setting of 0.80, it was determined that 15 participants were needed. To ensure a balanced allocation between study arms, we adjusted the sample size to 16 participants.

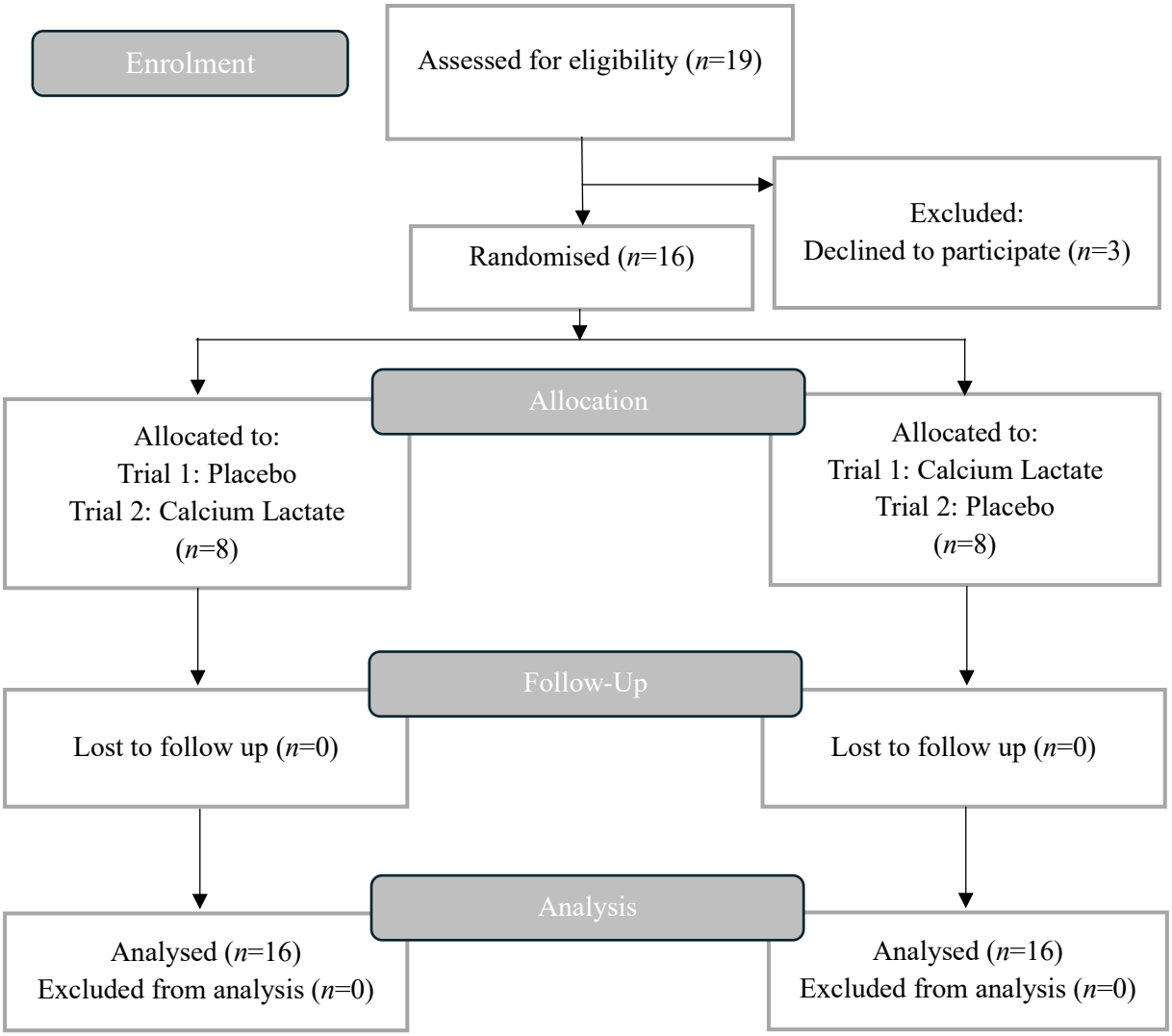


Figure 8.1 CONSORT Flow Chart Depicting Participant enrolment and trial arm allocation.

8.3.2 Experimental Design

A randomised, repeated-measures, double-blind crossover study was conducted. The participants visited the laboratory on four separate occasions. Visit 1 included anthropometry and a CPET to determine their gas exchange threshold GET and $\dot{V}O_{2peak}$. During visit 2, the participants completed a familiarisation trial comprising 3 of the 5 blocks of the main exercise protocol (thus, approximately 2 h of cycling). During visits 3 and 4, the participants completed the exercise protocol 70 min after consuming either calcium lactate or a placebo (Morris et al., 2011; Morris et al., 2016). The treatment order was randomised. For visits 3 and 4, the participants arrived at the laboratory at the same time of day (0900) (1 h post-prandial) separated by at least 4 days to allow for the recovery and control of their circadian rhythms. Prior to visits 3 and 4, the participants abstained from alcohol for 24 h, caffeine for 5 h, and strenuous exercise for 48 h. The participants were requested to maintain consistent training schedules between visits and adhere to dietary restrictions, with 7-day training and 24 h food diaries collected and reviewed to assess their compliance to these conditions. Upon participant arrival, the laboratory environment's temperature, barometric pressure, and humidity were recorded. Throughout the exercise protocol, the participants were permitted to drink water ad libitum, and their total water consumption was recorded upon completion.

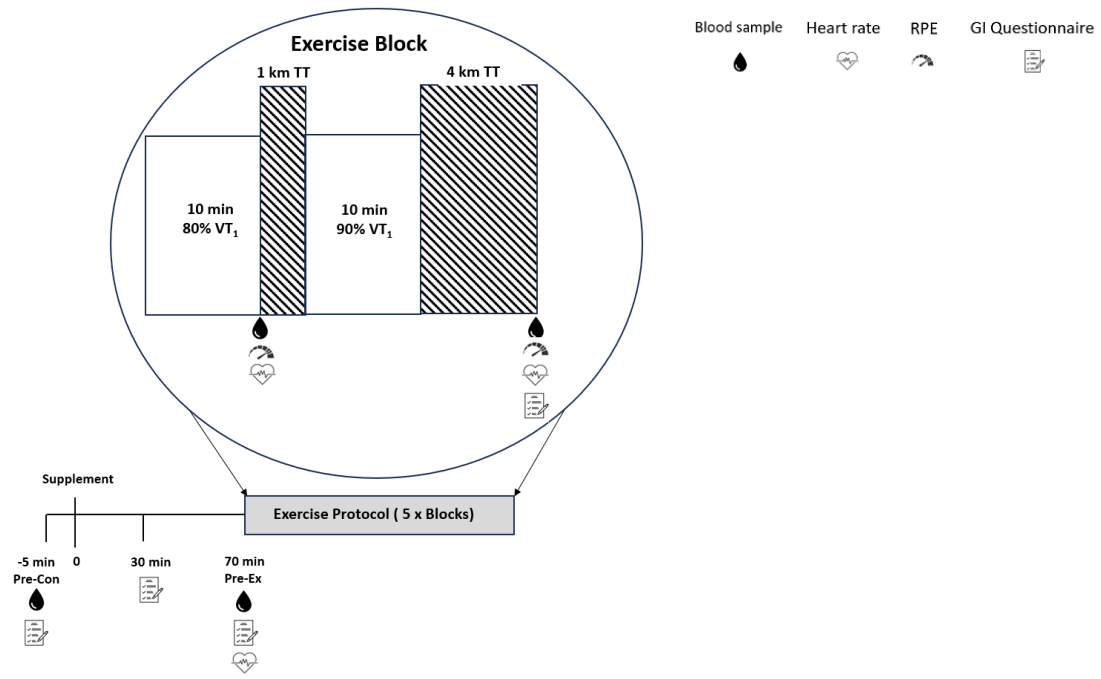


Figure 8.2 Schematic representation of the study

Pre-Con: Pre supplement; Pre-Ex: 70 min post supplement; VT_1: Ventilatory threshold; TT: Time trial.

8.3.3 Equipment and Measurements

Anthropometry was recorded, including height (to the nearest 0.01 m; Seca 217 stadiometer, Seca; Hamburg; Germany), body mass (to the nearest 0.1 kg; Seca 761 scales, Seca, Hamburg, Germany), and body composition using bioelectrical impedance (Bodystat Ltd., Isle of Man, British Isles). Exercise was performed using an electromagnetically braked cycle ergometer (Excalibur Sport; Lode, Groningen, The Netherlands). The positions of the saddle and handlebars were replicated for all trials. The participants wore a facemask (model 7940; Hans Rudolph, Kansas, MO, USA), and $\dot{V}O_{2peak}$ and pulmonary gas exchange variables were measured breath-by-breath (Version 3B, Cortex Medical, Leipzig, Germany). Fingertip capillary blood samples were collected pre supplement consumption, pre-exercise, and pre and post each exercise block **(Figure 8.2)** using 70 µL balanced heparin blood capillary tubes (Radiometer, Copenhagen, Denmark). Blood samples were immediately analysed (ABL90 Flex; Radiometer, Copenhagen, Denmark) for their concentrations of lactate [La^-], glucose

[glucose], bicarbonate [HCO_3^-], haemoglobin [Hb], potassium [K^+], sodium [Na^+], calcium [Ca^{2+}], and chloride [Cl^-], along with the pH and partial pressure of carbon dioxide PCO_2. The hydrogen ion concentration [H^+] was derived from the measured pH as the antilog. The strong ion difference ([SID]) was calculated as the sum of the strong ions minus the sum of the strong anions: [SID] = ([Na^+] + [K^+] + [Ca^{2+}]) − ([Cl^-] + [La^-]) (Johnson et al., 2014; Stickland et al., 2013). Changes in the blood volume from baseline were calculated from the changes in [Hb] (Harrison., 1982). Heart rate was measured continuously via telemetry (Sigma ID. GO, Sigma-electro, Neustadt, Germany). Ratings of perceived exertion (RPE) were recorded using the Borg scale (6–20) (Borg., 1982), immediately before (pre) and within the last few seconds (post) of each exercise block. Gastro-intestinal tolerance was assessed using a questionnaire based on previous studies (Carr et al., 2011; Miller et al., 2016).

The participants rated their level of gastro-intestinal intolerance using a Likert scale, assessing the symptoms of nausea, flatulence, stomach cramping, belching, stomach ache, bowel urgency, diarrhoea, vomiting, and stomach bloating. The participants indicated the severity of each symptom on a scale from 0 to 10, with 0 being “no symptom” and 10 being “severe symptom”. These severity ratings were recorded pre supplement consumption, 30 min post supplement consumption, immediately pre-exercise, and immediately after each exercise block. The time to complete the exercise protocol, which served as the primary outcome of the study, was recorded using the Lode Ergometry Manager 10 Software (Lode, Groningen, Germany).

8.3.4 Cardio Pulmonary Exercise Test (CPET)

The participants performed 3 min of rest and 3 min of unloaded cycling, followed by an incremental ramp protocol (35W · min^{-1} or 40W · min^{-1}) at their preferred cadence until task failure (cadence below 60 rpm, despite verbal encouragement). The $\dot{V}O_{2peak}$ was defined as the average of the exertional oxygen uptake achieved over the last 30 s of exercise. The GET was

determined using the modified V-slope method (Vanhatalo, et al., 2016) confirmed by patterns of change in the ventilatory equivalent and end-tidal gas measurements, later verified by an independent researcher. The power output at the GET was adjusted by subtracting two-thirds of the ramp increment per minute, i.e., the power output—0.67 × ramp increment, in order to convert the ramp exercise to a steady state. The GET was then used to determine the intensity of the steady-state exercise (80% and 90% GET) within the main exercise trial.

8.3.5 Supplementation Strategy

The participants consumed 147 mg・g^{-1} body mass of either calcium lactate (Special Ingredients Ltd., Chesterfield, UK) or a placebo (flour) within opaque gelatine capsules over a 5–10 min period 70 min before exercise. This dosage was selected to provide 120 mg・kg^{-1} body mass of lactate (Morris et al., 2011; Morris et al., 2016). The calcium lactate used was obtained from a factory-sealed container (Special Ingredients Ltd., Chesterfield, UK) and was weighed to the nearest milligram before being placed in the capsules. The number and colour of the capsules were consistent across treatments. The selection of the calcium lactate dosage was based on previous studies, where significant increases in peak blood [HCO_3^-] between pre and post consumption were observed (26.83 ± 2.53 vs. 29.50 ± 1.96 mmol−1 (Morris et al., 2011); 29 ± 2.9 vs. 32.0 + 1.6mmol.L^{-1} (Morris et al., 2016), with no further increases at higher doses.

8.3.6 Dietary Control

The participants were provided with a standardised evening meal and standardised breakfast prior to visits 3 and 4. The evening meal, consumed at 1900 h the night before visits 3 and 4, provided 40% of the participants' estimated energy requirements, with a specific macronutrient composition based upon 50% carbohydrates, 35% fat, and 15% protein (COMA., 1991). The

breakfast, consumed at 0800 h, provided 2 g of carbohydrates per kg of body mass (Burke et al., 2000; Jeacocke & Burke, 2010).

8.3.7 Exercise Protocol

The exercise protocol comprised 5 repeated exercise blocks. Each block consisted of 10 min of cycling at 80% GET followed by a 1 km TT, then 10 min at 90% GET followed by a 4 km TT. During the TTs, resistance to pedalling was set using the linear mode of the cycle ergometer, in which the power output was dependent on the cycling cadence. The linear factor for the 1 km TT and 4 km TT was calculated based on specific reductions in the absolute peak power during 1 km and 4 km TTs observed in previous research (Burke et al., 2000; Tomcik et al., 2018), and the participants' preferred cadence following familiarisation. Before each TT, the investigator provided a countdown, instructed the cyclists to complete the TT as quickly as possible, and provided verbal encouragement throughout. During the time trials, the participants were blinded to all performance data, except for the distance countdown.

8.3.8 *Statistical Analysis*

The data analysis was conducted using SPSS statistical software version 28.0 (IBM Corporation, Armonk, NY, USA). Initially, the accuracy of the data entry and the presence of missing values were examined. Some data points (n=16) were missing completely at random due to machine or human errors, and an expectation maximisation imputation method was used to replace these missing values. In some instances, data were systematically missing due to machine malfunctions, which affected the blood biochemistry data (n=2), and due to human error, which affected the heart rate and perceived exertion data (n=3), leading to the exclusion of these participant data. The normal distribution of the data was assessed using the Shapiro–Wilk test, and appropriate inferential statistics were conducted based on the results. Student paired t-tests were used to evaluate the differences between treatments (calcium lactate and

placebo supplement) in delta changes in the blood measures pre and post supplement consumption, environmental laboratory conditions, and total water consumption during the exercise. A two-way (Treatment × Time) repeated measures analysis of variance (ANOVA) was used to identify the differences in the time to complete each 1 km TT and each 4 km TT. Three-way (Treatment: 2 levels: calcium lactate, placebo) × Block (5 levels: exercise block 1 to 5) × Time (2 levels: pre and post each exercise block) ANOVAs were used to identify the differences in the concentrations of blood [La^{-}], [glucose], [H^{+}], [HCO_3^{-}], [Hb], PCO_2, [K^{+}], [Na^{+}], [Ca^{2+}], [Cl^{-}], and [SID], heart rate, and RPE. The homogeneity of variance was assessed using the Mauchly test, and in cases where the assumption of sphericity was violated, a Greenhouse–Geisser correction was applied. The effect sizes are reported using partial eta squared (η2 p), with magnitudes of small (η2 p = 0.01), medium (η2 p = 0.06), and large (η2p = 0.14) (Cohen, 1998). For the student paired t-tests, the effect sizes are presented as Cohen dz and interpreted as small (dz = 0.2), medium (dz = 0.5), and large (dz = 0.8) (Cohen, 1998) Statistical significance was set at $p < 0.05$. Data are presented as means with 95% confidence intervals. To examine any differences in gastro-intestinal symptoms over time for each treatment, a Friedman's test was performed. The effect sizes are presented as Kendall's W (Kendall coefficient of concordance) and interpreted as small (W = 0.1), medium (W = 0.3), and large (W = 0.5) (Cohen, 1998). Pairwise comparisons of gastro-intestinal symptoms following each exercise block between treatments were then conducted using the Wilcoxon signed-rank test. The effect sizes are interpreted as small (r = 0.1), medium (r = 0.3), and large (r = 0.5) (Cohen, 1998). Statistical significance was set at $p < 0.05$.

8.4 Results

8.4.1 Acid–Base Balance and Metabolic Measurements Pre and Post Supplementation

Table 8.1 presents the changes in the acid–base and metabolic measurements from pre to post supplementation for both the calcium lactate and placebo treatments. Significant differences in

the pre–post deltas were observed between the calcium lactate and placebo supplementation for [SID] ($p = 0.032$, $dz = 0.640$), [HCO_3^-] ($p = 0.019$, $dz = 0.714$), and [Cl^-] ($p = 0.006$, $dz = -0.868$). Specifically, there was a significant increase in [SID] and [HCO_3^-] and a significant decrease in [Cl^-] following calcium lactate supplementation compared to the placebo. Changes in other acid–base and metabolic measures were not significantly different between the treatment groups ($p > 0.05$).

Table 8.1 Acid–base balance and metabolic measurements pre and post supplementation (*n*=14).

	Pre supplementation	**Post supplementation**	Δ
Treatment			
Calcium Lactate			
[SID] $mmol{\cdot}L^{-1}$	39.44 (38.61, 40.28)	41.14 (40.12, 42.15)	1.69 (0.29, 3.10) *
[HCO_3^-] $mmol{\cdot}L^{-1}$	25.79 (25.11, 26.46)	26.68 (26.14, 27.22)	0.89 (0.07, 1.71) *
[H^+] $nmol{\cdot}L^{-1}$	38.52 (37.29, 39.75)	38.06 (36.98, 39.14)	-0.46 (-1.50, 0.59)
[K^+] $mmol{\cdot}L^{-1}$	4.91 (4.62, 5.20)	4.81 (4.62, 5.00)	-0.10 (-0.38, 0.18)
[Na^+] $mmol{\cdot}L^{-1}$	143 (142, 143)	142 (141, 143)	-0.57 (-1.52, 0.38)
[Cl^-] $mmol{\cdot}L^{-1}$	107 (106, 108)	105 (105, 106)	-2.07 (-2.77, -1.37) *
pCO_2 mm Hg	41.31 (39.84, 42.77)	42.68 (41.60, 43.76)	1.37 (0.01, 2.73)
[Ca^{2+}] $mmol{\cdot}L^{-1}$	1.24 (1.22, 1.26)	1.26 (1.25, 1.28)	0.02 (0.01, 0.03)
[La^-] $mmol{\cdot}L^{-1}$	2.14 (1.78, 2.50)	1.86 (1.63, 2.10)	-0.27 (-0.59, 0.05)
[Glucose] $mmol{\cdot}L^{-1}$	5.11 (4.80, 5.43)	5.11 (4.77, 5.46)	0.00 (-0.48, 0.48)
Placebo			
[SID] $mmol{\cdot}L^{-1}$	40.19 (39.16, 41.21)	40.20 (39.21, 41.20)	0.02 (-0.94, 0.97)
[HCO_3^-] $mmol{\cdot}L^{-1}$	25.95 (25.40, 26.49)	25.76 (25.21, 26.32)	-0.18 (-0.74, 0.38)
[H^+] $nmol{\cdot}L^{-1}$	38.62 (37.80, 39.44)	39.30 (38.21, 40.39)	0.68 (-0.51, 1.88)
[K^+] $mmol{\cdot}L^{-1}$	4.94 (4.60, 5.27)	4.97 (4.76, 5.18)	0.03 (-0.40, 0.47)
[Na^+] $mmol{\cdot}L^{-1}$	143 (142, 144)	142 (141, 143)	-1.00 (-1.78, -0.22)
[Cl^-] $mmol{\cdot}L^{-1}$	107 (106, 108)	106 (105, 107)	-0.64 (-1.42, 0.14)
pCO_2 mm Hg	41.88 (40.91, 42.86)	42.70 (41.40, 44.00)	0.82 (-0.45, 2.08)
[Ca^+] $mmol{\cdot}L^{-1}$	1.25 (1.23, 1.26)	1.25 (1.24, 1.26)	0.00 (-0.01, 0.02)
[La^-] $mmol{\cdot}L^{-1}$	2.08 (1.76, 2.40)	1.73 (1.42, 2.05)	-0.34 (-0.73, 0.04)
[Glucose] $mmol{\cdot}L^{-1}$	5.62 (5.27, 5.97)	5.29 (5.01, 5.58)	-0.32 (-0.86, 0.21)

Results are expressed as mean (95% confidence interval). Differences in the delta (pre to post supplementation changes) between treatments are indicated by * $p < 0.05$.

8.4.2 Performance Data

There was no main effect of Treatment on the time to complete each exercise block, indicating no change in the overall total time to complete the exercise protocol (calcium lactate: 133.60 min [130.28, 136.91]; placebo: 134.06 min [130.73, 137.36], p = 0.321, dz = 0.257).

Additionally, there were no interaction effects of Treatment × Time on the time to complete each 1 km TT (p = 0.708, η2 p = 0.019) or on the time to complete each 4 km TT (p = 0.275, η2 p = 0.082) **(Figure 8.3).** Furthermore, there were no differences in the laboratory environment's temperature, barometric pressure, and humidity between the treatments (all p > 0.05). In addition, the total water consumption during exercise did not differ between the treatments (p = 0.895).

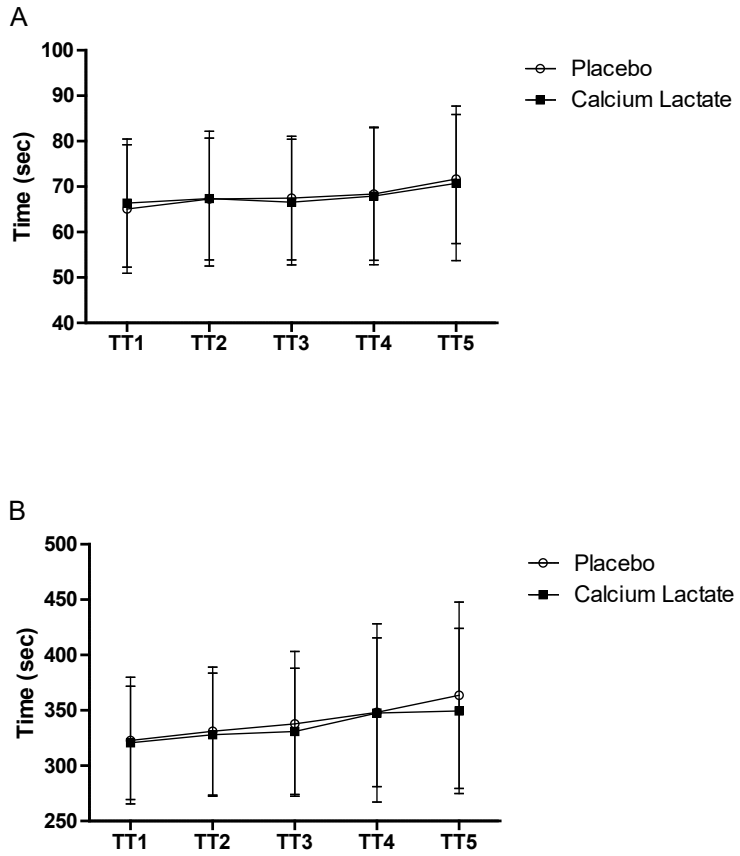


Figure 8.3 Time to complete each 1 km time trial (A) and time to complete each 4km time trial (B).
TT= Time trial. Results are expressed as mean (SD).

8.4.3. Heart Rate and Perceived Exertion

There was no main effect of Treatment ($p = 0.536$, $\eta 2p = 0.033$) or an interaction effect of Treatment × Block × Time on heart rate ($p = 0.298$, $\eta 2p = 0.095$). In contrast, there was a significant main effect of Treatment on RPE **(Figure 8.4)**, with a significant reduction in RPE with calcium lactate supplementation ($p = 0.012$, $\eta 2p = 0.423$); however, no interaction effects were observed (all $p > 0.05$).

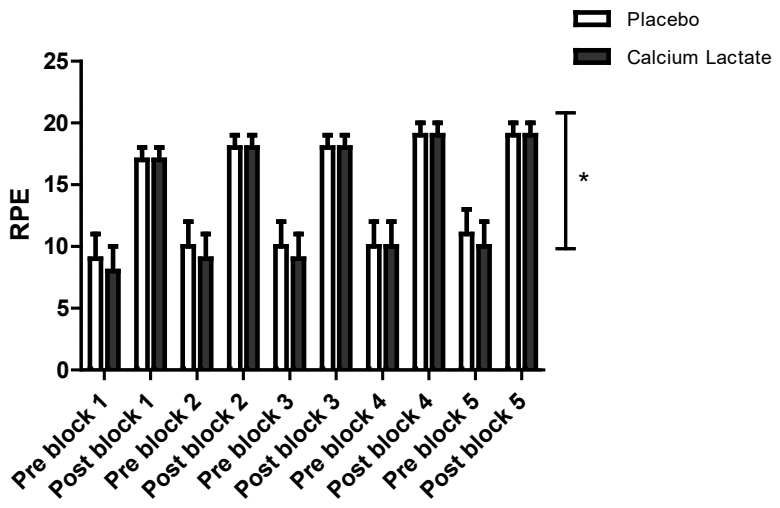


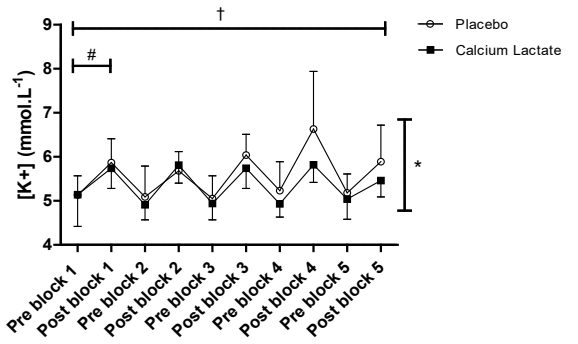
Figure 8.4 Ratings of perceived exertion pre and post each exercise block (*n*=13).
RPE = ratings of perceived exertion. Results are expressed as mean (95% confidence interval). * Indicates significant main effect of Treatment (* $p < 0.05$).

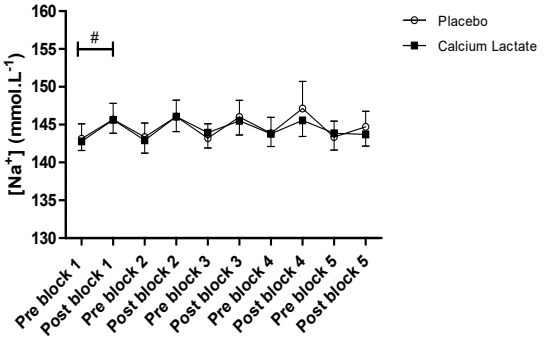
8.4.4 Acid–Base Balance and Metabolic Measurements during Exercise

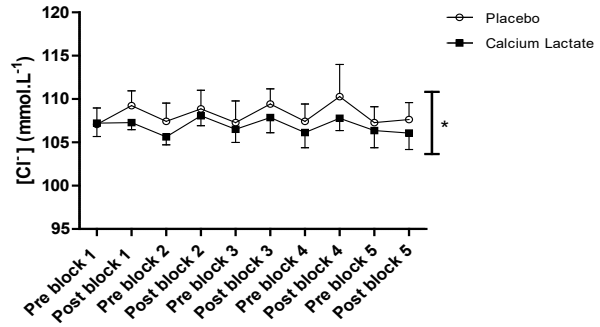
There was a main effect of Treatment on [K^+] (4% lower in calcium lactate than placebo) ($p = 0.002$, $\eta 2p = 0.528$) **(Figure 8.5).** Interaction effects of Treatment × Block ($p = 0.018$, $\eta 2p = 0.201$) and Treatment × Time ($p = 0.040$, $\eta 2p = 0.285$) were noted, though no three-way interaction effect was found. There was no main effect of Treatment on [Na^+] ($p = 0.298$, $\eta 2p = 0.083$), but there was a Treatment × Time interaction effect ($p = 0.016$, $\eta 2\ p = 0.370$). There was a main effect of Treatment on [Cl^-], with calcium lactate supplementation leading to lower [Cl^-] ($p < 0.001$, $\eta 2p = 0.598$), however, no Treatment interaction effects were observed (all $p > 0.05$). There was no main effect of Treatment on [La^-] ($p = 0.348$, $\eta 2p = 0.068$) or

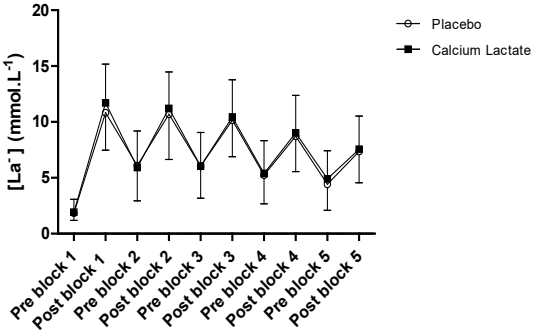
interaction effects of Treatment × Block × Time ($p = 0.615$, $\eta 2p = 0.040$). There was a main effect of Treatment on [Ca^{2+}], with calcium lactate supplementation leading to higher [Ca^{2+}] ($p < 0.001$, $\eta 2p = 0.855$). There was also a Treatment × Block interaction effect ($p < 0.001$, $\eta 2p = 0.619$), however, no Treatment × Block × Time interaction effect was observed ($p = 0.605$, $\eta 2p = 0.44$).

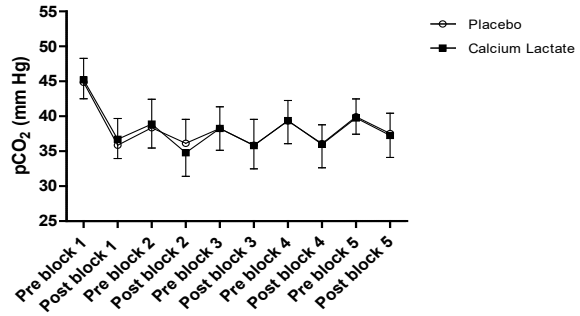
There was no significant main effect or interaction effects of Treatment on pCO_2 (all $p > 0.05$). There was a main effect of Treatment on [SID], with increased [SID] occurring with calcium lactate supplementation ($p = 0.026$, $\eta 2p = 0.327$). There was a main effect of Treatment on [HCO_3^-], with calcium lactate supplementation leading to higher [HCO_3^-] ($p = 0.041$, $\eta 2p = 0.284$). There was no main effect of Treatment on [H^+] ($p = 0.056$), although the effect size was large ($\eta 2p = 0.254$). For [HCO_3^-], [SID], and [H^+], there were no Treatment × Block × Time interaction effects ($p > 0.05$). There was no main effect of Treatment on [Glucose] ($p = 0.097$, $\eta 2p = 0.197$) and no Treatment × Block × Time interaction effect ($p = 0.642$, $\eta 2p = 0.046$). There was, however, a Treatment × Block interaction effect ($p = 0.028$, $\eta 2p = 0.246$), with less of a decline in [Glucose] observed in the calcium lactate group compared to the placebo group over the course of the exercise blocks.

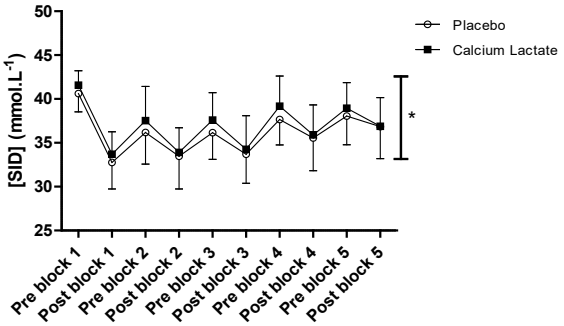

†
#
*
Placebo
Calcium Lactate
[K+] (mmol.L-1)
9
8
7
6
5
4
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5

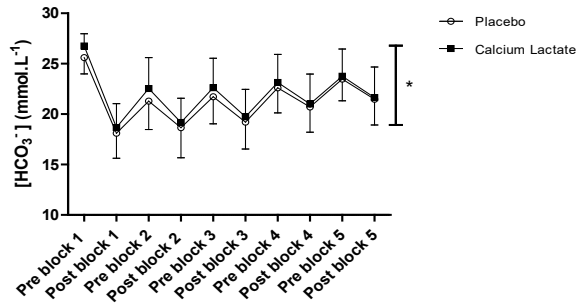

#
Placebo
Calcium Lactate
[Na+] (mmol.L-1)
160
155
150
145
140
135
130
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5

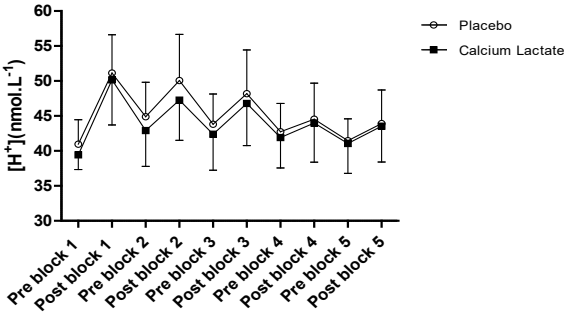

*
Placebo
Calcium Lactate
[Cl-] (mmol.L-1)
120
115
110
105
100
95
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5


Placebo
Calcium Lactate
[La-] (mmol.L-1)
20
15
10
5
0
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5


Placebo
Calcium Lactate
pCO2 (mm Hg)
55
50
45
40
35
30
25
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5


*
Placebo
Calcium Lactate
[SID] (mmol.L-1)
50
45
40
35
30
25
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5


*
Placebo
Calcium Lactate
[HCO3-] (mmol.L-1)
30
25
20
15
10
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5


Placebo
Calcium Lactate
[H+](nmol.L-1)
60
55
50
45
40
35
30
Pre block 1
Post block 1
Pre block 2
Post block 2
Pre block 3
Post block 3
Pre block 4
Post block 4
Pre block 5
Post block 5

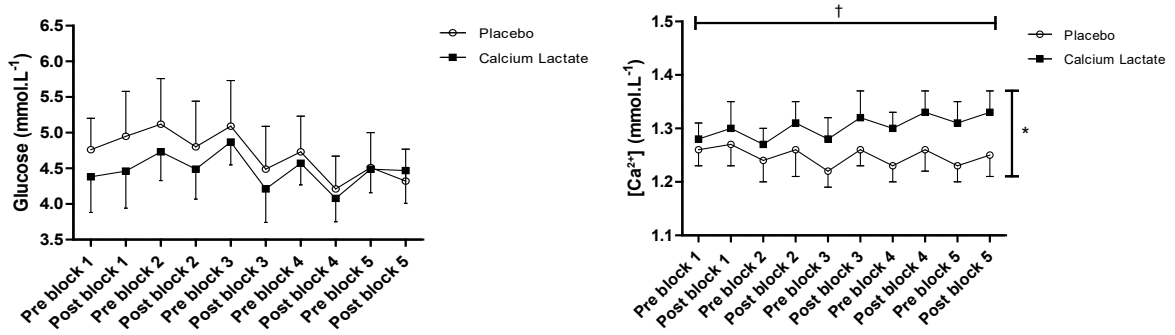


Figure 8.5 Blood acid–base balance and glucose pre and post each exercise block (*n*=14).

Results are expressed as means (95% confidence interval). * Indicates significant main effect of Treatment (* $p < 0.05$). † Indicates significant Treatment × Block effect (* $p < 0.05$). # Indicates significant Treatment × Time effect (* $p < 0.05$).

8.4.5 Gastro-Intestinal Tolerance

Flatulence ($p = 0.027$, $W = 0.171$), stomach cramps ($p = 0.046$, $W = 0.151$), belching ($p = 0.022$, $W = 0.179$), stomach ache ($p = 0.020$, $W = 0.182$), and bowel urgency ($p = 0.035$, $W = 0.161$) were all found to increase significantly during the exercise protocol following lactate supplementation, whereas no significant changes were found in nausea ($p = 0.103$, $W = 0.120$), diarrhoea ($p = 0.406$, $W = 0.063$), vomiting ($p = 0.607$, $W = 0.042$), or stomach bloating ($p = 0.115$, $W = 0.116$). In contrast, no significant increases in any symptoms were found during the exercise protocol following consumption of the placebo (all $p > 0.05$). Pairwise comparisons between interventions at individual time points only showed that, compared to the placebo, bowel urgency was significantly higher after calcium lactate supplementation following the third 4 km TT ($z = 2.060$, $r = 0.515$, $p = 0.039$).

8.5 Discussion

This study represents the first investigation into the effects of oral lactate supplementation on exercise performance during prolonged exercise that simulated the demands of endurance road race cycling. It was hypothesised that this specific type of activity, given lactate's proposed buffering capacity (Brooks., 1986; Fahey et al., 1991; Morris et al., 2011; Morris et al., 2016;

de Salles Painelli et al., 2014; van Montfoort et al., 2004) and potential impact on energy availability (Azevedo et al., 2007) may be particularly responsive to improvements. Our findings demonstrated that lactate supplementation positively influenced acid–base balance, with significant elevations in [HCO_3^-] and [SID], along with a reduction in perceived exertion. However, despite these changes, there were no discernible effects on cycling time trial performance. These results are in agreement with others that have shown increased blood [HCO_3^-] following lactate supplementation (Fahey et al., 1991; Morris et al., 2011; Morris et al., 2016; Northgraves et al., 2013; de Salles Painelli et al., 2014; Swensen et al., 1994) and reductions in perceived exertion (Peacock et al., 2017). However, in contrast to others (Morris et al., 2011; Morris et al., 2016; van Montfoort et al., 2004) lactate supplementation in the present study failed to yield exercise performance benefits and, consequently, our study provides evidence that challenges the efficacy of lactate supplementation as an ergogenic aid, particularly in the context of prolonged intermittent exercise. Acute calcium lactate supplementation decreased the resting blood [Cl^-] by 2 mmol · L^{-1}. Since other ions were unchanged at rest, the increased [Cl^-], therefore, accounted for the approximately equimolar increase in [SID] and, subsequently, the increase in [HCO_3^-]. Compared to the placebo, calcium lactate supplementation also resulted in a mean [SID] that was 0.74 mmol · L^{-1} higher during exercise. Since there were no differences in pCO_2 between treatments, the higher [SID] can largely account for the lower [H^+] (evidenced by the large effect size) and higher [HCO_3^-] after the calcium lactate supplementation (Stickland et al., 2013), although we cannot discount a slight role played by between-trial differences in the total weak acid concentration supplementation (Stickland et al., 2013). The higher [SID] during exercise after calcium lactate supplementation resulted from the net effect of changes in several strong ions. Specifically, while the lower [K^+] after calcium lactate supplementation would, by itself, reduce [SID], this was numerically offset by the higher [Ca^{2+}] and (to a greater extent) the lower [Cl^-], which

would both increase [SID]. The mechanisms that explain why the calcium lactate supplementation resulted in lower [Cl^-] at rest and, compared to the placebo, lower [Cl^-] and [K^+] during exercise, are beyond the scope of the present study, but could be related to differences in water shifts and, therefore, plasma volume (Lindinger et al., 1992; Miller et al., 2005) and/or alterations in ion transport systems (Hostrup et al., 2021). Reduced acid–base perturbation during exercise after calcium lactate supplementation may also influence the ensemble group III/IV muscle afferent feedback (Amann et al., 2020), which may explain, in part, the reduced RPE observed in the present study (Hureau et al., 2018; Johnson et al., 2015). Previous studies have demonstrated positive responses in acid–base balance following acute lactate supplementation. Morris et al. (2011; 2016) demonstrated, in two separate studies, improvements in acid–base balance using the same lactate dose and supplementation strategy as the current study, with significant increases in blood [HCO_3^-], but no significant changes in pH. However, in contrast, they observed significant improvements in intermittent exercise. Considering the evidence from Morris et al. (2011; 2016) it was reasonable to expect that, within the current study, the same dose of 120 mg · kg_{-1} body mass, administered 70 min before exercise, would enhance performance, particularly as higher doses have not been associated with additional improvements (Morris et al., 2016; de Salles Painelli et al., 2014) and the buffering effects of lactate are sustained for 140 min post-administration (Morris et al., 2011). There are, however, several differences between our work and that of Morris et al. (2011; 2016), which may have contributed to the differences shown in the performance effects. A notable difference was that the current study showed an increase in blood [HCO_3^-] of 4% (25.76 to 26.68 mmol · L^{-1}) between pre and post supplementation, which is lower than the 10% increase observed by Morris et al. (2011; 2016). The reasons that our study did not observe a similar increase in [HCO_3^-] following supplementation are unclear but may explain the lack of performance effects. Furthermore, the nature of the exercise within the current study

was significantly different compared to that of Morris et al. (2011; 2016) who evaluated the time to exhaustion following multiple bouts of high-intensity exercise of a significantly shorter duration. This type of exercise significantly increases acidosis, eliciting twice the increase in [H+] levels (Hebestreit et al., 1996) compared to our current findings. Consequently, it might be more responsive to the alkalising effects of lactate, which could lead to an enhanced performance. Furthermore, it appears clear that these differences in the exercise protocols likely led to the varying incidence of gastrointestinal symptoms reported. The ratings of perceived illness and stomach ache were low and insignificant, with no reports of gastro-intestinal symptoms affecting performance in the work of Morris et al. (2011; 2016). This is not surprising given the significantly shorter duration of exercise within their studies and that, within the current study, gastro-intestinal symptoms such as flatulence, stomach cramps, belching, stomach ache, and bowel urgency all increased as the exercise progressed, thus potentially impacting performance. Overall, the discrepancies between our study and the findings from Morris et al. (2011; 2016) indicate that the changes in acid–base perturbation and RPE after the calcium lactate supplementation in the present study were not sufficiently large enough to elicit an improvement in exercise performance. This suggests that the dosing strategy, including the form, amount, and frequency of lactate supplementation for performance improvement, requires further investigation (Brooks., 2023) particularly for this type of exercise protocol.

8.5.1 Strengths and Limitations

Our study has several strengths, including the randomised double-blind crossover design that allowed for the effects of calcium lactate to be directly compared against a placebo. Within the study, we implemented strict dietary control prior to exercise, with the provision of standardised meals and strict dietary restrictions in order to minimise any nutritional influence on metabolism and, subsequently, exercise performance. Furthermore, the study has a high

external validity, as the exercise protocol included is reflective of the intensities found within competitive cycling endurance events with bouts of moderate intensity exercise interspersed with high-intensity exercise, mimicking competitive road race cycling. As such, it is applicable to real-life competitive endurance events (Sanders & Heijboer., 2018; Vogt et al., 2006). There are several limitations in the present study that future research should address. Future studies exploring lactate's efficacy should consider using sodium lactate instead of calcium lactate. This change could potentially enhance the supplement's effects, as sodium lactate might support greater lactate uptake through sodium-coupled monocarboxylate transporters (Ganapathy et al., 2008), and sodium also plays a direct role in increasing the strong ion difference ([SID]). Moreover, considering the duration of our trial (approximately 2 h), it might have been beneficial to administer multiple doses of lactate to sustain the changes in the acid–base balance required to evoke a performance effect. However, studies evaluating the performance effects of frequent smaller doses of lactate are less convincing compared to studies using single higher doses (120 mg・kg^{-1} body mass and above) (Bryner et al., 1998; Fahey et al., 1991; Morris et al., 2011; Morris et al., 2016; van Montfoort et al., 2004). Future studies might, therefore, consider incorporating a single high dose prior to exercise followed by additional multiple doses in order to elicit greater and more sustained changes in acid–base balance and perceived exertion, which may then translate to an improved performance during prolonged exercise. However, this may prove difficult to implement due to the negative effect that this may have on gastro-intestinal symptoms. In addition, unlike others (Azevedo et al., 2007; Péronnet et al., 1997), we did not assess the lactates oxidation rate throughout exercise via isotope tracers and, therefore, could not assess the metabolism of lactate, which may have increased our understanding as to why there was no effect on performance.

8.6 Conclusion

The current study found no improvements in prolonged high-intensity interval cycling time trial performance following calcium lactate supplementation, despite reduced perceived exertion and changes in acid–base perturbation. These findings, in comparison to other studies, indicate that the dosing strategy utilised may have been insufficient to elicit the required influence on acid–base balance for performance enhancement, specifically for exercise of this intensity and duration. Future studies need to consider the optimal dose and form of lactate that can be practically administered, minimising potential gastro-intestinal side effects while maximising cycling time trial performance benefits.

8.6.1 Application to GSD

Given the absence of measurable performance enhancement and the progressive gastrointestinal symptoms observed in healthy, trained participants, it appears that lactate supplementation, at least in the form and dose administered, is unlikely to be a practical or therapeutic intervention for individuals with GSDs. The gastro-intestinal effects in particular following oral administration, raise significant concerns about its day-to-day tolerability and usability, particularly in populations already contending with the numerous physical challenges associated with these conditions. Consequently, alternative formulations, doses, or delivery methods would need to be carefully explored before considering lactate supplementation as a viable therapeutic strategy for individuals with GSD.

Future research should aim to comprehensively evaluate the metabolic and buffering properties of lactate, focussing on optimal dosing strategies, delivery mechanisms, and potential modifications to enhance tolerability and effectiveness. Additionally, consideration into the chronic effects of lactate supplementation are essential, in which short-term studies such as this fail to fully capture lactates long-term impact on gastrointestinal symptoms or any broader

effects over time. Overall, further research is needed to refine our understanding of lactate's properties, safety, and mechanisms of action. Only then can its potential as a novel therapeutic intervention in metabolic disorders be realistically considered.

Chapter 9 – General Discussion

9.1 Summary of Key Findings

This thesis aimed to investigate the exercise intolerance and the natural progression of GSD 3a. Recognising the widespread exercise intolerance, not just in GSD 3a but across the wider spectrum of GSDs, it sought to evaluate the effectiveness of exercise training as a therapeutic strategy and identify potential barriers and facilitators to physical activity participation. Beyond exercise, this thesis aimed to explore the role of lactate as a novel dietary treatment for glycogenolytic/glycolytic disorders such as GSD 3a. Establishing a thorough understanding of the extent of exercise intolerance, disease progression and the effectiveness of non-pharmacological treatment strategies aims to provide researchers and clinicians with essential information to develop targeted therapeutic interventions, optimising clinical outcomes and enhancing the QoL for this population.

To achieve these aims, exercise capacity including aerobic capacity and muscle strength was first quantitatively assessed in individuals with GSD 3a (*n*=7), providing benchmarking data on exercise limitation **(Chapter 3)**. Subsequently, a longitudinal follow-up of a subset of GSD 3a individuals (*n*=3) was conducted to assess the progression of exercise limitation and identify associated factors **(Chapter 4)**. Given the potential of exercise training programmes to mitigate exercise intolerance and disease progression, not only in GSD 3a but across the spectrum of GSDs, the effectiveness of such programmes was comprehensively reviewed **(Chapter 5).** Following this, a cross-sectional survey (*n*=55 part one, *n*=18 part two) was conducted to quantitively examine physical activity participation and identify barriers, facilitators and exercise preferences **(Chapter 6).** Building on this work, qualitative interviews (*n*=8) were subsequently conducted to gain in-depth, context-specific insights into individual level barriers and facilitators to activity **(Chapter 7)**. Lastly, oral lactate supplementation was investigated

in a healthy population (n=16) as a potential novel treatment for individuals with glycogenolytic and glycolytic deficiencies, such as GSD 3a **(Chapter 8)**.

The key findings from studies within this thesis are summarised as follows:

Chapter 3

- Aerobic capacity and knee extension strength were lower in GSD 3a compared to predicted values based on their demographic data.
- Muscle size and quality showed positive associations with both aerobic capacity and knee extension strength suggesting that muscle atrophy and neuromuscular impairments contribute to the functional decline observed.
- A high physical capacity group emerged, that had normal leg strength and relatively high aerobic capacity, and a low physical capacity group that displayed impaired strength and substantially lower aerobic capacity.
- The higher physical capacity sub-group were younger, had superior muscle size and quality, and engaged in more physical activity and reported higher health-related QoL.

Chapter 4

- Longitudinal case series analysis of individuals with GSD 3a found muscle strength progressively declined with age and disease stage, with a decline of 5% per year during the 3rd to 4th decade of life and 8% per year during 5th to 6th decade of life.
- This was accompanied by marked reductions in muscle volume, with a decline of 3% between 3rd to 4th decade of life and 9% between the 5th to 6th decade of life.
- Additionally, there was notable heterogeneity even among individuals of similar ages, highlighting inherent differences in the disease and the potential influence of lifestyle factors such as physical activity in attenuating disease progression.

Chapter 5

- A systematic review of the literature found that in GSD 5, aerobic exercise training improved VO_{2peak} by 14–111% with additional benefits to functional capacity and well-being.
- Strength training in GSD 5 increased muscle peak power by 100–151% and reduced disease severity.
- In GSD 2, a combination of aerobic and strength training improved VO_{2peak} by 9–10%, muscle peak power by 64%, functional capacity and well-being.
- RMT in GSD 2 improved respiratory muscular strength by 65-70%, with additional benefits in aerobic capacity, functional capacity and well-being.
- However, the current literature on the efficacy of exercise training programmes was both limited in scope and quality, with no studies investigating exercise training in other GSD subtypes.

Chapter 6

- The majority of those with GSDs (95%) reported that their GSD impacts daily activity, with muscular symptoms and fatigue commonly reported, particularly in those with muscular involvement and negatively impacting QoL.
- Physical activity levels were low overall and found to be associated with fatigue and motivation.
- Prominent barriers to physical activity included symptom severity, concerns that physical activity might worsen their condition, and a lack of motivation.
- Despite barriers, there was a strong interest in participating in physical activity programs (86%) particularly home-based or using outdoor public spaces, incorporating light to moderate cardiovascular and strengthening activities with ongoing professional input.

Chapter 7

- A deeper exploration into individuals insights revealed a wide range of barriers and facilitators to physical activity, categorised within 1) Physical, 2) Psychological, 3) Environmental, and 4) Social factors.
- Physical health emerged as a significant physical factor, heavily influencing engagement with physical activity. Disease-specific symptoms, such as fatigue (common across subtypes) and muscle-related symptoms or hypoglycaemia (prominent in subtypes affecting muscle and/or liver) were key contributors to these limitations
- Physical health challenges often influenced psychological factors, such as motivation, interest, and fear of symptoms or injury.
- Within environmental factors, accessibility to exercise facilities and their proximity were critical considerations, particularly for individuals with muscular symptoms.
- Social support, particularly from professionals, was crucial. Tailored exercise advice, monitoring, and feedback were especially important for individuals with muscular involvement.

Chapter 8

- Oral lactate supplementation in healthy trained individuals resulted in positive changes in acid-base balance, including significant increases in [HCO_3^-] and [SID], as well as reductions in RPE.
- However, there were no discernible effects on exercise performance.
- Given the absence of performance effect and progressive gastrointestinal symptoms, lactate supplementation, in the form and dose administered, is unlikely to be a practical therapeutic intervention in GSD.

9.2 Discussion of Key Findings

9.2.1 Exercise intolerance in GSD 3a: Cross-sectional and longitudinal Insights

Data from **Chapter 3** quantified for the first time the profound exercise intolerance and muscle impairment in GSD3a, demonstrating significantly lower aerobic capacity and muscle strength compared to predicted values. This research builds on the sparse cross-sectional studies available, including limited normative data on cardiovascular fitness (Hoogeveen et al., 2021; Preisler et al., 2013; Preisler et al., 2015) and leg strength in GSD 3a (Decostre et al., 2016) using commonly used, robust and validated technologies. Moreover, the role of muscle size and quality in exercise impairment was explored for the first time. This provided new insights, with the emergence of a high physical capacity group that were younger, with superior muscle size and quality, higher physical activity and better QoL.

Building on this work, a longitudinal follow up in **Chapter 4**, documented the progression of GSD 3a with a notable decline following 30 years of age in aerobic capacity and muscle strength, accompanied by marked reductions in muscle volume and muscle quality. However, in contrast to predictions of a 0.7% annual decline in muscle function based on cross-sectional literature (Decostre et al., 2016), the observed rate of decline did not follow a linear trajectory, but instead appeared to be progressive (5% per year during 3-4th decade of life and 8% during 5-6th decade of life) with vast heterogeneity. These novel findings highlight the individualised and complex progression of GSD 3a, underscoring the critical need for longitudinal assessments to accurately define the natural course of the disease. Such assessments would provide clinicians with essential data to evaluate the effectiveness of current and future treatments, including the identification of relevant endpoints and comparator normative data, which are key requirements for future clinical trials and drug discovery efforts.

9.2.2 The Therapeutic Potential of Exercise in GSDs

The significant decline in exercise tolerance in GSD 3a and across the spectrum of GSDs may be amenable to change, with evidence suggesting exercise to be of benefit (Preisler et al., 2015). Exercise has long been advocated as a therapeutic strategy and included in a growing number of therapeutic guidelines (Cupler et al. 2011; Kishnani et al., 2006; Kishnani et al., 2010; Lucia et al., 2021; Wicker et al., 2023). However, the research underpinning recommendations remains sparse and heterogenous, with only one prior systematic review including a limited number of studies in GSD 5 (Quinlivan et al., 2011). Subsequently, **Chapter 5** systematically reviewed the current evidence using a defined and reproducible strategy, establishing for the first time, the impact of exercise training across the broad spectrum of GSDs. This review clarified that supervised aerobic and/or resistance training is both safe and effective for adults with GSD 5, demonstrating improvements in $\dot{V}O_{2peak}$ (14-111%), peak power (100-151%), functional capacity, and well-being, as well as for adults with GSD 2, with improvements in $\dot{V}O_{2peak}$ (9-10%) and peak power (64%). However, these conclusions were largely based on the limited quality and quantity of evidence available, including primarily small uncontrolled intervention studies of short duration and highly varied exercise protocols, restricting the generalisability of findings. Importantly, this review revealed a critical gap in the current literature, in which the impact of exercise training in other GSD types, including GSD 3a has not yet been studied. Therefore, high-quality research is urgently needed to assess the efficacy of exercise as a therapeutic intervention across the full spectrum of GSD subtypes.

9.2.3 Physical Activity in GSDs: Facilitators, Barriers and Opportunity for Tailored Interventions

While exercise has been shown to benefit specific GSD subtypes within **Chapter 5**, the extent of physical activity engagement across the broader spectrum of GSDs remained unknown. To address this, **Chapter 6** quantitatively explored, for the first time, physical activity levels, behaviours, barriers, facilitators, and preferences among individuals with GSDs using an online survey. The findings revealed that the physical manifestations of GSD, particularly in those with muscular involvement, impair functional capacity and negatively impact QoL, aligning with previous research (**Chapter 3**; Chen et al., 2021; Derks et al., 2021; Gungor et al., 2016; Karazi et al., 2023). As expected, physical activity levels were generally low across the cohort (n=55), with nearly half of the respondents failing to meet general physical activity recommendations (Bull et al., 2020), aligning with prior research in GSD 5 (Karazi et al., 2023; Slipsager et al., 2024) and GSD 3a (Lee et al., 2011). Furthermore, physical activity levels were associated with fatigue, as previously noted in GSD 5 (Slipsager et al., 2024), as well as levels of self-determined motivation, which is recognised as crucial for both short- and long-term adherence to physical activity (Teixeira et al., 2012). Additionally, a range of perceived barriers to physical activity was reported, including symptom severity, concerns about worsening their condition, and lack of motivation, which mirror challenges observed in individuals with musculoskeletal disorders (McPhail et al., 2014) and rheumatoid arthritis (Wilcox et al., 2006). Interestingly, despite these barriers, a strong interest in participating in physical activity programs was revealed, particularly interventions involving light to moderate cardiovascular and strengthening exercises, either outdoors or at home, with ongoing professional support.

Expanding on the novel quantitative findings, **Chapter 7** delved deeper into the barriers and facilitators to physical activity at an individual level. Physical health emerged as a dominant theme influencing engagement in physical activity, with participants reporting muscular

symptoms, hypoglycaemia (depending on liver or muscular involvement), and fatigue. These findings align with barriers commonly described in individuals with chronic pain (Vader et al., 2021; Karlsson et al., 2018), musculoskeletal disorders (McPhail et al., 2014), Charcot-Marie-Tooth disease (Anens et al., 2015), and rheumatoid arthritis (Wilcox et al., 2006). Notably, these limitations were found to impact psychological factors, including motivation, interest, and fear, consistent with other clinical populations (Wilcox et al., 2006; Whipple et al., 2019). Environmental factors, such as access to exercise facilities and their proximity, were also identified as critical facilitators or barriers. This mirrors findings in the general population (Bartholomew et al., 2011; Yeo et al., 2014) and similar clinical groups (Bethancourt et al., 2014; Blonski et al., 2014; Dnes et al., 2021; Li et al., 2017; Meade et al., 2021 Whipple et al., 2019). Social factors, including support from family, friends, and professionals were found to play an integral role in physical activity engagement. Interestingly, even when professional advice was provided, participants often struggled to interpret or apply it. Consequently, participants emphasised a preference for professionals with expertise in GSD, who could provide supervision, reassurance, and tailored guidance. This increased confidence and promoted adherence, a finding echoed in other studies (Jones et al., 2006; Lia et al., 2017). It is therefore imperative that future interventions are tailored to address individuals' unique barriers and facilitators, using a goal-setting approach to promote successful exercise engagement. Those experiencing significant physical challenges may particularly benefit from home-based activities that can be done with others and delivered by professionals with expertise in both physical activity and GSD. Such interventions should include ongoing symptom monitoring, continued support, and feedback to optimise adherence and outcomes.

9.2.4 The Therapeutic Potential of Lactate in GSD

In addition to exercise training, **Chapter 8** evaluated the tolerability, safety, and efficacy of oral lactate supplementation in healthy individuals before considering its application as a potential dietary intervention for within GSD. Results demonstrated improvements in blood buffering capacity among healthy participants, consistent with findings from previous studies (Fahey et al., 1991; Morris et al., 2011; Morris et al., 2016; Northgraves et al., 2013; de Salles Painelli et al., 2014; Swensen et al., 1994) and reductions in perceived exertion (Peacock et al., 2017). However, in contrast to others (Morris et al., 2011; Morris et al., 2016; van Montfoort et al., 2004), lactate supplementation did not enhance exercise performance. Additionally, gastrointestinal symptoms, worsened as exercise progressed. Given the lack of measurable performance improvements and the side effects observed, oral lactate supplementation, at least in the form and dose tested, does not appear to be a practical or therapeutic option for individuals with GSD. These findings raise considerable concerns about lactates tolerability and practical usability, particularly in populations already facing substantial physical challenges. Furthermore, it remains uncertain whether oral lactate supplementation could have a more pronounced effect in these individuals, given their metabolic deficiencies. Alternative formulations, dosages, or delivery methods would need to be carefully investigated in animal models of GSD before lactate supplementation could be considered a viable therapeutic strategy for individuals with GSD.

9.3 Thesis Strengths and Limitations

The **Chapters 3-8** detail the specific strengths and limitations of each individual study included in this thesis. However, several overarching strengths and limitations apply to the entire body of work, warranting further discussion.

9.3.1 Addressing Research Deficits in GSD

A fundamental strength of this thesis lies in its provision of novel, comprehensive quantitative and qualitative data on adults with GSDs, addressing a significant knowledge gap in the field. Like many rare diseases, research into GSDs has historically been hindered by difficulties in obtaining funding (Zhu et al., 2021). This has resulted in a lack of high-quality research, a limitation recognised by government bodies, clinicians, and patients (Peeks et al., 2020; Real-world data, 2021; Sentner et al., 2016); ultimately limiting opportunities to improve patient care and advance drug development. Prior research, specifically in GSD 3 includes limited cross-sectional studies (Decostre et al., 2016; Hoogeveen et al., 2021; Preisler et al., 2013; Preisler et al., 2015) and retrospective longitudinal studies. While valuable, these retrospective reviews lack original data, are largely descriptive and lack detailed analyses of the progression of exercise intolerance and muscle impairment across the lifespan, as well as the associated contributing factors (Decostre et al., 2017; Hijazi et al., 2021; Sentner et al., 2016). This thesis overcomes these limitations by offering up-to-date, detailed cross-sectional and longitudinal data, which can contribute to improve clinical outcomes and guide future therapeutic research.

9.3.2 Cross-sectional and Longitudinal Contributions

A key strength of this work is its demonstration that the assessment of exercise intolerance, including aerobic capacity, muscular strength, size and architecture, is feasible in individuals with GSD 3a. By significantly expanding the limited literature, this study was the first to establish extensive normative reference values for aerobic fitness, muscle strength, and corresponding muscle size and quality, addressing critical gaps left by sparse cross-sectional and limited longitudinal studies. These cross-sectional findings highlight the profound reductions in aerobic capacity and muscle strength and offer valuable benchmarking data for clinicians and fellow researchers to monitor disease progression and help guide exercise training interventions (Kishnani et al., 2010). Moreover, the longitudinal follow-up provides

unique insights into the progression of exercise limitation, contrasting prior projections of a linear decline by revealing an accelerating deterioration in physical capacity and marked individual heterogeneity. This emphasises the urgent need for further longitudinal assessment to accurately capture the disease trajectory and subsequently highlights the importance of early therapeutic interventions. However, it is important to acknowledge that the small number of participants studied cross-sectionally (n=7) and longitudinally (n=3) may not fully represent the wider GSD 3a population or other GSD subtypes with muscular involvement. The limited sample sizes, which were to be expected given the rarity of the disease, introduce the potential for selection bias, which could skew the results toward fitter healthier individuals, thereby limiting the generalisability of the findings.

9.3.3 Utilisation of Robust and Validated Methodologies

This body of work employed extensive and validated quantitative measurement tools in GSD, an approach never previously undertaken. These included fixed isokinetic dynamometry and surface EMG for reliable assessments of muscle function, ultrasonography for precise structural evaluations, and validated questionnaires to capture additional relevant data. These methodologies ensured efficient, precise, and comprehensive data collection, which was especially critical given the small sample sizes, which was a challenge to be expected given the rarity of GSDs and the recruitment difficulties this creates. By adhering to standard operating procedures and utilising equipment commonly available in other research centres and hospitals, this work provides a robust framework that can be expanded upon to create a larger, more representative dataset. Furthermore, the use of validated methodologies facilitates comparisons with other studies, enhancing the potential for broader applicability and collaborative efforts to advance understanding in this field.

9.3.4 Novel Quantative and Qualitative Insights

This thesis was the first to both quantitatively and qualitatively explore physical activity levels, barriers, facilitators, and preferences across the spectrum of GSDs. The online survey captured a relatively large and diverse range of participants with various GSD subtypes (*n*=55), ensuring no exclusions due to geographic location or functional limitations. This approach enabled the efficient use of comprehensive and validated measurement tools, facilitating comparisons between GSD subtypes. Building on these findings, qualitative analysis of semi-structured interviews and focus groups (*n*=8) allowed for a deeper exploration of individual barriers and contextual factors, which had not been previously studied. Furthermore, Framework Analysis (Ritchie & Lewis, 2003) provided a systematic approach to comparing data within and between GSD subtypes, including those with muscular and/or involvement and those with solely liver involvement, uncovering novel, disease-specific insights. It is important to note however, that this work relied on participants' self-reported perceptions, which, while aligned with the research aims, may have led to overestimation or underestimation of their actual or potential physical activity levels. Additionally, the participant group may predominantly represent the most engaged and active individuals, potentially limiting the generalisability of the findings to the broader GSD population.

9.4 Directions for Future Research

The following recommendations are provided to advance knowledge regarding functional decline and the therapeutic efficacy of interventions in GSDs:

- Aim to continue longitudinal assessment of GSD 3a and across the broader spectrum of GSDs, using robust and validated methodologies. Such research will enhance our understanding of individuals disease trajectory and its associated factors, providing a strong foundation for developing more effective management and intervention

strategies. Ultimately, this will help improve clinical outcomes and QoL for individuals living with GSD.

- Aim to conduct larger multicentre randomised controlled trials to evaluate the efficacy, safety, and adherence of different exercise interventions in adults across the spectrum of GSDs. Comparing individual exercise components within these studies could provide deeper insights into the most effective training methods. Furthermore, longer-duration studies with multiple follow-up periods are necessary to determine whether the beneficial effects of exercise are sustained over the long term and to explore its potential role in preventing chronic conditions. Given the success of RMT and vibration training in GSD 2, as highlighted in **Chapter 5**, further investigation into these interventions is particularly warranted.
- Utilise the findings presented in this thesis to develop tailored exercise interventions. Based on this work these should incorporate light to moderate exercise, that can be done at home or in outdoor accessible spaces, that involve an individual's family and peers within group-based activity. Professional input was specifically important, thus opportunities where patients can interact with health professionals that have in depth knowledge of their condition and provide detailed information on exercise targets, intensity, frequency with ongoing monitoring may be particularly beneficial.
- Build on the findings of this thesis to further investigate the safety, tolerability, mechanisms of action, and effectiveness of lactate supplementation in healthy individuals. This may include an exploration of the chronic effects of lactate supplementation to fully capture its long-term impact on gastrointestinal symptoms or broader physiological effects over time. Only through further comprehensive research in health, can lactate's potential as a novel therapeutic intervention in GSD be realistically considered.

9.5 Conclusion

This thesis provides valuable insights into the profound exercise intolerance in those with GSD 3a. Longitudinal assessment clearly revealed the increasingly progressive and notably heterogenous decline in aerobic capacity and muscle strength, accompanied by corresponding alterations in muscle size and architecture. Existing evidence acknowledges this marked exercise intolerance is not just a hallmark of GSD 3a, but occurs across the wider GSD spectrum, posing a unique opportunity for intervention. Comprehensively reviewing the literature confirmed exercise training to be of benefit, with improvements in aerobic capacity, muscle strength and disease severity; however, this research is limited to GSD 2 and GSD 5. Despite the therapeutic benefit of exercise observed within specific subtypes, engagement in physical activity on the whole, remains low due to a plethora of challenges faced by this population. Encouragingly, there is a strong interest in participating in exercise interventions, particularly those incorporating light to moderate activities, delivered at home or in outdoor settings with social and continued professional support. In addition to physical activity, the potential of oral lactate supplementation, while offering initial promise in healthy participants, would need to undergo further investigation before its consideration in GSD. Consequently, further work is required to monitor disease progression and to develop tailored physical activity interventions aimed at attenuating the decline in functional capacity and enhance QoL in individuals with GSD.

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Appendices

Appendix A

Characteristics of GSDs (Adapted from Kanungo et al., 2018)

GSD type/Name	Phenotype MIM number	Enzyme Defect	Gene Defect (OMIM number)	Chromosome location
GSD0A/Liver GSD 0	240600	Liver glycogen synthase	GYS2 (138571)	12p12.1
GSD0B/Muscle GSD 0	611556	Muscle glycogen synthase	GYS1 (138570)	19q13.33
GSD1A/Von Gierke/Hepatorenal	232200	Glucose-6-phosphatase	G6PC (613742)	17q21.31
GSD1B/G6P transport defect	232220	Glucose-6-phosphate translocase	SLC37A4 (602671)	11q23.3
GSD2/Pompe/Cardiac GSD	232300	Acid maltase [alpha-1,4-glucosidase]	GAA (606800)	17q25.3
GSD3/Forbes/Cori/IIIa/IIIb	232400	Glycogen debrancher [amylo-1,6 glucosidase	AGL (610860)	1p21.2
GSD4/Andersen/Amylopectinosis/Neuromuscular/ Polyglucosan	232500	Glycogen brancher [amylo(1,4 to 1,6) transglucosidase]	GBE1 (607839)	3p12.2
GSD5/McArdle	232600	Myophosphorylase	PYGM (608455)	11q13.1
GSD6/Hers	232700	Liver glycogen phosphorylase	PYGL (613741)	14q22.1
GSD7/Tarui	232800	Muscle phosphofructokinase	PFKM (610681)	12q13.11
GSD9A1/XLG1/formerly GSD8	306000	Alpha-2 subunit of liver phosphorylase kinase	PHKA2 (300798)	Xp22.13
GSD9B/GSD IXb	261750	Beta subunit of liver and muscle phosphorylase kinase	PHKB (172490)	16q12.1
GSD9C/GSD IXc	613027	Hepatic and testis isoform—gamma subunit of phosphorylase kinase	PHKG2 (172471)	16p11.2

GSD9D/GSD IXd	300559	Alpha subunit of muscle phosphorylase kinase	PHKA1 (311870)	Xq13.1
GSD10/GSD X/PGAMM deficiency	261670	Muscle phosphoglycerate mutase	PGAM2 (612931)	7p13
GSD11/GSD XI/LDHA deficiency	612933	Lactate dehydrogenase A	LDHA (150000)	11p15.1
GSD12/GSD XII/Aldolase deficiency	611881	Fructose-1,6-bisphosphate aldolase A in red cell	ALDOA (103850)	16p11.2
GSD13/GSD XIII/Enolase 3 deficiency	612932	Beta-enolase	ENO3 (131370)	17p13.2
GSD14/GSD XIV/CDG1t/PGM1 deficiency	614921	Phosphoglucomutase-1	PGM1 (171900)	1p31.3
GSD15/GSD XV/GYG1 deficiency	613507	Glycogenin-1	GYG1 (603942)	3q24
Fanconi-Bickel syndrome/previously GSD XI	227810	None (glucose transport defect)	GLUT2/SLC2A2 (138160)	3q26.2
GSD Heart, lethal congenital	261740	Gamma-2 subunit of AMP-activated protein kinase/cardiac muscle phosphorylase kinase	PRKAG2 (602743)	7q36.1
Danon disease/lysosomal-associated membrane protein-2 deficiency/formerly GSD2b or GSD IIb	300257	[lysosomal-associated membrane protein-2 def-cy]	LAMP2 (309060)	Xq24
Brain GSD/Laforin deficiency (254780)	254780	Laforin; E3 ligase	EPM2A (607566); NHLRC1/EPM2B (608072)	6q24.3; 6p22.3

Appendix B

Information Sheet for Participants to Participate in the Study within Chapter 3

University College London Hospitals NHS
NHS Foundation Trust

NOTTINGHAM TRENT UNIVERSITY

Information Sheet for Participants (Version 4_22/12/2017)

You will be given a copy of this information sheet.

Title of Project: Exercise (in)tolerance in patients with rare glycogen storage disease (GSD); understanding the pathophysiology, improving assessment and producing normative data.

This study has been approved by the South Central - Berkshire B Research Ethics Committee Research Ethics Committee (Project ID Number): 195522

Invitation and brief summary

We would like to invite you to participate in this research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

We would like you to invite you to take part in the study entitled **'Exercise (in)tolerance in patients with rare glycogen storage disease (GSD); understanding the pathophysiology, improving assessment and producing normative data.**' We hope to recruit 30 volunteers with various glycogen storage disease to participate in a study looking at their levels of cardio-respiratory fitness.

If you decide to take part you will be required for testing on two days for approximately 3 hours on each visit. Each visit will be separated by at least 6 days in order to allow time for full recovery.

What's involved?

Explanation: purpose of and background to the research and invitation

This is a study to measure your cardio-respiratory fitness using 3 exercise tests and to analyse if fitness status is associated with disease severity, quality of life and daily activity levels. We will also measure your activity levels and take some measurements of your leg muscle size and function. These data will be very useful to help clinicians, fitness instructors and patients to have greater understanding of exercise test results for people with glycogen storage disease.

What would taking part involve?

If you agree to take part you will undergo three different cycle tests over two days, scheduled at least one week apart. These are; an incremental ramp test to determine how well your heart and lungs are working during exercise; a progressive constant-load moderate-intensity test for estimation of how efficiently you exercise; and a moderate-intensity exercise test to examine oxygen uptake speed, which is marker of how quickly your muscles and cardiovascular systems adapt to starting exercise. During each exercise test a device will analyse your breathing via a mask or mouth piece worn throughout each test. Other non-invasive monitors will be in place both as part of the study protocol and for your safety whilst exercising. These include oxygen levels measured with a finger probe, continuous electrocardiogram (ECG) and muscle oxygen levels. These protocols are routinely used in both research and clinical practice worldwide, with excellent safety records. Other assessments we will ask you to undergo are to have your leg muscles assessed for size, strength, and structure, and to wear an activity monitor for one week, which requires you to wear a watch-like device around your arm or waist whilst you go about your everyday life. Water and juice will be freely available throughout the day. Please also bring along a sugary drink of your choice.

Day 1:

On day 1 you will have your height, weight, sex and other basic information taken, you will also need to spend 20 minutes filling out three questionnaires to assess your activity levels, quality of life and the amount of pain you are experiencing. You will be asked if any particular type of exercise causes you difficulty. Following these tasks you will undergo (1) an incremental exercise ramp test, have your leg muscles assessed for (2) size and structure using ultrasound and (3) muscle strength. This will take approximately 3 hours in total with the exercise ramp test lasting approximately 15 minutes. At the end of day 1 you will be asked to wear a watch-like device that measures your activity levels for up to

one week. This is usually only a mild inconvenience as it is waterproof and can be worn in the shower and it can be worn at night. It does not require you to do anything other than wear it for most of the day. Once the week is complete, you can take the device off. We will collect the device at your second visit or we will provide you with a prepaid envelope in order for you to post it back to us.

1) Incremental ramp test

This will involve pedalling on a stationary exercise bicycle for approximately 15 minutes to assess the maximum amount of oxygen you can use during exercise. The workload will start very low and increase progressively until you reach the point at which you can no longer continue. A device will analyse your breathing via a mask worn throughout the test. The last 3-5 minutes of exercise will be at a high exercise intensity and the test stops when you decide you cannot exercise any longer.

2) Ultrasound

The size and make up of your muscle will be measured using ultrasound, which is a non-invasive method that uses sound waves to produce pictures of muscles, tendons, ligaments and joints throughout the body. Ultrasound is safe and non-invasive.

3) Muscle strength

A muscle dynamometer will be used to assess the strength of the leg and forearm muscles. This will take place at least 1 hour after the incremental ramp cycle test. It requires you to push your legs and arms against a set resistance to assess how strong you are. The test will consist of one warm up contraction which will last for 2-3 seconds at an intensity of less than 20% of maximum effort. Following this, we will ask you to complete two maximal contractions lasting no longer than 3 seconds each. In total, you will be asked to complete three contractions and you will have at least 10 minutes rest between each contractions.

The principal investigator and the medical doctor overseeing the tests will assess your reaction to each test. If on discussion with you we deem that the tests have caused an adverse reaction or that subsequent tests may cause harm, then you will not complete the remaining tests that day or undertake testing on day 2. Please let us know at any point during or between tests if you are experiencing any pain, cramp or difficulty with a test or if you are aware that any particular type of exercise is known to cause you difficulties. The test will then be stopped immediately. You will be asked before each test whether you feel able to proceed – please let the investigator know if you feel comfortable to continue.

Day 2.

On day 2 we will ask you to perform the following tests: (4) oxygen uptake speed to determine how quickly your muscle and cardiovascular system responds to exercise, and (5) exercise efficiency. These tests will be separated by at least one hour and you will rest

between them. Though tests 4 and 5 are quite long in duration, they are at exercise intensities at or below 60% of the maximum work achieved in test 1. You may not be able to complete all of the tests and you should stop if you feel pain or become too tired to continue.

4) Oxygen Uptake Speed

Oxygen uptake speed (or kinetics) is a measure of how long it takes your body to adjust to the demands of exercise. Fit people have short oxygen uptake speed as they adjust very quickly to starting exercise, whereas, unfit people have slow oxygen uptake speed as they adjust more slowly. To characterize oxygen uptake speed, you will perform three repetitions of a constant work rate of moderate intensity, each lasting 10 minutes, with 10 minutes easy cycling or rest in between.

5) Exercise efficiency

A 30 minute bout of exercise at 3 different workloads (all moderate in intensity) will be used to determine how much oxygen you use to produce a certain cycling work rate or running pace. In addition we will ask you to perform at higher intensities for up to 12 minutes, or as long as you can manage.

What are the possible benefits of taking part?

The major benefit of participating in this study is the opportunity to be part of a unique scientific research project that will hopefully lead to a greater understanding of your disease and how it can be managed.

What are the possible disadvantages and risks of taking part?

The study has been considered safe and has gained ethical approval from the South Central - Berkshire B Research Ethics Committee. During the initial health assessment we will determine your level of risk for the activities based on international guidelines and ensure the correct level of supervision and the appropriate monitoring equipment is provided. Specific risks that must however be mentioned are;

Exercise testing

The risk of exercise varies with the prevalence of underlying coronary artery disease in the population. Consequently, the risk of exercise stress testing to volitional fatigue also varies with the populations studied. Exercise stress testing performed in previously healthy individuals has a very low rate of cardiovascular events, whereas exercise testing in high-risk patients has a higher risk. The overall risk of exercise stress testing in a mixed population is approximately 4 cardiac events (i.e. 1 myocardial infarction and 3 cardiac arrests) per 10,000 tests. For your safety, in agreement with the American College of Cardiology/ American Heart Association (ACC/AHA) guidelines if you have any of the

following conditions (both absolute and relative) you will not be allowed to undergo exercise testing.

ACC/AHA Contraindications to Exercise Testing

Absolute

• Acute myocardial infarction (within 2 days)

• High-risk unstable angina*

• Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise

• Symptomatic severe aortic stenosis

• Uncontrolled symptomatic heart failure

• Acute pulmonary embolus or pulmonary infarction

• Acute myocarditis or pericarditis

• Acute aortic dissection

Relative

• Left main coronary stenosis

• Moderate stenotic valvular heart disease

• Electrolyte abnormalities

• Severe arterial hypertension‡

• Tachyarrhythmias or bradyarrhythmias

• Hypertrophic cardiomyopathy and other forms of outflow tract obstruction

• Mental or physical impairment leading to inability to exercise adequately

• High-degree atrioventricular block

Other potential issues related to exercising with glycogen storage diseases include fatigue, muscle pain (in 1 or more muscles), muscle cramping and swelling. Please let the investigator know immediately if you experience any of these symptoms. The test will then be stopped and you will be reviewed by the medical doctor.

Further supporting information

Do I have to take part?

No. Participation in the study is entirely voluntary. You will be allowed to withdraw from the study at any point for any reason. Similarly, you may withdraw from one experimental aspect, but continue with others if you wish. You may also withdraw your data from the study at any time up until it is used in the in the final report.

What if I feel unwell during the study?

During exercise tests we will be monitoring your heart with an ECG machine; if your heart starts to have insufficient blood flow (ischemia) or the rhythm of your heart beat changes in a dangerous way (arrhythmia) we will stop the test. At all times a trained medical doctor will be present during the study. We also have resuscitation equipment, medical oxygen and other emergency medical equipment available should you have a serious adverse reaction to any test. Initially, our medical doctor, who has advance life support training, would treat you and then you would be transferred to the main hospital via ambulance for further assessment and treatment.

Should you feel unwell at any time, the doctor can be consulted and you are under no obligation to continue the study. When your visit is complete, we will also contact you via telephone to establish if have had any adverse reactions to the exercise protocols. Furthermore, if you feel unwell at any time you should contact the inherited metabolic disease unit's 24 hour on-call consultant–led telephone service for advice. Contact is via the UCLH switchboard, telephone 0845 155 5000 / 020 3456 7890.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (details below).

If you remain unhappy and wish to complain formally, you can do this via the Principal investigator, Philip Hennis, who will aid you in this process (details below). In the event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against Nottingham Trent University or the National Health Service but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will I hear about the results?

The results will be made available to you on request, we will also present results a national patient conferences and meetings.

How will my information be kept confidential?

Your confidentiality will be maintained throughout the study in a way that ensures your data can always be tracked back to your source data. For this purpose, a unique identification code/number will be assigned to your data, and the file linking you to your unique identification code/number will be held securely on a password protected NHS computer, which will not hold other study data. Your Identifiable personal data will not be transferred outside the UK. Access to your medical notes will be strictly limited to the study collaborators/investigators and relevant regulatory authorities. All data collected will be stored in accordance with the Data Protection Act 1998. You will not be identified in any subsequent publications and ultimately your data will be disposed of in a secure manner

Involvement of General Practitioner / other healthcare practitioner

With your agreement, we will inform your GP that you are taking part in the study.

Who is organising and funding this study?

The study is sponsored by Nottingham Trent University (NTU) and is funded by grants from the Association for glycogen storage diseases (AGSD) and Manchester Metropolitan University.

What will happen to the results of the study?

Results will be reported in the scientific press and at national and international meetings, such that the gains of the research can be built upon. They may be used for additional or subsequent research projects. The research team recognise and respect your entitlement to privacy. Publication or presentation of data arising from this study will not allow identification of you. We will not directly or indirectly compromise your rights to confidentiality and anonymity.

What to expect during the consent process

If you decide to take part in this study you will be given a copy of this information sheet and a copy of the consent form to sign and keep. You will also be asked to fill in a brief health questionnaire and sign the consent form.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time and without giving a reason. You can be informed of the study's final conclusions if you wish. If you have any questions about the study we would be delighted to answer them for you.

Thank-you very much indeed for your help!

Further information and contact details

If you have any queries about the study, please contact one of the research team by telephone, email or post: The details are summarised below

Principal Investigator:

Philip Hennis PhD

Senior lecturer in Exercise Physiology, Department of Sport Science, Nottingham Trent University

New Hall Block 175, Clifton Campus, Clifton Lane, Nottingham, NG11 8NS

Tel: 07554436234

Email: philip.hennis@ntu.ac.uk

Co-investigator and clinical lead:

Dr Elaine Murphy,

Consultant in Inherited Metabolic Disease , Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG

Email: Elaine.Murphy@uclh.nhs.uk

All data will be collected and stored in accordance with the Data Protection Act 1998.

Appendix C

Statement of Consent to Participate in the Study in Chapter 3

Centre Number: 01

Study Number: 01

Participant Identification Number for this trial:

CONSENT FORM Version 3_22/12/2017

Title of Project: Exercise (in)tolerance in patients with rare inherited metabolic disorders; understanding the pathophysiology, improving assessment and producing normative data.

Name of Researcher: Philip Hennis

Please initial box

1. I confirm that I have read the information sheet dated..... (version 4_22.12.2017) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

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

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. (If appropriate) I agree to my General Practitioner being informed of my participation in the study. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix D

Letter of Invitation to Participate in the Study in Chapter 4

Dr. Philip Hennis
Nottingham Trent University
School of Science and
Technology
Clifton Campus
Nottingham
NG11 8NS

Letter of invitation: Version:1.0
<Insert date sent>
Principle Investigator: Dr. Philip Hennis.
Co-investigator and Clinical lead: Dr Elaine Murphy
IRAS ID: 303679

Dear patient,

We would like to invite you to participate in a research project entitled: **Longitudinal study of aerobic capacity and skeletal muscle characteristics in patients with rare inherited metabolic disorders (IMD).**

This research will take place at Nottingham Trent University in collaboration with the Charles Dent Metabolic Unit at the National Hospital of Neurology and Neurosurgery. Dr Philip Hennis (Senior Lecturer in Exercise Physiology) and PhD student Claire Bordoli will be conducting the research.

The purpose of this study is to increase our understanding of the degree of exercise intolerance and the rate of physical decline over time in inherited metabolic disorders. In addition, we hope to establish lifestyle factors that can impact the onset and/or severity of the decline. This will provide valuable information towards the development of interventions aimed at improving exercise tolerance and the onset and/or severity of disease progression.

Patients with the following are invited to participate:
Adult patients (18 years or above) with a diagnosis of a rare inherited disorder of metabolism including Glycogen storage disease, Fatty acid oxidation disorder and Phenylketonuria

Please find enclosed more detailed information.

Dr Philip Hennis or your consultant will be happy to answer any additional questions you might have about this study at any time.

Thank you for taking the time to consider taking part in this study – please email Dr Philip Hennis (email: philip.hennis@ntu.ac.uk) if you have further questions or wish to participate in the study.

Alternatively, you can contact Dr Elaine Murphy, Consultant in Inherited Metabolic Disease (elaine.murphy8@nhs.net) or Claire Bordoli, PhD Student at Nottingham Trent University (claire.bordoli2020@ntu.ac.uk)

Yours sincerely, Dr Philip Hennis, Dr Elaine Murphy and Claire Bordoli.

Appendix E

Information Sheet for Participants to Participate in the Study within Chapter 4

Information Sheet for Clinical Participants (Version 3_20/10/2022)

Title of Project: Longitudinal changes in aerobic capacity and skeletal muscle characteristics in participants with rare Inherited Metabolic Disorders (IMD).

This study has received a favourable ethical opinion (reviewed by SESREC01).

We would like to invite you to participate in this research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

We would like to invite you to take part in the study entitled "**Longitudinal changes in aerobic capacity and skeletal muscle characteristics in participants with rare Inherited Metabolic Disorders (IMD)"**

We hope that you will take part in this study as part of a group of 50 participants with various rare inherited metabolic disorders to help study how certain rare inherited metabolic diseases effect cardio-respiratory fitness, muscle function and bone health over time. If you decide to take part you will be required to complete a 7-day food diary (approximately 20 minutes), travel to and from Nottingham (approximately 3 hours) to attend one day of testing (approximately 6 hours). If you need to travel a long distance you may wish to stop the night in a hotel (approximately 8 hours). Following the testing day, you will be required to wear an activity monitor for 7 days and will be contacted via telephone on day 1,3 and 7 following testing (approximately 10 minutes per call). Costs associated with travel, accommodation, meals, and refreshments will be reimbursed (up to £250 per participant per year). This study is planned to be conducted for 10 years; however, funding has not been secured for the whole of the study duration. If the study were to be discontinued due to the lack of funding the initial results from the study will still be disseminated and we will notify you via email/telephone.

Brief Introduction

Rare inherited disorders of metabolism such as Glycogen Storage Diseases (GSD) and fatty acid oxidation disorders (FAOD) often result in high levels of fatigue and a reduced ability to exercise. In many types, this can progress throughout adult life. Despite wide awareness of this decline over time, very little long-term data is available. Other inherited metabolic

disorders such as Phenylketonuria (PKU) also require further study, particularly to investigate the impact of lifelong dietary restriction.
Long term studies such as this, will therefore allow us to increase our understanding of these rare disorders and may provide valuable information towards interventions aimed at improving the quality of life for those with these disorders.

Study Requirements:
Inclusion criteria: Adults (18 yrs. or above) with a diagnosis of a rare inherited disorder of metabolism including Glycogen storage disease, Fatty acid oxidation disorder and Phenylketonuria
Exclusion Criteria: Individuals who do not have the capacity to consent and those who are pregnant will not be allowed to take part in this study.

We will send a health screen questionnaire to you the week before your visit to establish if you are fit and able to undergo the day of testing. If you are pregnant or have given birth within the last 6 months you will not be allowed to undergo testing but you may re-enter the study 6 months after the birth.

What would taking part involve?
You will undergo two exercise tests:
1) An incremental ramp test on a stationary bike to determine how well your heart and lungs are working. During this exercise test, a device will analyse your breathing via a mask. Non-invasive monitors will be in place both as part of the study protocol and for your safety. These include oxygen levels measured with a finger probe, continuous electrocardiogram (ECG) and muscle oxygen levels. These protocols are routinely used in research and clinical practice worldwide, with excellent safety records.
2) Leg muscle exercise to assess muscle strength, activation, size, and structure.

We will also ask you to wear an activity monitor on your thigh for one week whilst you go about your everyday life. Every 3 years (year 0, 3, 6, 9) we would also like you to undertake x-ray imaging of your body, called DEXA scanning, to estimate your bone mineral density and body composition. In addition, we will record your current dietary treatment plan and obtain a 7-day food diary prior to each study day to assess your diet. All of these tests are non-invasive.

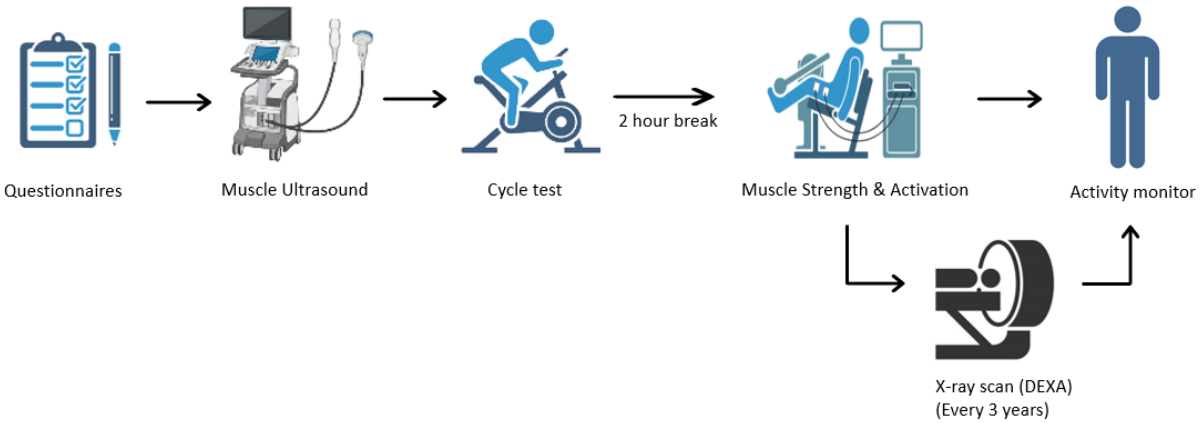
All exercise tests will be conducted in an exercise physiology laboratory in the presence of a medical doctor and an exercise physiologist. Tests will be conducted in a specific order to reduce the likelihood of one test affecting another, and to allow adequate time for recovery between exercise bouts. You will not be restricted from eating or drinking for the duration of the study, with water and juice being made freely available throughout the day. We will also provide a sugary drink. Throughout the day, you will be asked to stop the exercise if you believe continuing might result in muscle soreness and damage. The principal investigator and the

medical doctor overseeing the tests will assess your reaction to each test. If on discussion with you, we deem that the tests have caused an adverse reaction or that subsequent tests may cause harm, then you will not complete the remaining tests that day. Please let us know at any point during or between tests if you are experiencing any pain, cramp, or difficulty with a test or if you are aware that any particular type of exercise is known to cause you difficulties. The test will then be stopped immediately. You will be asked before each test whether you feel able to proceed – please let the investigator know if you feel comfortable to continue.

Day Protocol:

On arrival you will have your height, weight, body composition and other basic information taken. You will need to spend 20 minutes filling out questionnaires to assess your activity levels, quality of life and the amount of pain you are experiencing. You will be asked if any particular type of exercise causes you difficulty. In addition, your current dietary treatment plan will be recorded, and we will obtain a 7-day food diary prior to your visit for dietary assessment.

You will then complete 1) Muscle Ultrasound to assess your leg muscles size and structure and 2) an incremental ramp cycling test. Following a 2-hour break, you will have your leg muscles assessed for 3) muscle strength and 4) activation. You will also have your 5) Physical activity measured via an activity monitor. 6) Bone mineral density and body composition will be assessed via x-ray imaging every 3 years (year 0, 3, 6, 9). These tests will take approximately 6 hours in total, with the incremental cycle test lasting 15 minutes. At the end of the day, you will be asked to wear an activity monitor that will measure your activity for up to one week.



1) Muscle Ultrasound for muscle size and architecture

The size and make up of your leg muscles will be measured using ultrasound, which is a safe and non-invasive method that uses sound waves to produce pictures of muscles, tendons, ligaments and joints throughout the body.

2) Incremental ramp cycle test

This will involve pedalling on a stationary exercise bicycle for approximately 15 minutes to assess the maximum amount of oxygen you can use during exercise. The workload will start very low and increase progressively until you reach the point at which you can no longer continue. A device will analyse your breathing via a mask worn throughout the test and your heart rate, blood pressure and oxygen saturation will also be monitored. The last 3-5 minutes of exercise will be at a high exercise intensity and the test stops when you decide you cannot exercise any longer.

3) Muscle strength

A muscle dynamometer will be used to assess the strength of the leg muscles. This will take place at least 2 hours after the incremental ramp cycle test. It requires you to push your legs against a set resistance to assess how strong you are. The test will consist of one warm up contraction which will last for 2-3 seconds at an intensity of less than 20% of maximum effort. Following this, we will ask you to complete two maximal contractions lasting no longer than 3 seconds each. In total, you will be asked to complete three contractions and you will have at least a 5-minute rest between each contraction.

4) Muscle activation

Activation of the leg muscles will be measured via surface Electromyography (sEMG). This is a safe and non-invasive measurement which includes sensors being placed on the skins surface in order to measure electrical activity from the muscles during exercise.

5) Bone mineral density

If you participate in this trial, you will have four instances of x-ray imaging of your body, called DEXA scanning, to estimate bone mineral density and body composition.

6) Physical activity

At the end of the day, you will be fitted with an activity monitor, which just requires you to wear an activity monitor on your thigh for one week. You will be instructed on how to use it. This is usually only a mild inconvenience as it is waterproof and can be worn in the shower and at night. It does not require you to do anything other than wear it for most of the day. Once the week is complete, you can take the device off and we will provide you with a prepaid envelope for you to post it back to us.

Follow-Up

You will be contacted on day 1, 3 and 7 days following testing to establish if you have had any adverse reactions to the testing such as muscle pain, fatigue and any hospital admissions.

If the research procedures uncover any incidental health findings of clinical significance, the results will be reported to your medical team.

We can provide you with the opportunity to get in touch with previous participants who have already completed these tests. This may help you when deciding whether to participate

as they will be able to answer any questions and offer reassurance on any concerns you may have.

COVID-19 measures:

To help keep you and others safe and mitigate the spread of COVID-19, social distancing will be observed as much as possible during the completion of this study. All experimenters will wear a face covering during the trial. We also request, when you are not performing an experimental trial, that you also wear a face covering, which we will provide. If you develop any of the following symptoms you should not come to campus / lab, but instead consult the latest guidance on self-isolating:

- A new, continuous cough
- A high temperature
- A loss of, or change in, your normal sense of taste or smell

You should also avoid coming onto campus / into the lab and seek guidance on self-isolating if someone you live with has tested positive for COVID-19, or if you have been in close contact with someone who has had a positive test result. If any of the above applies to you, please inform one of the researchers as soon as possible.

In addition, we are cleaning and disinfecting all areas between participants. This includes all equipment, floors and surfaces with appropriate cleaning and disinfectant products.

What are the possible benefits of taking part?

The major benefit of participating in this study is the opportunity to be part of a unique scientific research project that will hopefully lead to a greater understanding of your disease and how it can be managed.

What are the possible disadvantages and risks of taking part?

The study has been considered safe and has gained ethical approval from …… During the initial health assessment, we will determine your level of risk for the activities based on international guidelines and ensure the correct level of supervision and the appropriate monitoring equipment is provided. Specific risks that must however be mentioned are:

Exercise testing

The risk of exercise varies with the prevalence of underlying coronary artery disease in the population. Consequently, the risk of exercise stress testing to volitional fatigue also varies with the populations studied. Exercise stress testing performed in previously healthy individuals has a very low rate of cardiovascular events, whereas exercise testing in high-risk participants has a higher risk. The overall risk of exercise stress testing in a mixed population is approximately 4 cardiac events (i.e., 1 myocardial infarction and 3 cardiac arrests) per 10,000 tests.

Potential issues related to exercising with metabolic disorders include fatigue, muscle pain (in 1 or more muscles), muscle cramping and swelling. Please let the investigator know immediately if you experience any of these symptoms. The test will then be stopped and you will be reviewed by the medical doctor. We have carried out a Nottingham Trent University Risk Assessment and put in place stringent safety procedures to help ensure exercise tests are conducted safely.

The DEXA scanning includes exposure to x-rays and brings a small risk of causing cancer years in the future. In this trial you will receive x-ray (radiation) exposure that you wouldn't have otherwise had, but this still amounts to the equivalent of only around a week of UK background radiation. This means that the risk is small enough to be considered trivial.

Further supporting information:

Do I have to take part?

No. Participation in the study is entirely voluntary. You will be allowed to withdraw from the study at any point for any reason. Similarly, you may withdraw from one experimental aspect, but continue with others if you wish and you may also withdraw your data from the study at any time up until it is used in the in the final report. The anonymised information collected will be used to support other research in the future and may be shared anonymously with other researchers.

What if I feel unwell during the study?

During exercise tests we will be monitoring your heart with an ECG machine; if your heart starts to have insufficient blood flow (ischemia) or the rhythm of your heart beat changes in a dangerous way (arrhythmia) we will stop the test. At all times a trained medical doctor will be present during the study. We also have resuscitation equipment, medical oxygen, and other emergency medical equipment available should you have a serious adverse reaction to any test. Initially, our medical doctor, who has advance life support training, would treat you and then you would be transferred to the main hospital via ambulance for further assessment and treatment.

Should you feel unwell at any time, the doctor can be consulted and you are under no obligation to continue the study. When your visit is complete, we will also contact you via telephone to establish if you have had any adverse reactions to the exercise protocols. Furthermore, if you feel unwell at any time you should contact the inherited metabolic disease unit's 24 hour on-call consultant–led telephone service for advice. Contact is via the UCLH switchboard, telephone 0845 155 5000 / 020 3456 7890.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (details below).

If you remain unhappy and wish to complain formally, you can do this via the Principal Investigator, Dr. Philip Hennis, who will aid you in this process (details below). In the event

that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against Nottingham Trent University or the National Health Service but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will I hear about the results?

Where possible you will be able to obtain your test results as the tests are completed. All of your final results will be made available to you on request. We will also present group results at national conferences and meetings.

Involvement of General Practitioner / other healthcare practitioner

With your agreement, we will inform your GP that you are taking part in the study.

Who is organising and funding this study?

The study is sponsored by Nottingham Trent University (NTU).

What will happen to the results of the study?

Group results will be reported in the scientific press and at national and international meetings, such that the gains of the research can be built upon. They may be used for additional and /or future research. The research team recognise and respect your entitlement to privacy. Publication or presentation of data arising from this study will not allow identification of you. We will not directly or indirectly compromise your rights to confidentiality and anonymity.

What to expect during the consent process

If you decide to take part in this study you will be given a copy of this information sheet and a copy of the consent form to sign and keep. You will also be asked to fill in a brief health questionnaire and sign the consent form.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time and without giving a reason. You can be informed of the study's final conclusions if you wish. If you have any questions about the study, we would be delighted to answer them for you.

How will my information be kept confidential?

The university research team will be provided with only your name, contact details, type of inherited metabolic disorder and if you have consented to participate. This will be provided by the NHS site in order for the university research team to organise your study visit. This will be the only identifiable data collected and will be given a unique identification code/number. Data will be stored in a folder on NTU secure servers, in which only members of the research team will have access. The file linking your personal details with the unique code will be stored securely in a separate computer folder, restricted to only necessary members of the research team. This ensures that personal data can no longer be attributed to a specific participant and is in line with the GDPR and the Data Protected Act 2018.

How will we use information about you?

We will need to use information from you for this research project.
This information will include your name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?
You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from **www.hra.nhs.uk/patientdataandresearch**
- by asking one of the research team
- by sending an email to NTU Data Protection Officer: dpo@ntu.ac.uk

Thank you very much indeed for your help!

Further information and contact details

If you have any queries about the study, please contact one of the research team by telephone, email or post. Alternatively, if you would like to communicate with someone who is not part of the study team, please communicate with the independent contact by telephone, email or post. The details are summarised below

Principal Investigator:
Philip Hennis PhD
Senior lecturer in Exercise Physiology, Department of Sport Science, Nottingham Trent University
New Hall Block 175, Clifton Campus, Clifton Lane, Nottingham, NG11 8NS
Tel: 07554436234

Email: philip.hennis@ntu.ac.uk

Co-investigator:
Claire Bordoli
PhD Student Nutrition and Exercise Physiology
Clifton Campus, Clifton Lane, Nottingham, NG11 8NS.
Email: claire.bordoli2020@my.ntu.ac.uk

Co-investigator and clinical lead:
Dr Elaine Murphy,
Consultant in Inherited Metabolic Disease, Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG
Email: elaine.murphy8@nhs.net

Independent contact:

Ryan Williams PhD
Lecturer in Exercise Physiology, Department of Sport Science, Nottingham Trent University
New Hall Block 175, Clifton Campus, Clifton Lane, Nottingham, NG11 8NS.
Tel: 0115 8486 182
Email: ryan.williams@ntu.ac.uk

Appendix F

Statement of Consent to Participate in the Study in Chapter 4

Centre Number: 01

Study Number: 01

Participant Identification Number for this trial:

CONSENT FORM Clinical Population Version 3_20.10.2022 (IRAS ID: 303679)

Longitudinal changes in aerobic capacity and skeletal muscle characteristics in patients with rare inherited metabolic disorders (IMD)

Name of Researcher: Dr. Philip Hennis and Claire Bordoli

	Please initial box
7. I confirm that I have read the information sheet dated version 3_20.10.22 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
8. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
9. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
10.	
11. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.	☐
12. I agree to my General Practitioner being informed of my participation in the study.	☐
13. I agree to take part in the above study.	☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

Appendix G

Prisma 2020 Reporting Checklist used within Chapter 5

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction Paragraph 6 (Page 6-8)
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction Paragraph 6 (Page 8)
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.1
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.	Section 2.2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2.2
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.	Section 2.3
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.	Section 2.5
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.	Section 2.5
	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.	Section 2.5
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.	Section 2.4

Section and Topic	Item #	Checklist item	Location where item is reported
			Supplement 2 Quality assessment
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.	Tables 2,4,6
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)).	Section 2.3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 2.5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section 2.5
	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.	Not preformed. The data were not suitable for synthesis due to the diversity in the populations, interventions, outcomes, and study designs.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	This analysis was not performed, as the data were not suitable for synthesis
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	This analysis was not performed, as the data were not suitable for synthesis

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Supplement 2 Quality assessment
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Supplement 2 Quality assessment
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.	Section 3.1 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement 1 Quality assessment
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.	Tables 1-6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	This analysis was not performed, as the data were not suitable for synthesis
	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.	This analysis was not performed, as the data were not suitable for synthesis
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	This analysis was not performed,

Section and Topic	Item #	Checklist item	Location where item is reported
			as the data were not suitable for synthesis
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	This analysis was not performed, as the data were not suitable for synthesis
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	This analysis was not performed, as the data were not suitable for synthesis
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	This analysis was not performed, as the data were not suitable for synthesis
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4
	23b	Discuss any limitations of the evidence included in the review.	Strength and Limitations paragraph (Page 29)
	23c	Discuss any limitations of the review processes used.	Strength and Limitations paragraph (Page 29)

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Further research paragraph (Page 30)
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.	Review not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Non applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
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.	Available on request form the author

Appendix H

Quality Assessment Tool used in Chapter 5

Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group															
Extractor name	author/year	1.Was the study question or objective clearly stated?	2. Were eligibility/selection criteria for the study population prespecified and clearly described?	3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	4. Were all eligible participants that met the prespecified entry criteria enrolled?	5. Was the sample size sufficiently large to provide confidence in the findings?	6. Was the test/service/intervention clearly described and delivered consistently across the study population?	7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Total score (out of 12)	Quality rating (God, Fair, or Poor)
		Yes (1), No(0), Other (CD, NR, NA)* "*CD, cannot determine; NA, not applicable; NR, not reported"													

Aerobic and musclar Intervnetions in McArdles	CB	Perez, *et al.* 2007	1	0	0	NA	0	1	1	NR	1	NA	0	NA	4	Poor
	CB	Haller *et al*, 2006	1	0	1	NA	0	1	1	NR	1	1	0	NA	6	Fair
	CB	Olivier *et. al*, 2005	1	0	1	NA	0	1	1	NR	0	0	0	NA	4	Poor
	CB	Mate-Munoz *et al*.2007	1	0	1	NA	0	1	1	NR	1	1	0	NA	6	Fair
	CB	Santalla, *et al*.2014	1	1	1	NR	0	1	1	NR	1	1	1	NA	8	Fair
	CB	Lucia *et al*. 2007	0	0	0	NA	0	1	1	NR	1	NA	0	NA	3	Poor
	CB	Porcelli *et al.* 2016	1	1	1	NR	0	1	1	NR	NR	1	0	NA	6	Fair
	CB	Cakir *et al.* 2017	1	0	0	NA	0	1	1	NR	1	0	0	NA	4	Poor
Aerobic and muscular interventions in Pompe	CB	Montagne *et al*, 2016	0	0	0	NA	0	1	1	NR	1	0	1	NA	4	Poor
	CB	Terzi *et al,* 2011	1	0	0	NA	0	1	1	NR	1	1	0	NA	5	Fair
	CB	Van den Berg, *et al*. 2015	1	1	1	1	1	1	1	NR	1	1	0	NA	9	Good
	CB	Faverjee *et al*. 2015	1	1	1	1	1	1	1	NR	1	1	0	NA	9	Good
	CB	Sechi *et al*, 2020	1	1	1	NR	1	1	1	1	0	1	0	NA	8	Good
	CB	Slonim, *et al*, 2007	1	0	1	NA	1	0	1	NR	0	1	1	NA	6	Fair
	CB	Khan *et al*, 2009	0	0	0	NA	0	1	1	NR	1	NA	0	NA	3	Poor
	CB	leutholtz *et al,* 1996	0	0	0	NA	0	1	1	NR	1	NA	0	NA	3	Poor
Respiratory Interventions in Pompe	CB	Jones *et al*, 2011	0	0	0	NA	0	0	0	NR	1	0	1	NA	2	Poor
	CB	jones *et al,* 2016	1	1	1	NR	0	1	1	NR	1	1	1	NA	8	Fair
	CB	Mitja *et al,* 2015	1	1	1	NR	0	1	1	NR	NR	1	1	NA	7	Fair
	CB	Aslan *et al*, 2016	1	1	1	1	0	1	1	1	NR	1	0	NA	8	Fair
	CB	Wenninger *et al*, 2019	1	1	1	NR	0	1	1	NR	1	1	1	NA	8	Fair
	CB	Martin, *et al,* 1983	0	0	0	NA	0	0	0	NR	1	0	1	NA	2	Poor

Quality Assessment Tool for controlled intervention studies																		
	Extractor name	author/year	1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	3. Was the treatment allocation concealed (so that assignments could not be predicted)?	4. Were study participants and providers blinded to treatment group assignment?	5. Were the people assessing the outcomes blinded to the participants' group assignments?	6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	9. Was there high adherence to the intervention protocols for each treatment group?	10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	Total score (out of 14)	Quaity rating (Good, Fair, or Poor)
			Yes (1), No(0), Other (CD, NR, NA)* "*CD, cannot determine; NA, not applicable; NR, not reported"															
Respiratory intervention Pompe	CB	Jones, *et al,* 2020	1	1	1	1	1	0	1	NR	1	NR	1	0	1	1	10	Fair/good

Appendix I

Online survey part 1 used in Chapter 6

Online Survey Part 1:

Investigating the Facilitators and Barriers to Exercise in Glycogen Storage Disease

(Page 1) Participant Information & Consent

Welcome to the Nottingham Trent University Survey investigating the Facilitators and Barriers to Exercise in Glycogen Storage Disease.

Please read and answer all questions.

This study will have two parts including
1) Online Survey (2 part survey)
2) Optional online Focus group and /or interview

Participant Information

Project description and procedure
This survey is part of research in the School of Science and Technology to investigate the Facilitators and Barriers to Exercise in Glycogen Storage Disease.

We will cover the following topics within 2 separate surveys.

This survey (part 1) will cover:

- Section 1: Information about you and your condition
- Section 2: Information about your physical health
- Section 3: Information about your quality of life and mental health
- Section 4: Information about your physical activity and fatigue

The following survey (part 2) will cover:

- Section 5: Information about your exercise behaviour
- Section 6: Information about your facilitators and barriers to exercise
- Section 7: Information about your exercise programme preferences.

Adults with Glycogen Storage Disease are invited to participate in this research.

Participation involves completing this **2-part survey which will take approximately 20 minutes per survey.**

Please complete each part in one sitting as questionnaires cannot be saved and reopened to complete at a later date. On completion of part 1 and part 2 your data will then be submitted and saved.

Please complete Part 1 and Part 2 at separate times due to the length of each questionnaire.

Some questions may appear to be very similar as **there may be some overlap with the validated questionnaires** included but **please answer all questions.**

At the end of the second survey (part 2) you will be asked if you are willing to take part in an optional **online focus group and/or interview.** The purpose of these will be to explore your relationship and attitudes towards exercise further.

Anonymity and confidentiality
All information collected as part of this online survey will be completely anonymous i.e., your responses will not be linked to you. Information collected from this survey may be published as part of the project, but you will not be identifiable.

If you decide to take part in the optional online focus group and/or interview we will ask you to provide your email address and create a 6-digit code. This allows the research team to arrange the online focus group and/or interview and ensure that further data collected will only be identified by your unique 6-digit code.

Consent, participation and withdrawal
To participate in this study, you must be aged **18 or over**. Participation in this study is **voluntary** and you have the right to stop the survey at any time and your data will not be saved. On completion of the survey your data will be saved and this will be anonymous.
If you complete the optional focus group and/ or interview, you can withdraw your data from this study after you have submitted your answers for up to two weeks after completion. In order to withdraw your data, you would need to email the researchers below and tell them your unique 6-digit code. This study has been approved by the school non-invasive ethics committee.

Contact Details
If you have any questions or concerns regarding this research, please contact:
Dr Philip Hennis: philip.hennis@ntu.ac.uk or Claire Bordoli: claire.bordoli2020@ntu.ac.uk

Thank you for helping with this important research and please complete the whole survey if possible.

Statement of agreement:
I have read and understood the statements above and by clicking 'OK' I am agreeing to participate (optional)

☐ OK

(Page 2) <u>Instructions to complete the questionnaire</u>

In order for us to obtain accurate data please follow these instructions:

- Please answer all questions as **accurately** and **fully** as you can, selecting all appropriate answers and expanding on answers where requested.
- Some questions may appear to be very similar, as **there may be some overlap between the validated questionnaires** included, particularly as the questionnaire continues but please answer all questions.
- If you are willing to take part in the **optional interviews and/or focus groups**, please ensure your **contact details** you supply at the end of the survey are accurate.

<u>(Page 3) Information about you (part 1 of 7)</u>

Please enter your age (years) * *Required*

.....

Which of the following best describes your gender? **Required*

- ☐ Male
- ☐ Female
- ☐ Prefer not to say
- ☐ Prefer to self-identify

If you selected "Prefer to self-identify", please specify:
(Free text box)

<u>(Page 4: Information about you continued)</u>

Please select your Ethnicity * *Required*

- ☐ White - English / Welsh / Scottish / Northern Irish / British
- ☐ White – Irish
- ☐ White - Gypsy or Irish Traveller
- ☐ White - Any other White background
- ☐ Mixed / Multiple ethnic groups - White and Black Caribbean
- ☐ Mixed / Multiple ethnic groups - White and Black African
- ☐ Mixed / Multiple ethnic groups - White and Asian
- ☐ Mixed / Multiple ethnic groups - Any other Mixed / Multiple ethnic background
- ☐ Asian / Asian British – Indian
- ☐ Asian / Asian British – Pakistani
- ☐ Asian / Asian British – Bangladeshi
- ☐ Asian / Asian British – Chinese
- ☐ Asian / Asian British - Any other Asian background
- ☐ Black / African / Caribbean / Black British – African
- ☐ Black / African / Caribbean / Black British – Caribbean
- ☐ Black / African / Caribbean / Black British - Any Other Black / African / Caribbean background
- ☐ Other ethnic group – Arab
- ☐ Other ethnic group - Any other ethnic group

- Prefer not to say

What is your marital status? **Required*

- Single
- Married
- Divorced
- Widowed
- Separated
- Living with partner
- Prefer not to say

What is your current employment status? ** Required*

- Employed full time
- Employed part-time
- Self-employed
- Student
- Retired
- Unemployed
- Homemaker
- Paid leave of absence (either partially or fully i.e., maternity leave, other, if other please specify).
- Prefer not to say
- Other

If you selected other, please specify:
(Free text box)

What is your employment type? **Required*

- Academic
- Professional
- Trades
- Services
- Prefer not to say

(Page 5) Information about your Physical Health (Part 2 of 7)

Do you know your weight? * *Required*

- Yes, in Kilograms (e.g., 80kg)
- Yes, in Stones and Pounds (e.g., 9 st 12lbs)
- No
- Prefer not to say

If you selected yes, please enter your weight in the units selected:

(Free text box)

Do you know your height? * *Required*

- Yes, in Centimetres (e.g., 180cm)
- Yes, in Feet and Inches (e.g., 5ft 10in)
- No
- Prefer not to say

If you selected yes, please enter your height in the units selected:
(Free text box)

What type of GSD are you diagnosed with? * *Required (Please select all that apply)*

- GSD 0a
- GSD 0b
- GSD 1a
- GSD 1b
- GSD 2
- GSD 3a
- GSD 3b
- GSD 4
- GSD 5
- GSD 6
- GSD 7
- GSD 9a
- GSD 9b
- GSD 9c
- GSD 9d
- GSD10
- GSD 11
- GSD 12
- GSD 13
- GSD 14
- GSD15
- Other

If you selected other, please specify:
(free text box)

How were you diagnosed with GSD? * *Required (Please select all that apply)*

- Genetic testing
- Enzyme testing
- Biopsy
- Clinical presentation

- Unknown

At what age were you diagnosed with a GSD? **Required*
(free text box)

Please state how much your GSD impacts your daily activities? * *Required*

- Not at all
- A little
- Somewhat
- Quite a bit
- A lot

Are you on dietary treatment for your GSD? **Required*

- Yes
- No

Please indicate which dietary treatment(s) you are currently on? *(Please select all that apply)*

- Complex carbohydrate and high protein diet
- Small frequent carbohydrate meals
- Uncooked Cornstarch
- Carbohydrate foods during the night
- Carbohydrate tube feeding during the night
- Low carbohydrate diet
- Ketogenic diet
- Other- please provide details

If you selected other, please specify:
(Free text box)

Please specify if you regularly (more than 3 times a week) take any of the following dietary supplements for primary or secondary consequences of GSD (such as vitamins, minerals, herbal extracts, fish oils or probiotics) ? (Please select all that apply)

- None
- Calcium
- Iron
- Vitamin D
- Multi-vitamin
- Multi-vitamin and minerals
- Omega-3 fish oil
- Other

If you selected other, please specify:
(Free text box)

Do you currently suffer from any other clinically diagnosed long term health condition(s)? **Required*

- ☐ Yes
- ☐ No
- ☐ Prefer not to say

If you selected yes, please specify:
(Free text box)

Please state how much your other clinically diagnosed long term health problem(s) impacts your daily activities? * *Required*

- ☐ Not at all
- ☐ A little
- ☐ Somewhat
- ☐ Quite a bit
- ☐ A lot

Do you currently or have you previously experienced any symptoms associated to GSD? **Required*

- ☐ Yes
- ☐ No

If Yes, please select the term(s) that best describe your symptoms and if you experience these currently and/or have experienced these previously

Please select the term(s) that best describes the symptoms you experience associated to GSD* *Required (please select all that apply)*

	Current	Previous	Never
Low blood sugar	☐	☐	☐
Muscle weakness	☐	☐	☐
Muscle cramps	☐	☐	☐
Tiredness	☐	☐	☐
Slow growth	☐	☐	☐
Obesity	☐	☐	☐
Problems with bleeding and blood clotting	☐	☐	☐
Kidney problems	☐	☐	☐
Low resistance to infections	☐	☐	☐
Breathing problems	☐	☐	☐
Heart problems	☐	☐	☐
Mouth Sores	☐	☐	☐
Gout	☐	☐	☐

Other	□	□	□

If you selected other, please specify the symptom(s) and if it is a current and/or previous symptom
(Free text box)

Do you suffer from muscular symptoms? **Required*

- □ Yes
- □ No

Do you regularly experience high levels of muscle pain, aches and cramps? **Required*

- □ Yes
- □ No

Have you experienced fixed contractures? *(a fixed tightening of muscles preventing normal movement) *Required*

- □ Yes
- □ No

If you selected yes, how many contractures do you experience per year?
(free text box)

If you selected yes, how many have you experienced in your lifetime?
(free text box)

Have you ever visited hospital due to the effects of over-exertion (e.g from contractures/ rhabdomyolysis)? **Required*

- □ Yes
- □ No

Are you unable to exercise due to muscle weakness? **Required*

- □ Yes
- □ No

Do you avoid exercise for fear of muscle pain, cramps or fixed contractures?

- □ Yes
- □ No

(Page 6) Information about your quality of life and mental health (part 3 of 7)
Quality of life: (36-Item Short Form Survey (SF-36) RAND 36-Item Health Survey 1.0 Questionnaire)

1) In general, would you say your health is:

- □ Excellent

- □ Very good
- □ Good
- □ Fair
- □ Poor

2. Compared to one year ago, how would you rate your health in general now?
   - □ Much better now than one year ago
   - □ Somewhat better now that one year ago
   - □ About the same
   - □ Somewhat worse now than one year ago
   - □ Much worse than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, Limited a lot	Yes, limited a little	Non, not limited at all
3. **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports	□	□	□
4. **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling or playing golf	□	□	□
5. Lifting or carrying groceries	□	□	□
6. Climbing **several** flights of stairs	□	□	□
7. Climbing **one** flight of stairs	□	□	□
8. Bending, kneeling, or stooping	□	□	□
9. Walking **more than one mile**	□	□	□
10. Walking **several streets**	□	□	□
11. Walking **one street**	□	□	□
12. Bathing or dressing yourself.	□	□	□

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

	Yes	No
13. Cut down **the amount of time** you spent on work or other activities	☐	☐
14. **Accomplished less** than you would like	☐	☐
15. Were limited in the **kind** of work or other activities	☐	☐
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	☐	☐

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	☐	☐
18. **Accomplished less** than you would like	☐	☐
19. Didn't do work or other activities as **carefully** as usual	☐	☐

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

- ☐ Not at all
- ☐ Slightly
- ☐ Moderately
- ☐ Quite a bit
- ☐ Extremely

21. How much **bodily** pain have you had during the past 4 weeks?

- ☐ None
- ☐ Very mild
- ☐ Mild
- ☐ Moderate

- □ Severe
- □ Very severe

22. During the **past 4 weeks,** how much did pain interfere with your normal work (including both work outside the home and housework)

- □ Not at all
- □ A little bit
- □ Moderately
- □ Quite a bit
- □ Extremely

These questions are about how you feel and how things have been with you during the **past 4 weeks.** For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks….**

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	□	□	□	□	□	□
24. Have you been a very nervous person?	□	□	□	□	□	□
25. Have you felt so down in the dumps that nothing could cheer you up?	□	□	□	□	□	□
26. Have you felt calm and peaceful?	□	□	□	□	□	□
27. Did you have a lot of energy?	□	□	□	□	□	□
28. Have you felt downhearted and blue?	□	□	□	□	□	□
29. Did you feel worn out?	□	□	□	□	□	□

30. Have you been a happy person?	□	□	□	□	□	□
31. Did you feel tired?	□	□	□	□	□	□

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visit with friends, relatives, etc.)?

- □ All of the time
- □ Most of the time
- □ Some of the time
- □ A little of the time
- □ None of the time

How TRUE or False is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	□	□	□	□	□
34. I am as healthy as anybody I know	□	□	□	□	□
35. I expect my health to get worse	□	□	□	□	□
36. My health is excellent	□	□	□	□	□

(Page 7) Information about your Physical Activity and Fatigue (Part 4 of 7)
Physical activity (IPAQ-SF):

We are interested in finding out about the kinds of physical activities that you do as part of your everyday life. The questions will ask you about the time you spent being physically active in the last 7 days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your housework, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the last 7 days. **Vigorous** physical activities refer to activities that take **hard physical effort** and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling? ** Required*

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7

How much time did you usually spend doing vigorous physical activities on one of those days? (minutes)
(free text box)

Please tick here if you are not sure.

- ☐ Not sure

Think about all the **moderate** activities that you did in the last 7 days. **Moderate** activities refer to activities that take **moderate physical effort** and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking. * *Required*

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7

How much time did you usually spend doing moderate physical activities on one of those days? (minutes) (Free text box)

Please tick here if you are not sure.

- ☐ Not sure

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure. During the last 7 days, on how many days did you walk for at least 10 minutes at a time? * *Required*

- ☐ 0
- ☐ 1
- ☐ 2
- ☐ 3
- ☐ 4
- ☐ 5
- ☐ 6
- ☐ 7

How much time did you usually spend walking on one of those days? (minutes)
(free text box)

Please tick here if you are not sure.

- ☐ Not sure

This question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television. During the last 7 days, how much time did you spend sitting on a week day? (hours)
(Free text box)

Please tick here if you are not sure.

- ☐ Not sure

Using the scale below, please indicate to what extent each of the following items is true for you. Please note that there are no right or wrong answers and no trick questions. We simply want to know how you personally feel about exercise. * *Required*

Using the scale below, please indicate to what extent each of the following items is true for you. Please note that there are no right or wrong answers and no trick questions. We simply want to know how you personally feel about exercise. * *Required*

	Not true for me (1)	(2)	Sometimes true for me (3)	(4)	Very true for me (5)
It's important to me to exercise regularly.	☐	☐	☐	☐	☐
I feel guilty when I don't exercise.	☐	☐	☐	☐	☐
I can't see why I should bother exercising.	☐	☐	☐	☐	☐
I enjoy my exercise sessions.	☐	☐	☐	☐	☐
I feel ashamed when I miss an exercise session.	☐	☐	☐	☐	☐
I take part in exercise because my friends/family/partner say I should.	☐	☐	☐	☐	☐
I think it is important to make the effort to exercise regularly.	☐	☐	☐	☐	☐
I don't see the point in exercising.	☐	☐	☐	☐	☐
I find exercise a pleasurable activity.	☐	☐	☐	☐	☐
I feel under pressure from my friends/family to exercise.	☐	☐	☐	☐	☐

Fatigue (Multidimensional Fatigue Symptom Inventory–Short Form MFSI-SF):

	Not at all	A little	Moderately	Quite a bit	Extremely
1. I have trouble remembering things	0	1	2	3	4
2. My muscles ache	0	1	2	3	4
3. I feel upset	0	1	2	3	4
4. My legs feel weak	0	1	2	3	4
5. I feel cheerful	0	1	2	3	4
6. My head feels heavy	0	1	2	3	4
7. I feel lively	0	1	2	3	4
8. I feel nervous	0	1	2	3	4
9. I feel relaxed	0	1	2	3	4
10. I feel pooped	0	1	2	3	4

11. I am confused	0	1	2	3	4
12. I am worn out	0	1	2	3	4
13. I feel sad	0	1	2	3	4
14. I feel fatigued	0	1	2	3	4
15. I have trouble paying attention	0	1	2	3	4
16. My arms feel weak	0	1	2	3	4
17. I feel sluggish	0	1	2	3	4
18. I feel run down	0	1	2	3	4
19. I ache all over	0	1	2	3	4
20. I am unable to concentrate	0	1	2	3	4
21. I feel depressed	0	1	2	3	4
22. I feel refreshed	0	1	2	3	4
23. I feel tense	0	1	2	3	4
24. I feel energetics	0	1	2	3	4
25. I make more mistakes than usual	0	1	2	3	4
26. My body feels heavy all over	0	1	2	3	4
27. I am forgetful	0	1	2	3	4
28. I feel tired	0	1	2	3	4
29. I feel calm	0	1	2	3	4
30. I am distressed	0	1	2	3	4

(Page 8) Final page:

Thank you very much for completing **Part 1** of the survey.

Please remember to complete Part 2 of the survey at your earliest convenience.

If completing this survey has led you to be concerned for any aspect of your health, we encourage you to contact your local health provider or GP.

If you have any questions or concerns regarding this questionnaire, please contact one of the investigators;

Dr Phil Hennis (philip.hennis@ntu.ac.uk) or Claire Bordoli (claire.bordoli2020@my.ntu.ac.uk).

If exercisers: Information about your Exercise Behaviours (Part 5 of 7)

Please tell us about your typical exercise behaviours.

Do you take part in exercise?

- ☐ Yes
- ☐ No

If answered yes (for exercisers):

a. What types of exercise did you typically engage in? Select all that apply. (*Multi-choice*).

- ☐ Cardiovascular/aerobic exercise (*e.g.,* running, walking, cycling, swimming)
- ☐ Resistance training with free-weights/machines
- ☐ Bodyweight exercises (*e.g.,* push-ups, pull-ups, sit-ups)
- ☐ Yoga/Pilates (or similar mobility-based exercise)
- ☐ Competitive sport (*e.g.,* tennis, football, golf, netball)
- ☐ Other

If other, please specify .....

b. During a typical 7-day week, how many times did you exercise? *Please select the single answer most appropriate to you*.

- ☐ 1 time per week
- ☐ 2-3 times per week
- ☐ 4-5 times per week
- ☐ 6-7 times per week
- ☐ 7 or more times per week

c. Where does your exercise typically take place? Select all that apply. (*Multi-choice*).

- ☐ Gym/leisure centre

- ☐ Home
- ☐ Public outdoor spaces
- ☐ Sport specific facilities (tennis court/football pitch/swimming pool etc.)
- ☐ Other

If other, please specify …….

d. How do you usually exercise? Select all that apply. (*Multi-choice*)

- ☐ Alone
- ☐ With a friend(s)/family member(s)
- ☐ As part of a larger class/team
- ☐ Supervised in person by a trainer
- ☐ Supervised virtually/online by a personal trainer
- ☐ Other

If other, please specify……

e. What are your main reasons for engaging in exercise? Select all that apply.

- ☐ To have fun
- ☐ To improve or maintain my physical health
- ☐ To improve or maintain my mental health
- ☐ To increase my physical strength
- ☐ To build muscle
- ☐ To control or lose weight
- ☐ To look good
- ☐ To feel good
- ☐ To reduce stress
- ☐ To increase self esteem
- ☐ To socialise and meet new people
- ☐ To feel a sense of achievement
- ☐ To train for and compete in sport
- ☐ Other

If other, please specify……

<u>If answered no (For non-exercisers):</u>

a. What are your main reasons for not exercising? (*Select all that apply*)

- ☐ I do not want to exercise
- ☐ Job/work commitments
- ☐ Providing care for my children
- ☐ Spending time with family
- ☐ Spending time with friends
- ☐ Providing care for a friend or family member who is dependent on my support
- ☐ Time spent on other hobbies/pastimes

☐ Other

If other, please specify.....

b. Are there any factors that would make you more likely to exercise? (*Free text input*)

Information about what makes it easier to exercise (*i.e., facilitators*) and what makes it more difficult to exercise (*i.e., barriers*) (Part 5 of 7)

	Strongly agree	Agree	Disagree	Strongly disagree
1) I enjoy exercise				
2) Exercise decreases feeling of stress and tension for me				
3) Exercise improves my mental health				
4) Exercise takes too much of my time				
5) I will prevent heart attacks by exercise				
6) Exercise tires me				
7) Exercise increases muscle strength				
8) Exercise gives me a sense of personal accomplishment				
9) Places for me to exercise are too far away				
10) Exercising makes me feel relaxed				
11) Exercising lets me have contact with friends and persons I enjoy				
12) I am too embarrassed to exercise				
13) Exercising will keep me from having high blood pressure				
14) It costs too much to exercise				
15) Exercising increases my levels of physical activity				

16) Exercise facilities do not have convenient schedules for me				
17) My muscle tone is improved with exercise				
18) Exercising improves functioning of my cardiovascular system				
19) I am fatigued by exercise				
20) I have improved feeling of wellbeing from exercise				
21) My spouse (or significant other) does not encourage exercising				
22) Exercise increases my stamina				
23) Exercise improves my flexibility				
24) Exercise takes too muscle time from family relationships				
25) My disposition is improved with exercise				
26) Exercise helps me sleep better at night				
27) I will live longer if I exercise				
28) I think people in exercise clothes look funny				
29) Exercise helps me decrease fatigue				
30) Exercising is a good way to meet new people				
31) My physical endurance is improved by exercise				
32) Exercising improves my self-concept				
33) My family members do not encourage me to exercise				
34) Exercising increases my mental alertness				

35) Exercise allows me to carry out normal activities without becoming tired				
36) Exercise improves the quality of my work				
37) Exercise takes too much time from my family responsibilities				
38) Exercise is good entertainment for me				
39) Exercise increases my acceptance by others				
40) Exercise is hard work for me 41) Exercise improves overall body functioning for me				
42) There are two few places for me to exercise				
43) Exercise improves the way my body looks				

Facilitators and Barriers to Physical Activity (IFAB Questionnaire) (Davergne, 2020)

Please take few moments to think about all the physical activity you did in the previous month: walking, jogging, gardening, other kind of sport… Now, think about all the things that have encouraged you, and all the things that prevented you form doing physical activity in the previous month. This questionnaire has 10 items. It aims to collect all the things that have encouraged you or prevented you from doing physical activity in the previous month. Please indicate for each item if it has rather encouraged you, prevented you, or had no impact on your physical activity in the previous month (only one answer). If needed, rate the importance.

A: Items that may have encouraged me or prevented me from doing physical activity in the last month.				
1. Level of symptoms (pain, fatigue, lack of mobility)				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity
☐	rather encouraged to do physical activity in the previous month			
☐	had no impact on my physical activity in the previous month			
2. Weather Conditions				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity
☐	rather encouraged to do physical activity in the previous month			
☐	had no impact on my physical activity in the previous month			

3. Presence or absence of support from others (friends, family)				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity
☐	rather encouraged to do physical activity in the previous month			
☐	had no impact on my physical activity in the previous month			
4. Presence or absence of support and/or advice from healthcare professionals				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity
☐	rather encouraged to do physical activity in the previous month			
☐	had no impact on my physical activity in the previous month			
B: Items that may have prevented me from doing physical activity in the last month.				
5. A belief that physical activity will make symptoms worse				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal negative impact on my physical activity
☐	had no impact on my physical activity in the previous month			
6. Lack of motivation				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal negative impact on my physical activity
☐	had no impact on my physical activity in the previous month			
7. Lack of knowledge on which exercises to do and how much				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal negative impact on my physical activity
☐	had no impact on my physical activity in the previous month			
C: Items that may have encouraged me from doing physical activity in the last month.				
8. Knowledge of benefits of physical activity for health				
☐	rather encouraged to do physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal positive impact on my physical activity
☐	had no impact on my physical activity in the previous month			
9. Knowledge of benefits of physical activity for mood				
☐	rather encouraged to do physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal positive impact on my physical activity
☐	had no impact on my physical activity in the previous month			
10. Confidence on how to exercise safely				
☐	rather encouraged to do physical activity in the previous month	Had no impact on my	0 1 2 3 4 5 6 7 8 9 10	Had a maximal positive impact on my physical activity
☐	had no impact on my physical activity in the previous month			

		physical activity		

(Items which can be considered as either barriers or facilitators are rated from -10 to 10, items which are barriers only are rated from -10 to 0, and items which are facilitators only are rated from 0 to 10. When an item is not affecting physical activity, score it at 0. If one question is missing impute the item as 0. If two questions are missing, we recommend not calculating the total score. The global score ranges -70 to 70. Results below -5 might justify a targeted intervention).

Information on your exercise programme preferences (Part 7 of 7)
(Modified Exercise Programme Preferences Questionnaire (Blaney *et al*. 2013)

Are you interested in taking part in an exercise programme?

- ☐ Yes
- ☐ No
- ☐ Not sure

Do you feel you could take part in an exercise programme?

- ☐ Yes
- ☐ No
- ☐ Not sure

What type of exercise would you be most interested in?

- ☐ Walking
- ☐ Strengthening exercises
- ☐ Flexibility exercises
- ☐ Aerobic exercises
- ☐ Swimming
- ☐ Circuit Training
- ☐ Yoga
- ☐ Tai chi
- ☐ Pilates
- ☐ No preference

What intensity would you like to exercise at?

- ☐ Light
- ☐ Moderate
- ☐ Light or moderate
- ☐ Moderate or vigorous
- ☐ Vigorous
- ☐ No preference

How long do you think you would be able to exercise for?

- ☐ Less than 10 min
- ☐ 10-20 mins
- ☐ 20-30 mins

- Over 30 mins
- Not sure

How often would you be interested in attending?

- Once per week
- Twice per week
- Three times per week
- More than three times per week
- No preference

What time of the day would you prefer to exercise?

- Morning
- Afternoon
- Morning or afternoon
- Afternoon or evening
- No preference

Who would you prefer to exercise with?

- Alone
- Other GSD patients
- General public
- Family
- No preference
- Other

Who would you prefer your exercise was delivered by?

- Specialist nurse
- Physiotherapist
- Other healthcare professional Fitness Instructor
- Not sure
- Other

Where would you prefer an exercise programme to take place? (Altered question- deleted cancer centre)

- Home
- Community centre
- Leisure centre
- No preference
- Not sure

How would you like to receive information on available exercise programmes?

- Telephone
- Email
- Post Flyer
- Social media
- No preference

Who would you like to receive this information from? (Altered, deleted oncologist option)

- □ Specialist nurse
- □ Practice nurse
- □ Physiotherapist
- □ GP
- □ Other healthcare professional
- □ No preference

Personalised Exercise Questionnaire (PEQ) : (Modified from Rodigues, 2017)

PLEASE READ THESE INSTRUCTIONS BEFORE STARTING:
This survey was created to better understand your exercise needs and goals.
By completing this survey, you will help us understand some of the difficulties you face in an exercise program. This information will be used to help us create better exercise/ physical activity program for you.
There are 6 sections and 38 questions. Please complete ALL questions relevant to you.
All answers will be kept strictly confidential and never associated with your name

SECTION ONE: My Support Network					
		No	Not sure	Yes	Not applicable
1. I prefer someone to supervise/assist me with an exercise:		□	□	□	□
If YES, under a:					
□	Healthcare professional (e.g., physiotherapist)				
□	Personal Trainer				
□	Other:				
2. A healthcare provider (e.g., physiotherapist, nurse, etc.) with a good attitude toward exercise is important to me:		□	□	□	□
3. Having friends/family with a good attitude toward exercise is important to me:		□	□	□	□
SECTION TWO: My Access to Exercise					
4. I have a place to exercise (indoor or outdoor) at home, place of work or near my home/work place:		□	□	□	□
If YES, how far:					
□	At home or at work				
□	< 5 km (< 3 miles)				
□	5 – 10 km (3-6 miles)				
5. I am able to get to an exercise site on my own: (Check "Not Applicable" if you exercise at home)		□	□	□	□
If NO, who could you ask:					
□	Family member/partner				

□	Friend				
□	Other:				
6. I have transportation to an exercise site: (Check "Not Applicable" if you exercise at home)		□	□	□	□
If YES, type of transportation:					
	Bike				
	Motor Vehicle (e.g., car)				
	Public transportation				
	Walking				
7. I have a safe place to exercise: (e.g., proper space to exercise, dry and clean floors, good lighting, etc).		□	□	□	□
8. I have an encouraging place to exercise: (e.g., pleasant people that motivate me)		□	□	□	□
9. I have an exercise location that is free of cost or reasonably priced (including parking fees):		□	□	□	□
SECTION THREE: My Exercise Goals					
How important are the following GOALS to YOU in an exercise program?					
	Not Important	Somewhat important	Very important	Not applicable	
10. Feel less tired	□	□	□	□	
11. Be able to walk longer	□	□	□	□	
12. Be more flexible	□	□	□	□	
13. Have better balance	□	□	□	□	
14. Fall less often	□	□	□	□	
15. Have less pain	□	□	□	□	
16. Increase muscle strength	□	□	□	□	
17. What is your MOST important exercise goal?					
SECTION FOUR: My Exercise Preferences					
18. Please list up to 3 things that HELP you to exercise more often:					
1.					
2.					
3.					
19. Where would you like your exercise program to be? (Check ALL that apply)					
□	Home				
□	Gym				
□	Community Centre				
□	Outdoors (e.g., parks, trails, sidewalks, etc.)				
□	Other:				
20. What is the best time for you to exercise? (Check ALL that apply)					
□	Morning (between 6:00 am to 12:00 pm)				
□	Afternoon (between 12:00 pm to 6:00 pm)				
□	Evening (between 6:00 pm to 11:00 pm)				
21. What is your preferred exercise schedule? (Check ALL that apply)					
□	Fixed time (same class offered at same time during the week)				

□	Multiple drop-in times (same class offered at different times of the week)
□	On my own time
22. What is your preferred exercise class size? (Check ALL that apply)	
□	I prefer to exercise alone
□	With a partner/trainer
□	Small group (less than 10 people)
□	Large group (more than 10 people)
□	Does not matter
23. How would you like to learn proper exercise technique? (Check ALL that apply)	
□	Taught by a healthcare professional (e.g., physiotherapist, nurse, etc.)
□	Taught by a trainer/health club staff
□	Learn on my own from an exercise video
□	Learn on my own from a website with pictures
□	Learn on my own using an app
□	Learn on my own using a print handout
□	Have a friend teach me
□	Have another person with osteoporosis teach me
□	None of the above
24. What level of exercise are you comfortable doing? (Check ALL that apply)	
□	Easy to perform
□	Challenging to perform (i.e., “I like a challenge”)
□	Slow paced exercises
□	Fast paced exercises
□	Easy to remember
SECTION FIVE: My Feedback and Tracking	
25. I would like to receive feedback about my progress:	
□	Yes
□	No
If YES, by: (Check ALL that apply)	
□	Email
□	In person
□	Social media (e.g., Twitter, Facebook, etc.)
□	Phone call
□	Text message
If you answered YES to question 25, please complete questions 26 and 27.	
If you answered NO to question 25, please skip to question 28.	
26. What type of feedback would you like to receive? (Check ALL that apply)	
□	Regarding my exercise progress and future improvements
□	Regarding proper exercise techniques
□	Other:

27. How often would you like to receive feedback about your exercise progress? (Please check only ONE answer)	
□	Daily
□	Weekly
□	Monthly
□	Yearly
28. I would like to give feedback on the exercise program:	
□	Yes
□	No
If YES, by (Check ALL that apply):	
□	Email
□	In person
□	Social media (e.g., Twitter, Facebook, etc.)
□	Phone call
□	Text message
29. I would like to track my exercise progress:	
□	Yes
□	No
If YES, using (Check ALL that apply):	
□	Cell phone/mobile
□	Diary/Log book
□	Wearable technology (e.g., Fit Bit, pedometer, watch etc.)
□	Other:
SECTION SIX: My Barriers to Exercise	
30. Do you have things that STOP you from exercising?	
□	Yes
□	No
If YES, how often does it stop you from exercising: (Check only ONE answer)	
□	Always
□	Very often
□	Sometimes
□	Rarely
31. Please list up to 3 things that STOP you from exercising more often:	
1.	
2.	
3.	
32. I do not exercise as often as I like because: (Check ALL that apply)	
□	I do not like exercise
□	I do not want to fall
□	I do not want to injure myself (e.g., breaking a bone or bruising)
□	I feel pain when I exercise
□	I feel bored when exercising
□	Other:

□	None of the above
33. I do not exercise as often as I like because I have difficulty: (Check ALL that apply)	
□	Understanding the exercise
□	Performing the exercise (i.e., I do not know how to exercise safely)
□	Other:
□	None of the above
34. I do not exercise as often as I like because I do not have: (Check ALL that apply)	
□	A place to exercise
□	Confidence (e.g., I feel self-conscious about my body)
□	Finances
□	Mobility (e.g., limited movements due to pain)
□	Proper quality of sleep
□	Transportation
□	Time (e.g., family priorities, work, etc.)
□	Willpower/motivation
□	Other:
□	None of the above
35. Do weather conditions stop you from exercising as often as you like? (Check only ONE answer)	
□	Always
□	Very often
□	Sometimes
□	Rarely
□	Never
36. I do not exercise as often as I like because I have medical conditions such as: (Check ALL that apply)	
□	Arthritis (e.g., hips, knees, etc.)
□	Cognitive concernés (e.g. Alzheimer, Dementia, Parkinson, etc.)
□	Heart condition (e.g., angina, heart failure, etc.)
□	Kidney disease (e.g., dialysis)
□	Lung disease (e.g. asthma, COPD, etc.)
□	Mental health issues (e.g., anxiety, depression, etc.)
□	Other:
□	None of the above
37. If you had fewer barriers would you spend more time exercising? (Please check only ONE answer)	
□	Yes
□	No
□	Not sure
38. Please check any mobility aids that you normally use:	
□	Cane
□	Walker
□	Crutches

□	Wheelchair
□	Other:
□	None

Final Questions

As part of this research would you be happy to take part in an online focus group and/ or online interview to further explore your attitudes and beliefs around exercise?
If yes, you will be taken to a link to provide your email address and asked to create a unique 6-digit code. This is so that we can contact you to arrange the focus group and /or interview and to ensure further data collected will only be linked to your unique 6-digit code. Please make a note of your unique code so this can be remembered.

- □ Yes
- □ No

Final page

Thank you very much for completing this survey.

If completing this survey has led you to be concerned for any aspect of your health, we encourage you to contact your local health provider or GP.
If you have any questions or concerns regarding this questionnaire, please contact one of the investigators; Dr Phil Hennis (philip.hennis@ntu.ac.uk) or Claire Bordoli (claire.bordoli2020@my.ntu.ac.uk).

Appendix J:

Online survey part 2 used in Chapter 6

Online Survey Part 2:

Investigating the Facilitators and Barriers to Exercise: Part 2

(Page 1) Participant Information & Consent

Welcome to the Nottingham Trent University Survey investigating the Facilitators and Barriers to Exercise in Glycogen Storage Disease.

Please read and answer all questions.

This study will have two parts including
1) Online Survey (2-part survey)
2) Optional online Focus group and /or interview

Participant Information

Project description and procedure
This survey is part of research in the School of Science and Technology to investigate the Facilitators and Barriers to Exercise in Glycogen Storage Disease.

Thank you for previously completing part 1 of the survey.

This survey (part 2) will cover:

- Section 5: Information about your exercise behaviour
- Section 6: Information about your facilitators and barriers to exercise
- Section 7: Information about your exercise programme preferences.

Adults with Glycogen Storage Disease are invited to participate in this research.

Participation involves completing this survey (part 2) which will take **approximately 20 minutes.**

Please complete **part 2 in one sitting as questionnaires cannot be saved and reopened to complete at a later date. On completion your data will then be submitted and saved.**

Some questions may appear to be very similar as **there may be some overlap with the validated questionnaires included but please answer all questions.**

At the end of the survey, you will be asked if you are willing to take part in **an optional online focus group and/or interview.** The purpose of these will be to explore your relationship and attitudes towards exercise further.

Anonymity and confidentiality
All information collected as part of this online survey will be completely anonymous i.e., your responses will not be linked to you. Information collected from this survey may be published as part of the project, but you will not be identifiable.

If you decide to take part in the optional online focus group and/or interview we will ask you to provide your email address and create a 6-digit code. This allows the research team to arrange the online focus group and/or interview and ensure that further data collected will only be identified by your unique 6-digit code.

Consent, participation and withdrawal
To participate in this study, you must be aged 18 or over. Participation in this study is voluntary and you have the right to stop the survey at any time and your data will not be saved. On completion of the survey your data will be saved and this will be anonymous.

If you complete the optional focus group and/ or interview, you can withdraw your data from this study after you have submitted your answers for up to two weeks after completion. In order to withdraw your data, you would need to email the researchers below and tell them your unique 6-digit code. This study has been approved by the school non-invasive ethics committee.

Contact Details
If you have any questions or concerns regarding this research, please contact:
Dr Philip Hennis: philip.hennis@ntu.ac.uk or Claire Bordoli: claire.bordoli2020@ntu.ac.uk

Thank you for helping with this important research and please complete the whole survey if possible.

Statement of agreement:
I have read and understood the statements above and by clicking 'OK' I am agreeing to participate (optional)

☐ OK

(Page 2) <u>Instructions to complete the questionnaire</u>
In order for us to obtain accurate data please follow these instructions:

- Please answer all questions as **accurately** and **fully** as you can, selecting all appropriate answers and expanding on answers where requested.
- Some questions may appear to be very similar, as **there may be some overlap between the validated questionnaires** included, particularly as the questionnaire continues but please answer all questions.

- If you are willing to take part in the **optional interviews and/or focus groups**, please ensure your **contact details** you supply at the end of the survey are accurate.

(Page 3) Initial information

In order for the research team to link this survey with part 1, please can you answer the following questions

Please enter your age (years) **Required*
(Free text box)

What type of GSD are you diagnosed with? ** Required (Please select all that apply)*

- ☐ GSD 0a
- ☐ GSD 0b
- ☐ GSD 1a
- ☐ GSD 1b
- ☐ GSD 2
- ☐ GSD 3a
- ☐ GSD 3b
- ☐ GSD 4
- ☐ GSD 5
- ☐ GSD 6
- ☐ GSD 7
- ☐ GSD 9a
- ☐ GSD 9b
- ☐ GSD 9c
- ☐ GSD 9d
- ☐ GSD10
- ☐ GSD 11
- ☐ GSD 12
- ☐ GSD 13
- ☐ GSD 14
- ☐ GSD15
- ☐ Other

If you selected other, please specify:
(free text box)

*Please enter the approximate date and time of when you complete the part 1 of this survey? *Required*
(Free text box)

***(Page 4)* Information about your Exercise Behaviours (Part 5 of 7)**

Please tell us about your typical exercise behaviours.

Do you engage in exercise?

- ☐ Yes
- ☐ No

If answer yes diverted to page 5 (exercise behaviours for exercisers)

If answer no, diverted to page 6 (exercise behaviours for non-exerciser)

(Page 5) Exercise behaviours (Exercisers)

a. What types of exercise did you typically engage in? Select all that apply. * *Required* (*Multi-choice*).

- ☐ Cardiovascular/aerobic exercise (*e.g.,* running, walking, cycling, swimming)
- ☐ Resistance training with free-weights/machines
- ☐ Bodyweight exercises (*e.g.,* push-ups, pull-ups, sit-ups)
- ☐ Yoga/Pilates (or similar mobility-based exercise)
- ☐ Competitive sport (*e.g.,* tennis, football, golf, netball)
- ☐ Other

If other, please specify (Free text box)

b. During a typical 7-day week, how many times do you exercise? *Please select the single answer most appropriate to you. *Required*

- ☐ 1 time per week
- ☐ 2-3 times per week
- ☐ 4-5 times per week
- ☐ 6-7 times per week
- ☐ 7 or more times per week

c. Where does your exercise typically take place? Select all that apply. **Required* (*Multi-choice*).

- ☐ Gym/leisure centre
- ☐ Home
- ☐ Public outdoor spaces
- ☐ Sport specific facilities (tennis court/football pitch/swimming pool etc.)
- ☐ Other

If other, please specify (Free text box)

d. How do you usually exercise? Select all that apply. * *Required* (*Multi-choice*)

- Alone
- With a friend(s)/family member(s)
- As part of a larger class/team
- Supervised in person by a trainer
- Supervised virtually/online by a personal trainer
- Other

If other, please specify (Free text box)

e. What are your main reasons for engaging in exercise? Select all that apply **Required (Multi choice)*

- To have fun
- To improve or maintain my physical health
- To improve or maintain my mental health
- To increase my physical strength
- To build muscle
- To control or lose weight
- To look good
- To feel good
- To reduce stress
- To increase self esteem
- To socialise and meet new people
- To feel a sense of achievement
- To train for and compete in sport
- Other

If other, please specify (Free text box)

(Page 6) Exercise behaviours (non-exercisers):

a. What are your main reasons for not exercising? (*Select all that apply*) *Required (Multi choice)

- I do not want to exercise
- Job/work commitments
- Providing care for my children
- Spending time with family
- Spending time with friends
- Providing care for a friend or family member who is dependent on my support
- Time spent on other hobbies/pastimes
- Other

If other, please specify (Free text box)

b. Are there any factors that would make you more likely to exercise? *Optional*

(*Free text input*)

(Page 7) Information about what makes it easier (i/e/, facilitators) and what makes it more difficult to exercise (i.e., barriers) (Part 5 of 7)

Facilitators and Barriers to Physical Activity (IFAB Questionnaire) (Davergne, 2020)

Please take few moments to think about all the physical activity you did in the previous month: walking, jogging, gardening, other kind of sport… Now, think about all the things that have encouraged you, and all the things that prevented you form doing physical activity in the previous month. This questionnaire has 10 items. It aims to collect all the things that have encouraged you or prevented you from doing physical activity in the previous month. Please indicate for each item if it has rather encouraged you, prevented you, or had no impact on your physical activity in the previous month (only one answer). If needed, rate the importance.

A: Items that may have encouraged me or prevented me from doing physical activity in the last month.				
1. Level of symptoms (pain, fatigue, lack of mobility)				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity
☐	rather encouraged to do physical activity in the previous month			
☐	had no impact on my physical activity in the previous month			
2. Weather Conditions				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity
☐	rather encouraged to do physical activity in the previous month			
☐	had no impact on my physical activity in the previous month			
3. Presence or absence of support from others (friends, family)				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity
☐	rather encouraged to do physical activity in the previous month			
☐	had no impact on my physical activity in the previous month			
4. Presence or absence of support and/or advice from healthcare professionals				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on	0 1 2 3 4 5 6 7 8 9 10	Had a maximal impact on my physical activity

☐	rather encouraged to do physical activity in the previous month	my physical activity		
☐	had no impact on my physical activity in the previous month			
B: Items that may have prevented me from doing physical activity in the last month.				
5. A belief that physical activity will make symptoms worse				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal negative impact on my physical activity
☐	had no impact on my physical activity in the previous month			
6. Lack of motivation				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal negative impact on my physical activity
☐	had no impact on my physical activity in the previous month			
7. Lack of knowledge on which exercises to do and how much				
☐	rather prevented me from doing physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal negative impact on my physical activity
☐	had no impact on my physical activity in the previous month			
C: Items that may have encouraged me from doing physical activity in the last month.				
8. Knowledge of benefits of physical activity for health				
☐	rather encouraged to do physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal positive impact on my physical activity
☐	had no impact on my physical activity in the previous month			
9. Knowledge of benefits of physical activity for mood				
☐	rather encouraged to do physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal positive impact on my physical activity
☐	had no impact on my physical activity in the previous month			
10. Confidence on how to exercise safely				
☐	rather encouraged to do physical activity in the previous month	Had no impact on my physical activity	0 1 2 3 4 5 6 7 8 9 10	Had a maximal positive impact on my physical activity
☐	had no impact on my physical activity in the previous month			

(Items which can be considered as either barriers or facilitators are rated from 0 to 10, items which are barriers only are rated from -10 to 0, and items which are facilitators only are rated from 0 to 10. When an item is not affecting physical activity, score it at 0. If one question is missing impute the item as 0. If two questions are missing, we recommend not calculating the total score. The global score ranges -70 to 70. Results below -5 might justify a targeted intervention).

(Page 8) Information on your exercise programme preferences (Part 7 of 7)
(Modified Exercise Programme Preferences Questionnaire (Blaney *et al*. 2013)

Are you interested in taking part in an exercise programme? **Required*

- Yes
- No
- Not sure

Do you feel you could take part in an exercise programme? **Required*

- Yes
- No
- Not sure

What type of exercise would you be most interested in? *Optional*

- Walking
- Strengthening exercises
- Flexibility exercises
- Aerobic exercises
- Swimming
- Circuit Training
- Yoga
- Tai chi
- Pilates
- No preference
- Other

If you selected other, please specify: (Free text box)

What intensity would you like to exercise at? *Optional*

- Light
- Moderate
- Light or moderate
- Moderate or vigorous
- Vigorous
- No preference

How long do you think you would be able to exercise for? *Optional*

- Less than 10 min
- 10-20 mins
- 20-30 mins
- Over 30 mins
- Not sure

How often would you be interested in attending? *Optional*

- Once per week
- Twice per week
- Three times per week
- More than three times per week

- No preference

What time of the day would you prefer to exercise? *Optional*

- Morning
- Afternoon
- Morning or afternoon
- Afternoon or evening
- No preference

Who would you prefer to exercise with? *Optional*

- Alone
- Other GSD patients
- General public
- Family
- No preference
- Other

If you selected other, please specify: (Free text box)

Who would you prefer your exercise was delivered by? *Optional*

- Specialist nurse
- Physiotherapist
- Other healthcare professional Fitness Instructor
- Not sure
- Other

If you selected other, please specify (Free text box)

Where would you prefer an exercise programme to take place?

- Home
- Community centre
- Leisure centre
- No preference
- Not sure

How would you like to receive information on available exercise programmes?

- Telephone
- Email
- Post Flyer
- Social media
- No preference

Who would you like to receive this information from?

- Specialist nurse
- Practice nurse
- Physiotherapist
- GP
- Other healthcare professional

☐ No preference

(Page 9) Personalised Exercise Questionnaire (PEQ) : (Modified from Rodigues, 2017)

PLEASE READ THESE INSTRUCTIONS BEFORE STARTING:
This survey was created to better understand your exercise needs and goals.
By completing this survey, you will help us understand some of the difficulties you face in an exercise program. This information will be used to help us create better exercise/ physical activity program for you.
There are 6 sections and 38 questions. Please complete ALL questions relevant to you.
All answers will be kept strictly confidential and never associated with your name

SECTION ONE: My Support Network					
		No	Not sure	Yes	Not applicable
1. I prefer someone to supervise/assist me with an exercise:		☐	☐	☐	☐
If YES, under a:					
☐	Healthcare professional (e.g., physiotherapist)				
☐	Personal Trainer				
☐	Other				
If you selected other, please specify:					
2. A healthcare provider (e.g., physiotherapist, nurse, etc.) with a good attitude toward exercise is important to me:		☐	☐	☐	☐
3. Having friends/family with a good attitude toward exercise is important to me:		☐	☐	☐	☐
SECTION TWO: My Access to Exercise					
4. I have a place to exercise (indoor or outdoor) at home, place of work or near my home/work place:		☐	☐	☐	☐
If YES, how far is it for you to travel?					
☐	At home or at work				
☐	< 5 km (< 3 miles)				
☐	5 – 10 km (3-6 miles)				
5. I am able to get to an exercise site on my own: (Check "Not Applicable" if you exercise at home)		☐	☐	☐	☐
If NO, who could you ask:					
☐	Family member/partner				
☐	Friend				
☐	Other:				
If you selected other, please specify (free text box)					
6. I have transportation to an		☐	☐	☐	☐

exercise site: (Check "Not Applicable" if you exercise at home)				
If YES, type of transportation:				
	Bike			
	Motor Vehicle (e.g., car)			
	Public transportation			
	Walking			
7. I have a safe place to exercise: (e.g., proper space to exercise, dry and clean floors, good lighting, etc).	☐	☐	☐	☐
8. I have an encouraging place to exercise: (e.g., pleasant people that motivate me)	☐	☐	☐	☐
9. I have an exercise location that is free of cost or reasonably priced (including parking fees):	☐	☐	☐	☐

SECTION THREE: My Exercise Goals				
How important are the following GOALS to YOU in an exercise program?				
	Not Important	Somewhat important	Very important	Not applicable
10. Feel less tired	☐	☐	☐	☐
11. Be able to walk longer	☐	☐	☐	☐
12. Be more flexible	☐	☐	☐	☐
13. Have better balance	☐	☐	☐	☐
14. Fall less often	☐	☐	☐	☐
15. Have less pain	☐	☐	☐	☐
16. Increase muscle strength	☐	☐	☐	☐
17. What is your MOST important exercise goal? (Free text box)				

SECTION FOUR: My Exercise Preferences	
18. Please list up to 3 things that HELP you to exercise more often:	
1. (Free text box)	
2.	
3.	
19. Where would you like your exercise program to be? (Check ALL that apply)	
☐	Home
☐	Gym
☐	Community Centre
☐	Outdoors (e.g., parks, trails, sidewalks, etc.)
☐	Other
If you selected other, please specify: (Free text box)	
20. What is the best time for you to exercise? (Check ALL that apply)	
☐	Morning (between 6:00 am to 12:00 pm)
☐	Afternoon (between 12:00 pm to 6:00 pm)
☐	Evening (between 6:00 pm to 11:00 pm)
21. What is your preferred exercise schedule? (Check ALL that apply)	
☐	Fixed time (same class offered at same time during the week)

□	Multiple drop-in times (same class offered at different times of the week)
□	On my own time
22. What is your preferred exercise class size? (Check ALL that apply)	
□	I prefer to exercise alone
□	With a partner/trainer
□	Small group (less than 10 people)
□	Large group (more than 10 people)
□	Does not matter
23. How would you like to learn proper exercise technique? (Check ALL that apply)	
□	Taught by a healthcare professional (e.g., physiotherapist, nurse, etc.)
□	Taught by a trainer/health club staff
□	Learn on my own from an exercise video
□	Learn on my own from a website with pictures
□	Learn on my own using an app
□	Learn on my own using a print handout
□	Have a friend teach me
□	Have another person with glycogen storage disease teach me
□	None of the above
24. What level of exercise are you comfortable doing? (Check ALL that apply)	
□	Easy to perform
□	Challenging to perform (i.e., “I like a challenge”)
□	Slow paced exercises
□	Fast paced exercises
□	Easy to remember
SECTION FIVE: My Feedback and Tracking	
25. I would like to receive feedback about my progress:	
□	Yes
□	No
If YES, by: (Check ALL that apply)	
□	Email
□	In person
□	Social media (e.g., Twitter, Facebook, etc.)
□	Phone call
□	Text message
If you answered YES to question 25, diverted to complete questions 26 and 27 on page 10	
If you answered NO to question 25, diverted to to question 28 on page 11	
26. What type of feedback would you like to receive? (Check ALL that apply)	
□	Regarding my exercise progress and future improvements
□	Regarding proper exercise techniques
□	Other

If you selected other, please specify: (Free text box)	
27. How often would you like to receive feedback about your exercise progress? (Please check only ONE answer)	
□	Daily
□	Weekly
□	Monthly
□	Yearly
28. I would like to give feedback on the exercise program:	
□	Yes
□	No
If YES, by (Check ALL that apply):	
□	Email
□	In person
□	Social media (e.g., Twitter, Facebook, etc.)
□	Phone call
□	Text message
29. I would like to track my exercise progress:	
□	Yes
□	No
If YES, using (Check ALL that apply):	
□	Cell phone/mobile
□	Diary/Log book
□	Wearable technology (e.g., Fit Bit, pedometer, watch etc.)
□	Other
If you selected other, please specify: (Free text box)	
SECTION SIX: My Barriers to Exercise (Page 12)	
30. Do you have things that STOP you from exercising?	
□	Yes
□	No
If YES, how often does it stop you from exercising: (Check only ONE answer)	
□	Always
□	Very often
□	Sometimes
□	Rarely
31. Please list up to 3 things that STOP you from exercising more often:	
1.	
2.	
3.	
32. I do not exercise as often as I like because: (Check ALL that apply)	
□	I do not like exercise
□	I do not want to fall
□	I do not want to injure myself (e.g., breaking a bone or bruising)
□	I feel pain when I exercise

□	I feel bored when exercising
□	Other
□	None of the above
If you selected other, please specify (free text box)	
33. I do not exercise as often as I like because I have difficulty: (Check ALL that apply)	
□	Understanding the exercise
□	Performing the exercise (i.e., I do not know how to exercise safely)
□	Other
□	None of the above
If you selected other, please specify: (free text box)	
34. I do not exercise as often as I like because I do not have: (Check ALL that apply)	
□	A place to exercise
□	Confidence (e.g., I feel self-conscious about my body)
□	Finances
□	Mobility (e.g., limited movements due to pain)
□	Proper quality of sleep
□	Transportation
□	Time (e.g., family priorities, work, etc.)
□	Willpower/motivation
□	Other
□	None of the above
If you selected other, please specify: (free text box)	
35. Do weather conditions stop you from exercising as often as you like? (Check only ONE answer)	
□	Always
□	Very often
□	Sometimes
□	Rarely
□	Never
36. I do not exercise as often as I like because I have medical conditions such as: (Check ALL that apply)	
□	Arthritis (e.g., hips, knees, etc.)
□	Cognitive concernés (e.g. Alzheimer, Dementia, Parkinson, etc.)
□	Heart condition (e.g., angina, heart failure, etc.)
□	Kidney disease (e.g., dialysis)
□	Lung disease (e.g. asthma, COPD, etc.)
□	Mental health issues (e.g., anxiety, depression, etc.)
□	Other
□	None of the above
If you selected other, please specify: (Free text box)	
37. If you had fewer barriers would you spend more time exercising? (Please check only ONE answer)	
□	Yes

□	No
□	Not sure
38. Please check any mobility aids that you normally use:	
□	Cane/Walking stick/ Hiking pole
□	Walker
□	Crutches
□	Wheelchair
□	Other
□	None
If you selected other, please specify: (Free text box)	

(Page 13) Invitation to focus group/interview

As part of this research would you be happy to take part **in an online focus group and/ or online interview** to further explore your attitudes and beliefs around exercise? If yes, you will be taken to a page to provide your email address and asked to create a **unique 6-digit code.** This is so that we can contact you to arrange the focus group and /or interview and to ensure further data collected will only be linked to your unique 6-digit code.

□ Yes
□ No

(Page 14) Final page

Thank you very much for completing this survey.
If you would like to take part in an online focus group and/or interview, please provide your contact details via this link: https://ntusurvey.onlinesurveys.ac.uk/focus-groupinterview-contact-details

If completing this survey has led you to be concerned for any aspect of your health, we encourage you to contact your local health provider or GP.

If you have any questions or concerns regarding this questionnaire, please contact one of the investigators;

Dr Phil Hennis (philip.hennis@ntu.ac.uk) or Claire Bordoli (claire.bordoli2020@my.ntu.ac.uk).

Appendix K

Focus group/Interview guide used in Chapter 7

Focus Group/Interview Guide:

Just before we get started with the focus group, I would like to take a few moments to review the consent for this study. You have been invited to participate in a 45-to-60-minute focus group. We will talk to you about your experiences and thoughts on participating in exercise. With your permission, we will be taking audio recording of the interviews as well as handwritten notes.

1) Tell me about your experience with exercise (past and present)

Prompt: Do you do any exercise? What types of exercise? What time? Where?

2) Describe your thoughts about your current activity levels?

Prompts: Do you feel you do enough exercise? Would you like to do more exercise?

***3*) Have you received any advice regarding exercise and GSD?**

Prompts: Who was this from? What form? Was this helpful?

4) What are your thoughts on exercising with GSD?

Prompts: Do you think it is important to exercise? Do you think exercise would be beneficial? Do you think GSD affects your ability to exercise? Are there any specific symptoms that effect your ability to exercise?

5)Tell me about the factors that you feel make it easier to exercise? (Wilcox et al 2006; Mcphail et al. 2014)

Prompts: Any physical benefits? (Symptom management, improvements in mobility and function, improvements strength and flexibility, overall health, weight loss).

Any psychological benefits? (Independence, improvements in attitudes/beliefs, emotional benefits, enjoyment, behavioural (goal setting, scheduling exercise)

Any environmental? (Cost, equipment, location, access, time)

6) Tell more about the factors that you feel make it harder for you to exercise? (Wilcox et al 2006; Mcphail et al, 2014)

Prompts: Any Physical barriers? (Pain, fatigue, mobility, comorbid conditions)

Any Psychological barriers? (Fear, perceived negative outcomes)

Any social barriers? (Lack of support, No one to exercise with, competing responsibilities)

Any environmental barriers? (Lack of programs of facilities, environmental conditions, transportation, time constraints, costs, poor communication).

7) If you were designing an exercise programme for those with GSD, what would the ideal exercise programme look like to you?

a. Tell me about the type, duration, frequency of exercise etc.

b. What sort of strategies or techniques do you think would help you to follow the exercise intervention? (Such as social support, resources, goal setting, monitoring, feedback)

c. What would be the best way to notify you of an exercise training intervention?

d. What would be the best way to communicate with you throughout the exercise intervention? (How often to receive feedback? What form such as telephone, email, face to face)

8) What would you like to gain from an exercise programme?
Such as to improve your physical health, improve mental health, symptom management, socialise, sense of achievement, to improve in sport, for enjoyment, improve strength, to look good, feel good…

Finally, is there anything else you would like to add that we have not explored?

Now that we have discussed your thoughts on exercise, we would just like to spend the last 10 minutes or so gathering your views on future research priorities.

1) What do you think should be the top (non-pharmaceutical) research priorities for GSD?
Prompt: Such as the management of symptoms/complications through dietary management, physical activity interventions, mental health support…

2) What more could be done to understand the disease?
Prompt: Do you think we need more observational studies monitoring the disease?
Do you think we need more interventional studies?

3) What type of variables within research studies need to be included?
Prompt: Do we need to include more functional variables such as strength tests, walking tests…
Prompt: Do we need to include lab-based variables such as blood tests, biopsies…

Appendix L

Information Sheet for Participants to Participate in the Study within

Chapter 8

Participant Information Sheet (PIS)

"The effect of oral lactate compared to a placebo on exercise performance during simulated road-race cycling."

We would like to invite you to participate in this original research project undertaken as part of a PhD programme. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Brief Introduction:

Lactate is a substance that is naturally produced by cells within the body when sugar is broken down to provide energy. Research has shown that acute consumption of oral lactate during low to moderate exercise appears to have no effect on performance. During high intensity exercise, the results appear to be mixed, with some studies showing promising results and others showing no effect. In contrast, oral lactate on exercise of moderate intensity followed by high intensity exercise appears to have a positive effect on performance. This may be due to the fact that during exercise including low and high intensities several physiological and metabolic effects occur. These include depletion of carbohydrate that is stored in the muscle and/or liver and fatigue. The provision of lactate may counteract the effects of the depletion of carbohydrate and fatigue via several potential mechanisms. Therefore, it would be valuable to investigate if oral lactate consumption is of benefit for performance gains throughout a simulated cycling road-race including low intensity exercise with bouts of high intensity exercise in which cyclists will become glycogen depleted and fatigued.

Study Requirements:

Inclusion criteria: You must be an endurance trained male cyclist, 18-45 years old and healthy (i.e. free from disease). You should have a minimum of 1 year experience in cycling, particularly accustomed to riding for prolonged periods (3-4 hours) and have a weekly training volume of ≥60km.

Exclusion criteria: Positive Covid-19 test in the past 6 months, allergies or intolerances to foods provided during the study (diet alterations can be made in most cases- please inform the investigator if this applies).

Location:

Erasmus Darwin Building on Nottingham Trent University Clifton, Campus, College Drive, Nottingham, NG11 8NS. You will be required to attend by motorised transport (e.g bus, car or taxi).

Study demands and testing protocol:

If you volunteer for this study, you will be required to visit the laboratory on 3 occasions. The first session will be a preliminary visit in which you will be provided with a detailed explanation of the study procedures and measurements that will be taken. We will take anthropometry including weight, height and body composition and a health questionnaire will be completed. We will complete preliminary testing to determine your maximum oxygen uptake and ventilatory threshold. After a 30-minute rest you will then undertake a familiarisation session where we will provide a detailed explanation of the study procedures and measurements that will be taken, and you will complete a section of the exercise protocol that will take place within the main experimental visits. Following familiarisation, you will complete 2 experimental study days. The day before the experimental study day you will consume the pre-prepared standardised evening meal provided by the researchers in its entirety and then not consume any food or drink other than plain water that day. On the following day (the experimental study day) you will consume the prepared standardised breakfast previously provided to you by the researchers and then not consume any food and drink (other than plain water) until you arrive at the lab. Once you arrive you will take 1 of 2 randomly assigned dietary supplements including lactate or a placebo. You will then complete an exercise protocol consisting of 10 minutes cycling at sub ventilatory threshold, then a 1km TT, then 10 minutes at sub ventilatory threshold, followed by a 4km TT. This will be repeated 5 times in total. Measurements to be taken will include finger prick blood samples, continuous heart rate, continuous gas samples and perceived exertion and exercise tolerance using validated questionnaires. Food diaries will also be collected to assess adherence to dietary restrictions before testing.

Restrictions for testing:

You should consume the pre-prepared evening meal in its entirety and not consume any food or drink (other than plain water) after this. You should then consume your standardised breakfast in its entirety and not consume any food and drink (other than plain water) before you arrive to the lab. You should arrive ready for testing in a well hydrated state by drinking regularly prior to testing. You should avoid caffeine (e.g tea and coffee) for 5 hours before testing and refrain from alcohol, and strenuous activity 48 hours before experiments. You should maintain similar dietary regimens in the days between each exercise testing day.

COVID-19 measures:

To help keep you and others safe and mitigate the spread of COVID-19, social distancing will be observed as much as possible during the completion of this study. All experimenters will wear a face covering during the trial. We also request, when you are not performing an experimental trial, that you also wear a face covering, which we will provide. If you develop any of the following symptoms you should not come to campus / lab, but instead consult the latest guidance on self-isolating:

- A new, continuous cough
- A high temperature
- A loss of, or change in, your normal sense of taste or smell

You should also avoid coming onto campus / into the lab and seek guidance on self-isolating if someone you live with has tested positive for COVID-19, or if you have been in close contact with someone who has had a positive test result. If any of the above applies to you, please inform one of the researchers as soon as possible.

In addition, we are cleaning and disinfecting all areas between participants to ensure there can be no spread of COVID. This includes all equipment, floors and surfaces with appropriate cleaning and disinfectant products.

You will need to have a negative lateral flow test before attending the lab.

Potential benefits to you:

Lactate has also been shown to have beneficial effects on exercise performance, however, the effects of lactate consumption has not been investigated during performance exercise that simulates road-race cycling. Therefore, by investigating the effect of lactate compared to a placebo we will be able to assess if lactate has any benefits on exercise performance during these events. In addition to gaining knowledge in this area, you will also gain experience in undertaking a sports science research trial and its application to research.

Potential risks to you:

Nausea, dizziness, and light-headedness can sometimes be experienced during and following exercise testing. Some muscle soreness may be experienced during and in the days following the exercise trials.

Taking a finger prick blood sample may cause brief discomfort and result in soreness at the punctured site during the procedure and in the days following a test. There is a risk of bruising and light-headedness. Although it is extremely unlikely, high intensity exercise has been known to reveal unsuspected heart or circulation problems and very rarely these have had serious or fatal consequences. Gastro-intestinal distress such as constipation, diarrhoea, nausea, vomiting or stomach ache however these are uncommon.

You can withdraw from the study at any timepoint by informing one of the researchers and you are not obliged to give a reason. If at any point you decide to withdraw from the study your data will be destroyed.

How will my information be kept confidential?

We will keep all information that we collect from you strictly confidential and store it in a locked office at Nottingham Trent University, and on password-protected computers/user accounts there. We will use a secure online server that only the researchers can access. We will assign you a unique code so that your information and data are anonymised. Your information may be retained for up to 5 years, but will be disposed of securely when no longer required, in line with Data Protection Legislation. We don't destroy your signed informed consent form.

What will happen to the results of this study?

The results will contribute to the write-up of a PhD project. We may present the findings of this study at a scientific conference and publish the results in a scientific journal. We will anonymise all data so

you can't be identified in any report or publication. You will receive a copy of the final findings, as well as your own results if you wish.

Who has reviewed this study?

The Nottingham Trent University Human Ethics Committee.

Contacts:

If you have any questions or require more information about this study, please contact me using the following contact details:

Claire Bordoli : claire.bordoli2020@my.ntu.ac.uk

Dr. Phillip Hennis: philip.hennis@ntu.ac.uk

Version V1, 09/09/2021

Appendix M

Statement of Consent to Participate in the Study in Chapter 8

Participant Statement of Consent to Participate in the Investigation Entitled:

"The effect of oral lactate compared to a placebo on exercise performance during simulated road-race cycling."

1) I……agree to partake as a participant in the above study.
2) I understand from the participant information sheet (V1, 09/09/21), which I have read in full, and from my discussion(s) with Claire Bordoli and Dr. Philip Hennis that this will involve me attending NTU on 3 occasions which will include completing preliminary exercise testing and attending experimental trials where you will consume oral supplements and complete an exercise protocol that simulates road-race cycling.
3) It has also been explained to me by Claire Bordoli and Dr. Philip Hennis that the risks and side effects that may result from my participation are as follows: Nausea, dizziness, and light-headedness can sometimes be experience during and following exercise testing. Some muscle soreness may be experienced during and in the days following the exercise trials. Taking a blood sample may cause brief discomfort and there is a risk of bruising. The electrodes placed on the chest skin in order to fit the heart monitor may very rarely cause a minor allergic skin reaction. Although it is extremely unlikely, high intensity exercise has been known to reveal unsuspected heart or circulation problems and very rarely these have had serious or fatal consequences.
4) I confirm that I have had the opportunity to ask questions about the study and, where I have asked questions, these have been answered to my satisfaction.
5) I undertake to abide by University regulations and the advice of researchers regarding safety.
6) I am aware that I can withdraw my consent to participate in the procedure at any time and for any reason, without having to explain my withdrawal and that my personal data will be destroyed and that my medical care or legal rights will not be affected.
7) I understand that any personal information regarding me, gained through my participation in this study, will be treated as confidential and only handled by individuals relevant to the performance of the study and the storing of information thereafter. Where information concerning myself appears within published material, my identity will be kept anonymous.
8) I confirm that I have had the University's policy relating to the storage and subsequent destruction of sensitive information explained to me. I understand that sensitive information I have provided through my participation in this study, in the form of questionnaires and test data will be handled in accordance with this policy.

9) I understand that as part of this study I will be consuming a supplement. I am aware that elite sports people (i.e., international, or national standard) may undergo either out of or in-competition (or both) doping tests and appreciate that the supplement being studied could be contaminated with a substance that appears on the banned lists.

10) I confirm that I have completed the health questionnaire and know of no reason, medical or otherwise that would prevent me from partaking in this research.

11) I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.

12) It has been explained to me that there may be additional risks arising from the current COVID pandemic and that COVID specific cleaning protocol are being used. I have had explained to me the NTU recommendations for undertaking 'Research with human participants' and undertake to abide by the special measures which have been explained to me for this study together with such Government Guidelines that are at the time prevailing.

Participant signature: Date:

Independent witness signature: Date:

Primary Researcher signature: Date:

*When completed: 1 for participant; 1 for researcher site file; 1 to be kept in medical notes (if appropriate).