ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
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East Midlands Research into Ageing Network (EMRAN) Discussion Paper Series

ISSN [2059-3341]

Issue 47, April 2022

NIHR Nottingham Biomedical Research Centre (BRC) Musculoskeletal theme: virtual conference proceedings 24th & 25th February 2022

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East Midlands Research into Ageing Network (EMRAN) is a research collaboration across the East Midlands to facilitate applied research into ageing and the care of older people. EMRAN receives support from National Institute of Health Research Applied Research Collaboration East Midlands (NIHR ARC-EM)

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15//04/2015 V1

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
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SUMMARY

This paper gives summaries of the keynote lectures given and the research abstracts presented at the NIHR Nottingham Biomedical Research Centre Musculoskeletal theme virtual conference held on 24th and 25th February 2022.

The purpose of the conference was to stimulate collaboration within the broad field of musculoskeletal research, by having presentations showing different techniques and topics, given by our experts and our PhD students. Collaboration was encouraged by inviting colleagues to contact each other by email to start a conversation - an invitation that we extend through this paper, and extend to interested colleagues anywhere in the world.

This conference was funded by the NIHR Nottingham Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

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Covid research in the NIHR Nottingham Musculoskeletal BRC theme

Professor Ana M Valdes

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Since the beginning of wave 1 of Covid the scientists and clinicians within the BRC MSK theme have been actively involved in helping find answers to the pandemic.
Although we do not do respiratory medicine, many of our skills and the way we do research has meant that we have been able to make important scientific contributions which have had impact on policy.
There are three types of work we have undertaken

1) Collaborating with the Zoe Covid App we have helped analyse and interpret data collected by the app and this has been used to identify the most predictive symptoms of Covid, the side effects and effectiveness of vaccines and boosters and to look at the differences in symptoms and severity between different variants
2) By setting up a cohort of healthcare workers from Nottingham University Hospitals (PANdemic Tracking of Healthcare workERs or PANTHER). We have been following their antibodies since wave 1, we were able to see how different was the response to two vaccine doses to various variants in doctors and nurses with a previous infection and those without and to show that within healthcare settings both in Nottingham and London the most protected doctors and nurses were those working in Intensive Care.
3) Investigating the molecular responses to Covid. So for example we have been involved in a recent paper that showed that T-cell responses in people with previous immunity to other (common cold) coronaviruses made them totally immune to Covid. And another study that found that the T-cell and B-cell responses of people with previous Covid infection and one dose were highly protected against novel variants. This was used in a White House press conference.

We are right now working on new studies about the Omicron and understanding the B-cell and antibody responses.

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Public and Patient Involvement and Engagement in Translational Research

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Translational research aims to convert or 'translate' basic research into results that can directly benefit and improve the health of individuals and patients. Observations in the laboratory, clinic or community can then be turned into new interventions which can include new methods for diagnosis, alternative treatments and therapies, improved medical procedures and recommended behavioural changes. Translational research can be described as '*bench to beside'* when discoveries found in the laboratory are applied to studies in humans, or '*beside to practice'* which speeds up the adaptation of best practices into community settings. There is also 'reverse or back translation' also known as '*bedside to bench'* which starts with the actual, real-life experiences of the patients or observations in a clinical trial. Researchers then work backwards to discover the mechanisms behind these experiences and observations.

Patient and Public Involvement (PPI) has been key to all the Nottingham Biomedical Research Centre's translational research. Several studies will be presented in this session including CORE-Kids, a study aiming to develop a set of outcome measures that should be used in trials involving children with broken bones and included PPI from children and their parents during a special event at Twycross Zoo. A further project will be the Pain at Work (PAW) toolkit, developed as a digital tool kit for people with chronic or persistent pain at work with important input and collaboration from patients and members of the Burning Nights charity. Finally, we will be joined by PPI members of the BRC Musculoskeletal theme's Complex Intervention Research Team who will discuss how they have been involved in translational research and what they feel both they and the research studies have benefit from having public and patient involvement.

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Serum levels of pro-resolving lipid mediators are raised following traumatic knee injury in active healthy adults and metabolites of soluble epoxide hydrolase are associated with persisting knee pain at 2 years

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Knee injury is a complex pathology that can lead to chronic pain and is a major risk factor for osteoarthritis (OA). The molecular mechanisms that initiate and drive the development of early disease (or its resolution) are currently poorly understood, though we have described an immediate inflammatory response to the injury. Bioactive lipids are a distinct class of biological molecules that have a diverse range of physiological and pathological functions, which include a fundamental role in the initiation and resolution of inflammation. The aim of this study was to assess potential associations between bioactive lipids and knee pain scores, and to probe potential mechanisms which may suggest new therapeutic targets for knee pain or OA.

A subgroup of KICK participants (n=45/150, median age 30) were defined with traumatic knee injury and longitudinal PROMs and serum sampling at baseline (within 8 weeks), 3 months, and 2 years after injury. Serum levels of 41 bioactive lipids were quantified by LC-MS/MS.

At baseline, levels of omega-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), along with their pro-resolution metabolites 17-, and 14-hydroxydocosahexaenoic acid (HDHA), and 18-hydroxyeicosapentaenoic acid (18-HEPE) were significantly higher, compared to later times, and to age- and sex-matched healthy controls. Pro-inflammatory eicosanoids, including prostaglandin D2, leukotriene B4, thromboxane B2, and 11-dehydroxy-thromboxane B2 were lower post-injury, compared to later times, or healthy controls.

Linear regression analyses were performed between serum levels of lipids and the knee injury and osteoarthritis outcome score (KOOS) at the 3 different times. At baseline, higher levels of 11,12-, and 14,15-dihydroxyeicosatrienoic acid (DHET) were associated with greater knee pain, whereas higher levels of EPA and 18-HEPE were associated with lower pain levels. At 2 years, higher levels of 5,6-, 8,9-, 11,12-, and 14,15-DHET, and the precursors 5,6-, and 14,15-EET, were associated with higher pain.

Higher levels of pro-resolving lipids and lower levels of pro-inflammatory lipids following knee injury suggest an activation of resolution pathways and a shift toward tissue homeostasis. The association of the EET/DHET pathways with increased pain at 2 years possibly highlights the therapeutic potential of targeting the soluble epoxide hydrolase pathway for knee pain, given its role in other pain settings.

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Risk factors for poor recovery from a significant ankle ligament injury: SALI study

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Introduction
Ankle sprains are among the most common musculoskeletal injuries, accounting for 3-5% of all UK Emergency Department visits. Despite being classed as a minor injury, it is not uncommon for residual symptoms, such as pain, swelling, muscular weakness, and instability to last for months and years after injury. Thus, understanding the epidemiology of these injuries is important for improving patients' musculoskeletal health and decreasing the burden of ankle sprains and the associated sequela.
Purpose
Examine risk factors for suffering from poor recovery following an ankle sprain.
Methodology
A multicentre cohort study recruited patients with an acute ankle sprain (aged 18-70) from nine Emergency Departments and two Urgent Care Centres in the UK. Data was collected using self-reported questionnaires at time of injury, then 3 and 12 months after injury. Poor recovery was defined as patients self-reporting pain, lack of confidence in the ankle or functional disability in the Foot and Ankle Outcome Score.
Results
47% and 25% of participants suffered with poor recovery 3 and 12 months post ankle sprain.
A significant difference between those who do and do not recover well 3 months post injury was found for body mass index ($p=0.042$), alcohol consumption ($p=0.007$), highest education ($p=0.017$), mechanism of injury ($p=0.003$), and smoking (amount per day) ($p=0.046$). No significant difference ($p>0.005$) was found for age, body mass, height, sex, ethnicity, smoking status, weight-bearing status, plus previous injury to; either, same, and opposite ankle.
12 months post ankle sprain there was a significant difference for body mass ($p=0.001$), height ($p=0.005$), and body mass index ($p<0.001$) between those who do and do not recover well, but no significant difference ($p>0.005$) in age, smoking (status, amount per day), alcohol consumption (status, and amount of unit per week), sex, ethnicity, and highest education.
Conclusion
Higher body mass index, alcohol consumption smoking status, highest education and mechanism of injury are associated with poor recovery 3 months post injury and body mass, height, and body mass index are associated with poor recovery 12 months post ankle sprain. Poor recovery can lead to increased diagnostic and higher demands for further appointments and rehabilitation services.

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Towards a common definition of Hospital Acquired Deconditioning (HAD) in working-age adults: a scoping review protocol

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Aim
To understand what research tells us about what hospital-acquired deconditioning is and what it looks like in adults.
Introduction
Some hospital stays result in people coming home weakened and less able than when they entered hospital. These changes are not always due to being unwell but happen due to being in bed more and being less active because of how hospitals can be set up. This can be known as hospital-acquired or associated deconditioning or HAD. People who get HAD can need to stay longer in the hospital or go to another place to rebuild their strength, or they may need carers when they leave the hospital because looking after themselves is tricky. Currently, one in three older adults gets HAD, but we don't know how many younger or middle-aged adults are affected. Part of the problem is that HAD is used differently by different groups of hospital staff or healthcare researchers. This scoping review is the first stage project to develop a framework for healthcare professionals to identify and manage HAD by pulling together the different descriptions of HAD.
Methods
This study follows the Joanna Briggs Institute scoping review guidelines, and reporting will follow the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist. All source types which provide a definition or description of HAD assessment or management in adults over 18 in-hospital care will be included. Literature that describes deconditioning due to specific diseases is excluded to focus on HAD rather than condition-specific complications. Sources must be written in English. Eight electronic medical databases and grey literature (unpublished) platforms were searched from 1st January 1990 to 31st January 2022 (in progress). Reference lists will be checked using Web of Science. Two separate reviewers will screen and collect data; disagreements will be resolved through agreement or a third person. Findings will be summarised and presented visually with a written explanation.
Clinical Relevance
HAD is potentially avoidable harm in hospital care with multiple parts. While trials to treat or prevent have been done, future studies will benefit from clarifying what HAD means.

ISSN: 2059-3341
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Approaches to co-production in care homes: a scoping review protocol

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Introduction

Older people living in care homes often have complex needs which require support from care home staff and healthcare services. Co-production involves patients, the public, carers, professionals and academics working together as equals to solve problems and improve services. Co-production approaches may help to develop improved ways of working which are acceptable to residents, staff and care providers. However, there is a lack of guidance about how to use co-production approaches in this setting. Previous research exploring the use of co-production approaches in care homes could inform future co-production projects.

Aim

To map co-production approaches used in care homes for older adults in previous research.

Method

The scoping review will be carried out to map studies published in academic journals which used co-production in care home settings providing care for older people. Best practice guidance for completing a scoping review and reporting the findings will be followed. Seven electronic databases (AMED, ASSIA, CINAHL, EMBASE, MEDLINE, PsychInfo, Social Care Online) will be searched to find relevant studies. Titles and abstracts of these studies, followed by the full text articles, will be independently screened against eligibility criteria by two reviewers. Citations will be searched to identify any other relevant studies. Key information of relevance to the research question will be extracted from each study by one reviewer and checked by another. Information from across all studies will then be summarised and presented using tables and diagrams. This information will be used to make recommendations for future co-production research in care homes for older people based on the gaps in what is known about this topic. A collaborator group of care home representatives and health professionals will be involved in interpretating the review's findings from their perspectives. We expect that the findings from this review will guide future co-production research and help ensure that future studies in care homes address the priorities of people who live and work in these settings.

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Investigating the digestibility, bioavailability and utilisation ("Di-Bi-Uti") of selected protein sources in older individuals using dual stable isotope tracer techniques

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Introduction & Aims

Ageing is associated with progressive loss of muscle mass and function (sarcopenia) associated with a greater risk of falls, frailty, and premature mortality. As such, strategies to mitigate age-associated declines in skeletal muscle are necessary. Skeletal muscle is regulated by a dynamic balance between muscle protein synthesis (MPS) and breakdown (MPB), with the principal stimulator of MPS being dietary protein-derived essential amino acids (EAA). A contributing factor to muscle loss with age is changes in digestive capacity, limiting the uptake and thus availability of EAA from dietary protein. Further, what protein sources (plant/dairy) or blends results in the greatest EAA availability and stimulation of MPS in older adults remains unknown. Our aim is to use advanced dual isotope tracer techniques to gain greater insight into protein digestibility, bioavailability and utilisation in response to different protein blends in older adults.

Methods

We will recruit 32 healthy older individuals (~70 y) who will be randomly assigned to consume 1 of 4 distinct proteins blends (i.e., n=8 / experimental group). After an overnight fast, volunteers will consume a universally labelled ^{13}C spirulina and a ^{2}H labelled free amino acid mix alongside protein blends, to determine digestibility. Blood samples will be collected regularly throughout, with plasma AA analyzed using gas chromatography mass spectrometry (GC-MS). Further, subjects will receive a primed constant intravenous infusion of a stable isotopically labelled AA. Baseline muscle thigh biopsies will be collected to determine fasted MPS, with further biopsies being collected 2 and 4 h after protein consumptions to determine fed-state MPS via GC-MS.

Potential Impact

This study will define optimal protein blends exhibiting superior profiles of digestion and ensuing induction of muscle anabolism in older people. The results from this trial will as such inform upon core features of best nutritional practices for age-related muscle maintenance.

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Leucine and older aged postprandial skeletal muscle anabolism: a literature review

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The opening thesis aim was to highlight contemporary knowledge in relation to the specific skeletal muscle anabolic effects of the dietary protein-derived amino acid (AA) leucine; in isolation and enriched protein sources, in contexts of exercise, ageing and physical (in)activity.

By way of background, skeletal muscle mass is regulated by the dynamic relationship between muscle protein building (i.e., synthesis; MPS) and breakdown (MPB), both of which are influenced day-to-day by dietary protein intake and physical (in)activity behaviours. In terms of mechanisms, dietary protein intake increases MPS by virtue of the essential amino acid (EAA) not the non-essential amino acid constituents (those that can be made in the body). When protein intake is in close proximity to exercise, this increases the sensitivity of muscle to EAA permitting long-term remodelling (e.g., muscle growth/fatigue resistance). In contrast, ageing, disease and physical inactivity, are associated with a blunted muscle building capacity to protein feeding and exercise ("anabolic resistance"), contributing to observed declines in muscle health. It follows that optimising nutrition is a critical factor for muscle maintenance.

Notably, the single EAA: leucine, is the most potent stimulator of the cellular mechanisms that drive increases in MPS, exhibiting ~3-fold potency compared to other EAA. Reflecting this, maximal MPS stimulation can be achieved not only with large protein intake but also following low doses of "leucine-enriched" proteins. Such is the potency of leucine that, during periods of physical inactivity (i.e., bed rest/immobilisation), rather than high protein diets which may be undesirable in older/clinically vulnerable populations, enriched-leucine may be consumed alongside ± muscle stimulation (i.e., electrical stimulation, massage, exercise). Accordingly, leucine-enriched protein supplements (~3 g leucine) can negate the need for older adults to consume large quantities (~40 g) of protein, mitigating common issues of satiation, to maximise muscle anabolism - ideally alongside some aspect of muscle exercise.

Based upon this review, we will investigate if a novel purified whey protein from Arla Foods (~20% greater leucine content) has superior muscle building properties compared to a regular whey; at rest and following acute/chronic exercise - to improve muscle health of older adults.

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Mechanistic target of rapamycin (mTOR) signaling in aged human skeletal muscle

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Sarcopenia is an age-related health problem without safe and effective treatments. The mechanistic target of the rapamycin complex 1 (mTORc1) pathway positively regulates proteostasis in muscle. However, studies show mTOR signalling is, counterintuitively, hyperactive in aged muscle and a potential cause of sarcopenia. We comprehensively analyzed mTOR cell signalling across age (young/old) and sex (men/women). This project was approved by the University of Nottingham Ethics Committee, complied with the Declaration of Helsinki (2015), and was registered at https://clinicaltrials.gov/(NCT02505438). This experiment included 29 human muscle biopsy samples (fasted-state, *vastus lateralis*) collected from: young men (22±4y, BMI; 24±3, N=6), older men (69±4y, BMI; 27±2, N=8), young women (22±3y, BMI; 22±2, N=7) and older women (67±4y, BMI; 26±2, N=8). Following protein extraction/standardization, mTOR and targets were quantified by immunoblotting: including mTOR (Ser^{2448}), ribosomal protein S6 kinase 1 (p70S6K1 Thr^{389}), 4E-binding protein 1 (4E-BP1 $Thr^{37/46}$), ribosomal protein S6 (rps6 $Ser^{235/236}$), tuberous sclerosis complex 2 (TSC2 Thr^{1462}), adenosine monophosphate kinase (AMPK Thr^{172}), and serine-threonine protein kinase (AKT Ser^{473}). Data were quantified via densitometry and normalized to Coomassie blue staining to account for loading error. Data were tested for normal distribution using a Shapiro-Wilk test. Comparisons between age/sex were performed by independent t-tests or non-parametric equivalent, with the alpha level of significance set at $P<0.05$. All analyses used Graph Pad Prism (version 9.0, La Jolla, US). Initial results showed that mTOR Ser^{2448} was unaffected by age; however 70S6K1 Thr^{389} was higher with mix sexes in older age (1.5-times) ($P<0.05$) than the young comparator group. Additionally, rps6 $Ser^{235/236}$ in both older men and mix sexes was higher than in younger counterparts (2-times; $P<0.05$ and 1.9-times; $P<0.01$, respectively); in contrast, no differences in 4E-BP1 $Thr^{37/46}$ were noted. AMPK Thr^{172} in older men and women was 5.2-times ($P<0.001$), and 3.2-times ($P<0.05$) greater than in younger counterparts; and mix sexes 5.6-times ($P<0.01$) higher. Finally, while upstream Akt Ser^{473} exhibited no difference, TSC2 Thr^{1462} was two-thirds lower ($P<0.01$) in younger than older subjects (mix sex). We report striking elements of hyperactive mTOR/AMPK signaling in human muscle supporting the notion of mTOR inhibition strategies e.g. rapamycin, to ameliorate sarcopenia in older age.

ISSN: 2059-3341
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The impact of genetic variation within the vitamin D pathway upon skeletal muscle function: a systematic review

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Studies *in vitro* have demonstrated a key molecular role for 1,25-dihydroxyvitamin D (1,25D) in skeletal muscle function, with vitamin D-deficiency being associated with muscle pain and weakness. Despite this, our understanding of the overall role of vitamin D in muscle health is lacking, relative to more well-studied targets such as the skeleton. In particular, the impact of vitamin D-related genetic variants on skeletal muscle remains unclear. Therefore, we reviewed existing studies that have investigated relationships between skeletal muscle function and single nucleotide polymorphisms (SNPs) within vitamin D-related gene pathways. A systematic review of articles published between January 2000 and July 2021 was performed by searching PubMed, EMBASE and Web of Science for articles investigating associations between functionally relevant variants of key genes within the vitamin D pathway and skeletal muscle function outcomes. Human research articles were included regardless of language or article type; the Quality of Genetic Association Studies (Q-Genie) tool was used to assess article quality/risk of bias. Twenty-one articles were included for final analysis, of which 20 only studied genetic variation of the *VDR* gene. Of the included articles 81% solely included participants aged ≥50 years and of the 9 studies including individuals of ethnic minorities, only 2 included Black participants. 20 different VDR SNPs were investigated across studies in relation to muscle function, with multiple studies identifying associations with muscle outcomes and BsmI (rs1544410), FokI (rs2228570), ApaI (rs7975232), and A1012G (rs4516035). Whilst A1012G was significantly associated with improved handgrip strength, results for other SNPs varied between studies and were primarily driven by older Caucasian participants, therefore limiting generalisation of findings. Only one study included SNPs of 10 other vitamin D related genes (*CYP24A1, DBP, CYP27B1, CYP27A1, CYP2R1, DHCR7, CYP3A4, CUBN, RXRA, LRP2*) but no significant associations were found. To conclude, this review exemplifies that research into the impact of genetic polymorphisms of vitamin D-related genes in relation to muscle function is largely restricted to the *VDR* gene. It demonstrates a need for future investigations into genes other than the VDR, which may yield a more comprehensive understanding of the role of the vitamin D axis within muscle.

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Investigating the physiological characteristics of frailty using magnetic resonance imaging

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Frailty is a syndrome associated with the decreased ability to combat incidents that occur as a result of the ageing process, such as falls and illness. Despite this knowledge of the negative consequences of the syndrome, the physiological characteristics (i.e., the structure and function of organs and body tissues) differentiating healthy and frail older people remain poorly defined, which prevents the development of biological and scientifically based interventions to prevent and reverse frailty. Limited understanding of the physiological characteristics may be in part attributed to studies to date focusing analysis on single targets (e.g., heart or brain) in isolation. Accordingly, recent findings suggest frailty is likely to result from a disorder in multiple physiological systems (integrated groups of organs and tissues) simultaneously, suggesting single organ investigations are providing limited insight into the physiological basis of the syndrome. Blood based biomarkers are emerging but will require confirmation with robust measures of organ structure and function to determine the presence of multisystem dysregulation as a feature of the frailty state.
Magnetic resonance imaging (MRI) is a powerful tool to non-invasively quantify the structural and physiological characteristics of various organs simultaneously within an individual, implying MRI may be an effective method to investigate multi-system dysregulation during frailty. For example, a single MRI scan session can provide a multitude of organ structure and function measures, such as organ volume, scar tissue, adiposity, blood flow and oxygen extraction. Therefore, this study aims to characterise and compare the structural and physiological characteristics of non-frail, pre-frail (a state which is understood to develop into frailty, if untreated) and frail older people using multi-organ focused MRI techniques. Furthermore, MRI will be dovetailed with measurements of cognition, muscle function and motor unit recruitment to bring insight of the progression from health to pre-frailty to frailty. This could aid in determining if clusters of structural and physiological characteristics are common to the condition, and which develop first. Similarly, which characteristics may be indicative of frailty severity. Future studies may then be designed to target specific physiological traits with interventions to diminish the syndrome's progression.

ISSN: 2059-3341
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Determining the impact of short-term targeted force accuracy training on neuromuscular function in older adults: a future study

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Introduction
It is well-established that as people age, they experience loss of muscle mass and strength via a progressive condition known as sarcopenia (Piasecki *et al.*, 2018). In addition, ageing is also known to affect motor coordination and balance. Alongside overall losses of muscle mass, motor unit loss is also evident with advancing age, with a ~40% reduction in motor units at 70 years of age when compared to young adults (Piasecki *et al.*, 2016). The motor unit is the fundamental component of voluntary muscle contraction, comprising a neuron, an axon, neuromuscular junctions, and associated skeletal muscle fibres, and poor communication between the nerve and muscle may lead to smaller, weaker muscles which are more difficult to control. As such, poor nerve-muscle communication in advancing age may explain the increased risk of falls and fractures, and the subsequent negative impacts on the quality of life, associated with sarcopenia (Wilkinson *et al.*, 2018). Therefore, effective and feasible interventions aimed at minimising these risks are required.

Aim
To determine the efficacy of low-intensity, targeted force accuracy training for improving aspects of neuromuscular function in different lower limb muscles of older adults.

Protocol
Thirty healthy volunteers aged between 65-85 years (50% female) will be recruited to complete 4-weeks (3 sessions per week) force accuracy training using the thigh (vastus lateralis) and lower leg (tibialis anterior) muscles of one leg. Multiple aspects of neuromuscular function (including strength, balance and nerve-muscle communication) will be assessed before and after the force accuracy training, and after 2 and 4-weeks of de-training, in both the trained and untrained leg.

Potential impact
The study will aid our understanding of how nerve-muscle communication and associated physical function can be altered in response to motor control training in older adults. This study also has potential to establish a feasible and effective exercise training modality to improve functional outcomes in older adults, including those who may not be able to perform traditional exercise aimed at improving muscle function (i.e., resistance exercise training). These findings may be used by health professionals prescribing exercise to older adults.

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

Feasibility and efficacy of neuromuscular electrical stimulation in fragility fracture patients: a PhD study

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Introduction
Fragility fractures (e.g. hip, leg, pelvis or vertebrae) and their management can exacerbate muscle weakness, increasing the risk of further falls and fractures. Although muscle strengthening exercise is known to be effective, it is unachievable for many patients. Neuromuscular electrical stimulation (NMES) – electrical stimulation of the muscle causing contraction and mimicking strengthening exercise - is a potential intervention. However such treatment is not in routine use due to insufficient evidence of its effectiveness. My PhD, which began 01/02/21, explores the use of NMES in this group, via a systematic review of the existing literature, and a feasibility trial.
Systematic review
The review was registered on PROSPERO and the protocol was published. Eligible studies were RCTs of older people admitted acutely to hospital, comparing NMES to no treatment or other usual treatments, against a range of outcomes, primarily muscle strength.
The review is in progress and 40 eligible studies have been identified.
Feasibility study
The feasibility of applying NMES in older hospitalised patients with fragility fractures remains unexplored. In this study, consenting participants will be randomised to NMES in one leg whilst the other acts as the control. Feasibility outcomes include recruitment rate and the number of NMES treatments given. Efficacy measures include muscle ultrasound parameters, muscle strength, mobility, and pain at discharge and ADL at six months.
We identified 285 fragility fracture patients over the first 3 months of recruitment, but recruited only 7, who were discharged before we could deliver more than 3 NMES sessions - mainly due to short length of stay.
Conclusion
We have already concluded that NMES as currently planned is not feasible in the acute setting. We now plan to test the feasibility of recruitment from rehabilitation settings, and home-based NMES.

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

Motor nerve activation strategies in strength-matched males and females

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Increases in skeletal muscle force are regulated by recruiting additional motor nerves, known as motor units (MU), and by increasing the speed at which they fire, known as the firing rate (FR). Males typically have larger muscles and greater muscle strength, and we have previously shown that females have higher MUFR when performing low and mid-level contractions. Also, it is apparent that with increasing age, MUFR typically decreases in females more than that observed in males. This may contribute to the 'male-female disability-survival paradox' in which females tend to live longer but experience greater disability in older age. However, it remains unclear if these differences in MUFR are attributable to inherent sex differences such as muscle strength, or if MUs function differently in men and women. The purpose of this study was to determine sex differences in individual MU features of the vastus lateralis muscle in young males and females that were matched for strength.

Twenty-four healthy young participants (12M/12F) were recruited based on similar leg muscle strength (<4% mean difference). Intramuscular needle electrodes were used to measure electrical signals from muscles during 10% and 25% of maximum voluntary contraction (MVC), and the MUFR was calculated.

Females had a 16% higher MUFR at 10% MVC (p=0.002) and 8% higher at 25% MVC (p=0.052) compared to males. There was a significant interaction between sex and contraction level in MUFR (p=0.024) with males exhibiting a 10% increase (p<0.001) when moving from low- to mid-level contractions, with only a 2% increase in females (p=0.488).

Females have higher MUFR than males when producing the same muscle force. When moving from a low- to a mid-level contraction, males increase MUFR much more than females. These data highlight clear sex differences in the way in which motor nerves control muscles of similar strength in males and females. Understanding these key differences in young people may help to address the age-related sex disparity of neuromuscular dysfunction.

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

Pharmaceutical interventions to promote nerve-muscle interaction in older age.

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Muscle mass declines with advancing age, known as sarcopenia, and this results in a loss of muscle mass and function. One contributing factor to the loss of muscle fibres is a loss of the nerves supplying them. It is possible to rescue these fibres from loss by growing new branches from existing nerves, but this is less successful in older age. The process of growing new branches is regulated by the mammalian target of rapamycin (mTOR) signalling pathway. This pathway may be overactive in older age and therefore may prevent growth of new axonal branches. Drugs which can inhibit the mTOR pathway may restore this signalling balance and help prevent muscle loss in older adults. Therefore, the aim of this research is to assess the effects of an mTOR inhibitor – Rapamune – and resistance exercise (strength) training on nerve-muscle communication in older people. Healthy males over the age of 55 will take part in the study, randomised to take either Rapamune or a placebo tablet for 16 weeks. During this period, they will also complete strength training on one leg 3 times each week. Before, after and at two time points during the 16-week intervention period we will record muscle size using ultrasound, muscle and motor nerve activity using electromyography and muscle function via a battery of different tests (i.e., balance and power). We will also study how well the motor nerve can communicate with the muscle, and markers of nerve-muscle function by collecting small muscle biopsies and blood samples throughout the study.
We predict that both groups will improve muscle mass and strength in the strength training leg but that those taking Rapamune, the mTOR inhibitor, will improve to a greater extent. We also expect those taking Rapamune to improve nerve-muscle communication. This research is not only important to determine the effects of mTOR inhibition and resistance training on the neuromuscular system and the mechanisms of this pathway but may also offer a therapeutic alternative to mitigate muscle mass and functional losses in those unable to exercise.

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

A randomised controlled trial to assess the efficacy of a postoperative semi-supervised exercise program in patients who have undergone elective curative surgery for colorectal cancer

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Cancer is still primarily a disease of ageing. It causes loss of muscle mass and function which also occur naturally as patients get older due to the condition known as sarcopenia. These losses can be further compounded by cancer treatments such as surgery and chemotherapy. Although surgery is considered the gold standard treatment of solid organ cancers to try to achieve a cure, postoperative patients require a long recovery period, with no clear direction on what is safe and effective in terms of exercise therapy. It has previously been shown that patients with cancer can safely exercise and that it can help with both physical and mental health. However, very few studies have focused on what exercise can be done to try and get postoperative cancer patients back to their previous level of fitness.
This study will provide a 12-week intervention, comprising home-based aerobic and resistance exercise training to determine if (compared to a no-intervention control group) such an intervention can improve fitness and postoperative recovery, as well as other factors associated with quality of life such as fatigue and sleep. Thirty-four patients who will have surgery for colorectal cancer will be recruited from the Colorectal Cancer Clinic at Royal Derby Hospital and divided across the two groups. To determine the impact of the intervention, all patients will have a cardiopulmonary exercise test (CPET; the gold-standard measure of physical fitness) on a static cycle ergometer, blood tests (for markers of inflammation and whole-body health) and assessments of physical function (e.g., strength and balance) before surgery and at approximately 6, 12 and 18 weeks after surgery. We will also use sophisticated movement trackers (ActivPAL4) to monitor the type and intensity of movement being done by both groups at various points throughout the study, including during their perioperative hospital stay. The patients will also complete questionnaires about various lifestyle factors such as their sleep quality and mood.
This study may serve as evidence for a standardised, exercise-based rehabilitation programme to be offered by clinicians to postoperative surgical patients if any aerobic, strength or qualitative improvements are observed, potentially improving patient-related outcomes.

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

Impaired function of motor nerves following 2 weeks of muscle disuse

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When muscle is inactive it reduces in size and in its ability to perform activities of daily living i.e., rising from a chair, also known as functional capacity. Evidence suggests that a reduction in muscle size is not the only thing responsible for a reduction in functional capacity, with the nervous system likely having a role to play. We hypothesised that after a period of inactivity, muscle would respond differently to signals from motor nerves- the nerves which cause muscles to move under normal circumstances.
To test this hypothesis, we recruited ten young, healthy male volunteers to have one of their legs immobilised for 15 days. Before and after immobilisation, we measured the size and functional capacity of a muscle in the thigh. We also measured how well signals from the motor nerves travelled to and within the muscle while it was using approximately the same effort required to climb stairs. These signals were measured by inserting a small pin electrode into the muscle to record electrical activity.
After immobilisation, we saw that muscle size and functional capacity were reduced. In agreement with previous research, the loss of functional capacity was greater than the loss of size. In addition, signal transmission from nerve to muscle was disrupted after immobilisation. The firing rate of nerves, which determines how much force muscle can produce, was also reduced after immobilisation.
Signal transmission disruption may be caused by a breakdown at the nerve-muscle junction which can decrease the efficiency of muscle functional capacity. Reduced firing rate may suggest a disturbance to the signal reaching the muscle, potentially at the spinal cord or along the nerve itself. These changes suggest that declines in motor nerve function do contribute to immobilisation-induced declines in functional capacity, which are greater than can be explained by reduced muscle size alone. Future work will determine if these changes occur after a shorter period of immobilisation and if different muscles (i.e., those which lose more or less size) show the same changes.

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

Acute unilateral exercise to influence bilateral neuromuscular properties among healthy older adults: a future study

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Introduction
Ageing is associated with an accelerated decline of skeletal muscle function, resulting in detrimental outcomes such as mobility disorders, frailty, increased risk of falls and a reduction in general health status (Wilkinson et al., 2018). This decline in muscle function is partly explained by an increase in motor unit size and reduced motor unit number (Piasecki *et al.*, 2018), and the consequential reduced control of muscles (Enoka & Duchateau, 2017). Although the age-related loss of motor neurons and muscle fibres are irreplaceable, the structure and function of the musculoskeletal system can be improved through exercise training (McPhee et al., 2016). Intriguingly, numerous studies have shown that training one limb (unilateral) can positively impact the other limb; the so-called the 'cross-education' effect. However, the effects of unilateral exercise on bilateral motor unit function in older people is currently unexplored. Therefore, this study will determine the 'cross-education' effects of a single bout of unilateral fatiguing resistance training exercise on bilateral neuromuscular function.

Aim
To determine the impact of an acute, fatiguing, unilateral exercise training session on bilateral neuromuscular properties and functional outcomes in healthy older adults.

Protocol
Thirty healthy older adults aged between 65-85 years will be recruited to perform a single session of unilateral leg extensions (using thigh muscles of one leg) using a standard weightlifting machine. The effects of this training session on motor nerve function (neural drive), motor unit properties and functional outcomes (such as balance, gait, and muscle control) will be assessed in both the trained and untrained leg using a battery of assessment tools (e.g., electromyography (EMG) and gait analysis).

Potential Impact
This pilot study will further support understanding of the functional and neurophysiological changes that may occur in both legs following an acute, unilateral exercise training session in older adults. Quantifying the 'cross-education' effect older adults in terms of nerve-muscle interaction could have implications for unilateral exercise prescription, and may be transferrable to clinical settings, including those often experienced by older adults i.e., single leg fracture, post-injury immobilisation and stroke.

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

Effects of exercise on central sensitisation in humans: a systematic review and meta-analysis

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Introduction
Chronic pain is a major cause of disability worldwide. There is often discrepancy between the reported pain levels and the observable pathology. Central sensitisation (CS) has been implicated in this discrepancy. It is usually associated with worse treatment outcomes, so improving CS may benefit a wide range of conditions. Exercise has the potential to decrease CS in pain-free populations. Pain relief following exercise might be dependent on exercise type and dosage, and on underlying pathology. Although, the underlying mechanisms are not completely understood, it was found that exercise has effects on the descending inhibitory pathways, facilitatory pathways, and might have effects on brain neurobiology. The optimal dose and type of exercise reducing CS are not known and there is uncertainty about the response variation between people with and without central sensitisation features. A systematic review is needed to address these unknowns, and to aid the design of an optimal exercise intervention to improve pain by reducing CS.
Aims
Identify the exercise intervention/s types and dosage/s associated with the greatest reductions in indices of CS in adults.
PICO
P: Adult humans. I: Exercise. C: Follow-up measurements compared to baseline. Outcome: CS mechanistic outcomes
Method
An initial MEDLINE search strategy has been developed and then adapted into the other databases (MEDLINE, EMBASE, AMED, CINAHL, SPORTDiscus, CENTRAL, PEdro, SCOPUS). Two independent reviewers will extract the data, assess risk of bias and quality for the studies.
A narrative synthesis of the eligible articles will be conducted. After that, a meta-analysis will be performed for the randomised controlled trials. Then, studies will be split into subgroups, including subsets of type of exercise, dosage of aerobic exercise, population type, follow-up periods. Additionally, meta-regression will be performed to assess sources of variation in the results.
Results
Number of papers in the search after removal of duplicates was 79649. Screening of papers is currently ongoing.
Discussion
The findings might help to underpin the exercise intervention and dosage that will optimally reduce CS for subsequent use in clinical trials.
Limitations
1. Exclusion of non-English studies. 2. Likely methodological, clinical, or quality heterogeneity. 3. Dosage of some exercise modalities might be difficult to quantify.
PROSPERO registration number: CRD42022312776

ISSN: 2059-3341
BRC MSK Conference 24/25 February 2022
www.nottingham.ac.uk/emran

Metabolomics reveals differences in response to aerobic exercise training and withdrawal in ageing and COPD

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Differences in whole-body and muscle specific mitochondrial responses to aerobic exercise training (AET) have previously been observed between COPD patients, healthy older and young controls. The underlying mechanism behind this discrepancy is as yet unknown but may be related to post-transcriptional regulation. Such regulatory changes may be detectable in the metabolome. Here, we implemented an untargeted metabolomics approach to link systemic plasma metabolome changes to skeletal muscle adaptations to AET in healthy young (HY), healthy older (HO) and COPD volunteers.
HY (n=10, 18-35yrs), HO (n=10, 60-80yrs) and COPD (n=19, 60-80yrs) underwent 8-weeks AET (65% VO_2^{PEAK}) followed by 4-weeks exercise withdrawal. Clinical measurements of body composition, acquired by dual-energy X-ray absorptiometry (DXA), and muscle strength were acquired before and after intervention. Venous blood samples were drawn before, during and after AET, with plasma metabolites analysed using ultra-high performance liquid chromatography coupled to a high-resolution mass spectrometer. Linear mixed-effect models were fitted to explore differences between each group at baseline and the effect of exercise on the plasma metabolome. Significance was determined when $p<0.05$ following correction for false discovery rate. Correlation between the global plasma metabolome and clinical endpoints was assessed by canonical correlation analysis, with correlation between individual metabolites (drawn from significance testing) and clinical endpoints determined by the Pearson correlation coefficient.
At baseline, 52 metabolites were significantly different ($p<0.05$) between COPD and HO, and 107 metabolites were significantly different between HO and HY. Time-course profiling revealed that AET largely impacted metabolites in energy metabolism pathways. After AET, 105 metabolites changed significantly in HY and 65 changed significantly in HO. There were 0 significant metabolites in COPD. Correlation analyses showed that changes in the global plasma metabolome were highly correlated with clinical measurements, but metabolites identified as important in the response to exercise were not ($p>0.05$).
These findings show untargeted metabolomics can be used to identify metabolites informative of both age and COPD. The metabolic response of skeletal muscle to AET was robust in HY, blunted in HO and absent in COPD. Changes in the global plasma metabolome over time were highly correlated with body composition and muscle strength measures.