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# Longitudinal physiological changes in inherited metabolic disorders

**Submission date**
28/04/2022

**Recruitment status**
Recruiting

**Registration date**
03/05/2022

**Overall study status**
Ongoing

**Last Edited**
18/05/2022

**Condition category**
Nutritional, Metabolic, Endocrine

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

## Plain English summary of protocol

Background and study aims
Rare inherited disorders of metabolism (IMD) 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 increase our understanding of these rare disorders and as such the aims of this study are to:
1. Establish changes in heart, lung function and skeletal muscle characteristics over time in people with rare IMD
2. Gain a greater understanding of the underlying mechanisms of the diseases
3. Identify the impact of physical decline on health and wellbeing
4. Establish risk factors for high rates of physical decline
This will increase our understanding of rare IMD and may provide valuable information for interventions aimed at improving the quality of life of those with these disorders.

Who can participate?
Patients aged 18 years and over with various rare inherited metabolic disorders and age- and sex-matched healthy volunteers

What does the study involve?
Participants will be required for testing for 1 day (about 6 hours) per year for 10 years. On arrival participants will have their height, weight, body composition and other basic information taken. They will also need to spend 20 minutes filling out questionnaires to assess activity levels, quality of life and the amount of pain they are experiencing. They will be asked if any particular type of exercise causes them difficulty. In addition, their current dietary treatment plan will be recorded, and they will complete a 7-day food diary before the visit for dietary assessment. They will then complete the following assessments. The incremental ramp cycle test will involve pedalling on a stationary exercise bicycle for about15 minutes to assess the maximum amount of oxygen they use during exercise. The workload will start very low and increase progressively until they reach the point at which they can no longer continue. A device will analyse their

breathing via a mask worn throughout the test and 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 participants decide they cannot exercise any longer.
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 participants to push their legs against a set resistance to assess how strong they 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, they will be asked to complete two maximal contractions lasting no longer than 3 seconds each. In total, they will be asked to complete three contractions and will have at least 5-10 minutes rest between each contraction.
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 skin's surface in order to measure electrical activity from the muscles during exercise.
The size and makeup of participants' 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.
At the end of the day, participants will be fitted with an activity monitor, which just requires them to wear an activity monitor on their thigh for 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. Once the week is complete, participants will be provided with a prepaid envelope for them to post it back.
Health-related quality of life and pain will be assessed via questionnaires.
Bone mineral density will be measured via a DEXA scan every 3-5 years. This involves lying flat for 10 minutes and being scanned using a fine x-ray beam. This is safe as the amount of radiation received is very small (less than most x-ray scans).
Participants will be contacted each day following the tests until they report being fine and having a muscle pain score the same as before testing. On 1, 3 and 7 days following testing, the researchers will establish if they have had any adverse reactions to the testing such as muscle pain, fatigue and any hospital admissions.

What are the possible benefits and risks of participating?
The major benefit of participating in this study is the opportunity for participants to be part of a unique scientific research project that will hopefully lead to a greater understanding of IMD and how these can be managed. Potential issues related to exercising with metabolic disorders include fatigue, muscle pain (in one or more muscles), muscle cramping and swelling. If participants experience any of these symptoms the test will then be stopped and they will be reviewed by the medical doctor.

Where is the study run from?
Nottingham Trent University (UK)

When is the study starting and how long is it expected to run for?
July 2021 to July 2032

Who is funding the study?
Nottingham Trent University (UK)

Who is the main contact?
Dr Philip Hennis
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# Contact information

### Type(s)
Principal investigator

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# Additional identifiers

### Integrated Research Application System (IRAS)
303679

# Study information

### Scientific Title
Longitudinal study of aerobic capacity and skeletal muscle characteristics in patients with rare inherited metabolic disorders

### Study objectives
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 poor exercise capacity. Cross-sectional studies on these patients have shown muscle weakness, profound exercise limitation and poor physical function (Hennis, et al. 2022). In many types, this can progress throughout adulthood until the individual is reliant on a wheelchair to mobilise. Despite wide awareness of this decline in physical function, very little longitudinal data are available. Only through large-scale longitudinal studies will we begin to fully understand the magnitude of exercise intolerance and the rate of physical decline in these patients, to then establish lifestyle factors that can impact the onset and/or severity of this decline.

Other inherited metabolic disorders which fall outside of disorders of energy metabolism and do not specifically present with a muscle phenotype also warrant further study. In phenylketonuria (PKU) for example, the impact of recommended lifelong dietary restriction (Singh, Cunningham, Mofidi, et al. 2016; van Wegberg, MacDonald, Ahring, et al. 2017; Ingwood) on exercise intolerance, muscle strength and architecture and bone mineral density (BMD) is not well established.

Identifying the change in these physical outcomes and assessing the impact of diet and lifestyle choices are therefore justified, particularly within a largescale longitudinal study.

The purpose of this longitudinal study is to build upon the very little longitudinal data available to begin to fully understand the magnitude of exercise intolerance in these patients, the rate of physical decline and begin to establish lifestyle factors that can impact the onset and/or severity of the decline. This research will enable us to greatly increase our understanding of rare inherited metabolic disorders (IMD) and will provide valuable information towards interventions aimed at improving exercise tolerance and the onset and/or severity of disease progression within these patients.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Approval pending, Nottingham Research Ethics Committee

## Primary study design
Observational

## Study design
Multicentre longitudinal case-control study

## Study type(s)
Other

## Health condition(s) or problem(s) studied
Rare inherited metabolic disorders such as glycogen storage diseases (GSD), phenylketonuria (PKU) and fatty acid oxidation disorder (FAOD)

## Interventions
Participant recruitment:
The researchers include consultants in inherited metabolic disease who routinely care for the potential participants. Patients' existing clinical care teams will identify them as suitable for the study. Eligible patients will either be approached during their routine outpatient clinic visit or will be sent an invitation letter and information sheet. Sufficient time (no less than 24 hours) will be given to patients to decide if they wish to participate. They will then be contacted by telephone. Should they be interested in the study, they will be given the opportunity to ask questions. If they wish to proceed, written consent will be obtained, and they will be enrolled in the study. Following consent, we will endeavour to complete their year one visit within 3 months. This should be a sufficient amount of time to arrange a date and test the participant. In addition, an age- and sex-matched healthy control group will be recruited by the research team from Nottingham Trent University staff and the local community.

Study design and methodology:
This will be a largescale longitudinal study involving the annual assessment of aerobic capacity, muscle function, movement behaviours, markers of overall health and wellbeing in patients with rare inherited metabolic diseases. In addition, bone mineral density (BMD) will be measured every 3-5 years and each patient's recommended dietary treatment plan will be recorded and the researchers will obtain a 7-day food diary prior to each study day for dietary assessment. The aim is to conduct this study over 10 years.

The study was designed by exercise physiologists and physicians specialising in rare metabolic disorders. The study has also been considered by the Association for Glycogen Storage Disease (AGSD) and their scientific panel, which includes patients and medical professionals. Both the AGSD and its patient members are keen to support the study and take part in research looking at their condition.

Timetable for the stages of the research:
The initial study will be conducted for 10 years with each participant tested annually. The researchers aim to test 50 individuals with IMD and 50 age and sex-matched healthy controls. The number of participants with IMD has been decided pragmatically rather than by a formal calculation as these diseases are rare and this is primarily a descriptive study and thus formal sample size calculations are not applicable.

In total, participants will undergo two exercise tests over one day, these include a cardiopulmonary exercise test (CPET) and a knee extension exercise to determine maximum voluntary contraction (MVC). All exercise tests will be conducted in an exercise physiology laboratory in the presence of an exercise physiologist and a medical doctor namely either Dr William Kinnear or Dr Elaine Murphy. 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. Those with GSD and FAOD will not be restricted from eating or drinking for the duration of the study. Individualised dietary guidance will be prescribed to those with PKU to adhere to on the day of testing in line with the most recent European Guidelines (van Wegberg AMJ, MacDonald A, Ahring K, et al. 2017). An isotonic sports drink providing 32.5 g carbohydrate (18 g sugar) will be made available for each participant and, where diet allowed, patients will be encouraged to drink it prior to the exercise test to potentially reduce exercise-induced muscle pain. Throughout the day, patients will be asked to stop the exercise if they believed continuing might result in muscle soreness and damage.

On arrival patients will have their height, weight, and body composition (via bioelectrical impedance) measured and resting measures of pain (assessed using the numeric pain rating scale). They will then undergo CPET and spirometry using an incremental ramp test. They will have their leg muscle assessed for strength using dynamometry, activation using EMG, and size and architecture using B-mode ultrasonography. They will also have their physical activity measured via an activity monitor and quality of life and pain assessment will be completed via questionnaires. When bone mineral density is measured this will be done via a DEXA Scan.

Assessments:
1. CPET and spirometry using an incremental ramp cycle test: Participants will perform a symptom-limited, incremental ramp protocol to volitional exhaustion using an electromagnetically braked cycle ergometer. Breath by breath gas exchange data will be analysed to determine peak oxygen consumption ($VO_2$ peak) and anaerobic threshold/ gas exchange threshold (AT). The test takes 15 minutes to complete, starting at a very low intensity that increases over time. The last 3-5 minutes of exercise will be at a high intensity and the test stops when the participant decides they cannot exercise any longer. In addition to gas analysis, continuous heart rate and peripheral oxygen saturation measurements will be made, blood pressure every 3 minutes and a 12 lead ECG continuously monitored.
2. Knee Extension Exercise: This will be completed following a minimum of 2 hours rest, during which the patients can eat lunch and complete questionnaires (described below). A muscle dynamometer will be used to assess the strength (maximum voluntary contraction) of the leg muscles. Participants will be briefed, follow a series of warm-up knee isometric contractions, and then commence the MVC protocol (2-3 isometric knee extension at 80 degrees with 5-10 minutes rest between contractions).

3. Surface electromyography (EMG): This is a non-invasive procedure and will be conducted during exercise protocols to measure muscle activation.
4. B-Mode ultrasonography: This will assess the size and makeup of the participant's leg muscles. This is a non-invasive method that uses sound waves to produce pictures of muscles, tendons, ligaments, and joints throughout the body. Ultrasound is safe, non-invasive and does not use ionising radiation.
5. Physical Activity Monitor: Following completion of the exercise testing protocol, participants will be 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 accelerometry physical studies (Scott et al, 2012). The accelerometer's frequency will be recorded at 60Hz and will be worn for between 6 and 7 consecutive days. On return of the accelerometer, the data will be downloaded and converted to 60-second epoch files (GNEEActiv Software version 3.3, Activinsights Lts., Kinbolton, United Kingdon). Analysis of the data will be conducted using GENEActiv macro file version 9, using validated activity cut off points (Esliger et al, 2011).
6. Quality of life and pain assessment: Health-related quality of life will be estimated using the 36-Item Short-Form Health Survey questionnaire (SF-26) and pain assessed using the numeric pain rating scale.
7. DEXA scan: This will be conducted to measure bone mineral density at Nottingham Trent University. These assessments will be conducted over 1 day (up to 6 hours in total) with the exercise ramp test lasting approximately 15 minutes.
In addition each patient's recommended dietary treatment plan will be recorded and we will obtain a 7-day food diary prior to each study day for dietary assessment.

Follow-Up:
Participants will be contacted each day following the test until they report being fine and having muscle pain score the same (+-1) as prior to testing. 1, 3 and 7 days following each testing day to establish if they have had any adverse reactions to the protocols. This will include recording muscle pain, feelings of fatigue and any hospital admissions.

## Intervention Type
Other

## Primary outcome(s)
1. Cardio-respiratory fitness and spirometry including gas analysis where $VO_2$ peak and anaerobic threshold (AT) measured using breath by breath gas analysis during an incremental ramp cycle test once per year for 10 years
2. Muscle architecture measured using B-mode ultrasonography once per year for 10 years
3. Muscle strength measured using muscle dynometry once per year for 10 years
4. Muscle activation measured using surface EMG once per year for 10 years

## Key secondary outcome(s)
1. Pain measured using the visual analogue scale (VAS) four times per year for 10 years, once prior to exercise testing and then at 24, 48 and 72 hours after testing
2. Dietary assessment carried out using a 7-day food diary prior to each testing day once per year for 10 years
3. Quality of life (QoL) measured using a quality-of-life questionnaire (36-Item Short-Form Health Survey questionnaire SF-26) once per year
4. Bone mineral density measured using a DEXA machine once every 3 years for 10 years
5. Physical activity measured using a physical activity monitor (tri-axial GeneActiv Original

Accelerometer) over 1 week, once per year and a physical activity questionnaire completed once per year for 10 years

### Completion date
01/07/2032

## Eligibility

### Key inclusion criteria
Adult patients (≥18 years) with a diagnosis of a rare inherited disorder of metabolism including glycogen storage disease, fatty acid oxidation disorder and phenylketonuria

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
18 Years

### Sex
All

### Key exclusion criteria
1. Individuals who do not have the capacity to consent
2. Pregnancy
3. Individuals with contraindications to exercise testing, as stated by the American College of Cardiology/American Heart Association Guidelines for Exercise Testing included below:
3.1. Acute myocardial infarction (within 2 days)
3.2. High-risk unstable angina
3.3. Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
3.4. Symptomatic severe aortic stenosis
3.5. Uncontrolled symptomatic heart failure
3.6. Acute pulmonary embolus or pulmonary infarction
3.7. Acute myocarditis or pericarditis
3.8. Acute aortic dissection Relative
3.9. Left main coronary stenosis
3.10. Moderate stenotic valvular heart disease
3.11. Electrolyte abnormalities
3.12. Severe arterial hypertension
3.13. Tachyarrhythmias or bradyarrhythmias
3.14. Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
3.15. Mental or physical impairment leading to inability to exercise adequately
3.16. High-degree atrioventricular block

### Date of first enrolment

01/05/2022

**Date of final enrolment**
01/07/2032

# Locations

**Countries of recruitment**
United Kingdom

England

**Study participating centre**
**Nottingham Trent University**
School of Science and Technology
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**Study participating centre**
**National Hospital for Neurology and Neurosurgery**
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# Sponsor information

**Organisation**
Nottingham Trent University

**ROR**
https://ror.org/04xyxjd90

# Funder(s)

**Funder type**
University/education

**Funder Name**
Nottingham Trent University

**Alternative Name(s)**
NTU

**Funding Body Type**
Private sector organisation

**Funding Body Subtype**
Universities (academic only)

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**
The data-sharing plans for the current study are unknown and will be made available at a later date

**IPD sharing plan summary**
Data sharing statement to be made available at a later date