ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

East Midlands Research into Ageing Network (EMRAN) Discussion Paper Series

ISSN [2059-3341]

Issue 37, 24th February 2021

NIHR Nottingham Biomedical Research Centre (BRC) Musculoskeletal theme: virtual conference proceedings 27th January 2021

Barros FF[1,2,3] and Gladman JRF[1,2,3] on behalf of the NIHR Nottingham Biomedical Research Centre Musculoskeletal theme[1,2,3]

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 was set up with support from National Institute of Health Research Applied Research Collaboration East Midlands (NIHR ARC-EM)

Address for correspondence:
Doctor Fabricio Barros, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham Health Science Partners, Derby Road, Nottingham, NG7 2UH
Email: fabricio.barros@nuh.nhs.uk

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Affiliations

[1] NIHR Nottingham Biomedical Research Centre, UK

[2] University of Nottingham, UK

[3] Nottingham University Hospitals NHS Trust, UK

ORCID

Barros FF: 0000-0002-7682-9670

Gladman JRF: 0000-0002-8506-7786

SUMMARY

This paper primarily provides summaries of the keynote lectures given and the research abstracts submitted to the NIHR Nottingham Biomedical Research Centre Musculoskeletal theme virtual conference held on 27th January 2021. Over 180 people registered for this event, including people from USA, Australia, Greece, Portugal, Finland, Colombia, Saudi Arabia, Pakistan and Indonesia.

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.

CONTENTS

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Changing a world of pain

David Walsh

Professor of Rheumatology, co-Director Pain Centre Versus Arthritis, Director UKRI/VA Advanced Pain Discovery Platform, Academic Rheumatology, University of Nottingham

Honorary Consultant Rheumatologist, Sherwood Forest Hospitals NHS Foundation Trust and Nottingham University Hospitals NHS Trust.

Chronic pain permeates the lives of millions in the UK, and musculoskeletal conditions are its commonest cause. Pain Centre Versus Arthritis has unravelled fundamental genetic, molecular, psychological and social mechanisms of pain, translated with the NIHR Nottingham BRC into diagnostic and stratification tools, novel therapeutics and ways of managing pain. Biochemical, cellular and structural changes in arthritic joints each can trigger pain, and, alongside changes in spinal and brain processing, exacerbate the pain experience. Conversely, peripheral and central mechanisms can be used to switch off or suppress pain. Different mechanisms correspond to the heterogeneous patient experience of pain, often changing over time. Despite pain's complexity, simple solutions are needed that can be accessed by the people most affected. Two strategies in focus are `mechanistic stratification' and `complex care packages'. Self-report questionnaires and wet and imaging biomarkers might identify which single treatment will offer greatest benefit for an individual's pain problem. The underlying cause of pain is often elusive or incurable, but harnessing multimodal interventions through `care packages' may offer benefit more rapidly and effectively than does trial and error with treatments offered one at a time. Pain is a social as well as clinical problem. Research and solutions need to be acceptable, accessible and effective across genders, social class and ethnic groups. Such an aim can only be achieved through partnership with the diverse individuals who suffer pain. The NIHR Nottingham BRC leads the world in pain research, through its science, training, educational resources and contributions to national and international policy.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Care Homes, Frail Older Patients and How to Work with Them.

Adam Gordon

Professor of the Care Older People, University of Nottingham
Consultant Geriatrician, University Hospitals of Derby and Burton NHS Foundation Trust

420,000 older people live in 15000 care homes across the UK. These provide 24 hour care, with or without nursing support. The average resident is 85 years old, has 6 diagnoses, takes 8 drugs and is in the last 24 months of their life. 70-80% of residents have dementia. Care homes provide structured, individualised person-centred care with a focus on asset-based approaches to health and wellbeing. There is potential, within this context, to introduce health and wellbeing interventions that may improve quality of life, ameliorate frailty trajectories, relieve symptoms and modify the need for intensive healthcare interventions. Opportunities for research include nutrition and supplementation, incorporating exercise into care home routines, sleep interventions, outdoor mobility and daylight exposure, and a series of condition or syndrome specific approaches. Research during the COVID-19 pandemic has extended to include point-of-care diagnostics, and infection and outbreak control and prevention, as well as the role that staff play in facilitating these. Understanding how interventions can be delivered in the care home context requires an understanding of organisational structures, and human factors, and how both can influence successful implementation. For all interventions, attention must be paid to resource limitation and opportunity costs with in the sector. This presentation will discuss these issues and practical steps that researchers new to the sector can follow to ensure that their work is context sensitive and therefore likely to deliver findings with generalisability and real-world impact.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

An Introduction to Metabolomics and its Application to Musculoskeletal Research

Daniel J Wilkinson

Assistant Professor, MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Clinical, Metabolic and Molecular Physiology, University of Nottingham, Royal Derby Hospital Centre, Derby, UK

The utility of high throughput OMICs technologies (transcriptomics, proteomics and metabolomics) for providing insight into human physiology and health has great potential via the identification of RNAs, proteins and metabolites capable of predicting or explaining physiological outcomes as diverse as, responses to exercise training, or the aetiology of diseases such as Type II diabetes and cancers. As such, these approaches have become increasingly important in the study of skeletal muscle mass regulation, given that the maintenance of skeletal muscle mass is strongly linked to human health and positively associated with reduced risk of developing a number of non-communicable diseases. It thereby follows that OMICs technologies have been extensively employed to investigate links between specific skeletal muscle RNA's, protein or metabolites, and muscle mass regulation/health, in an attempt to develop prognostics of future health outcomes/disease risk, or identify potential drug targets for the future regulation of metabolic health. While less developed than both transcriptomics and proteomics, metabolomics; the study of all the low molecular weight inorganic and organic molecules present in a biological sample, is proving an increasingly powerful tool within human clinical research. This is due to the fact that the metabolome acts as a direct read out of what is/has been happening within the cell, tissue or organ of interest. The level/concentration of a metabolite is determined by the activities of all associated enzymes/proteins and all effectors regulating these enzymes/proteins (i.e genes). Therefore, metabolite levels may provide more meaningful information regarding the regulation of developmental, physiological or pathological change than transcriptomics and proteomics put together. This talk will provide a general introduction to metabolomics, its application to musculoskeletal research, considerations for its use in human clinical research and a discussion of recent exciting developments within the field that will help to strengthen its validity in the near future.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Expanding the Reach of Patient and Public Involvement and Engagement in a Changing World

Kate Frost

Head of Patient and Public Involvement, Research and Innovation, Nottingham University Hospitals NHS Trust. COVID-19 PPI Task Force, Research and Innovation, Nottingham University Hospitals NHS Trust, Nottingham, UK

The COVID-19 Pandemic brought about a variety of challenges for involvement in healthcare research, which quickly led to our traditional methodology for involving and engaging patients and the public becoming redundant. Nationally and locally, we experienced the rapid development of a wealth of COVID-19 Research proposals, whilst the majority of non-urgent non-COVID-19 research stopped. Data from the Health Research Authority (HRA), evidenced these challenges undoubtedly led to the proportion of research teams involving patients and the public reducing dramatically; down from nearly 80% of all research the HRA reviews to just 20% for COVID-19 research. In response to these unprecedented circumstances, not only did we have to respond rapidly to our new virtual environment, but also now more than never, ensure that the patient voice was at the heart of COVID-19 Research.

The COVID-19 Patient and Public Involvement Rapid Response Task Force mobilised in April 2020 to bring together patient contributors from across Nottingham University Hospitals, the Biomedical Research Centre, and Clinical Research Facility. This large patient community with a breadth of lived experience and expertise, adapted to remote methods of involvement to work in partnership with researchers and ensure urgent COIVD-19 research had the patient voice at his core. A collaborative partnership with the Task Force has now born new initiatives to PPI methodology in our new virtual world. This includes the creation of a Virtual Research Lounge, bringing patients, the public, researchers and clinicians together to have conversations about research. Further, a new online community platform, the Nottingham Research Hubb; to information share, offer involvement/participation opportunities and diversify those whom we involve in research with targeted marketing campaigns co-produced with local communities.

Overall, this session intends to share the PPI initiatives that the pandemic catalysed, barriers faced and lessons learnt.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Neuromuscular function and motor unit firing following 4 weeks of motor control training

Ely IA, Dooley S, Sarah BJM, Atherton PJ, Phillips BE, Piasecki M
Contact: isabel.ely@nottingham.ac.uk

Age-related declines in muscle strength and motor control (MC) are largely explained by declines in motor unit (MU) number and the influence of MU remodelling. Forms of (e.g.) resistance exercise training may attenuate these decrements and improve neuromuscular function; however, such training is often unachievable for older individuals. We therefore investigated whether targeted motor control training (MCT) could lead to improved muscle functional capacity and control, and alterations of individual MU function.

Six healthy young volunteers (4F/2M; 25.2±5.8 years; 22.5±4.0 $kg.m^{-2}$) underwent a 4-week supervised, unilateral, MCT intervention. MCT was completed 3x/week, consisting of 6 complex isometric muscle contractions for the knee extensors (KE) and dorsiflexors (DF) in a randomised order at 10, 25 and 40% maximal voluntary contraction (MVC). Levels of MC (derived from complex force tracking (CFT) tasks which differed to the MCT) and force steadiness (FS) were determined at each contraction intensity. Intramuscular electromyography (iEMG) was utilised to sample individual MUs from the vastus lateralis (VL) and tibialis anterior (TA) muscles during sustained contractions, pre- and post-intervention. Data were analysed by paired Student's t-test. Statistical significance was accepted at $p<0.05$.

MVC and FS showed no differences for KE and DF following MCT. CFT improved following MCT for the KE and DF at each contraction intensity (KE: 10% MVC; -39.24%, $p=0.005$, 25% MVC; -28.62%, $p=0.043$, 40% MVC; -29.13%, $p=0.015$; DF: 10% MVC; -25.73%, $p=0.002$, 25% MVC; -33.35%, $p=0.0006$, 40% MVC; -30.06%, $p=0.049$). MU firing rate (FR) variability significantly reduced post-intervention in VL only ($n=5$, -16.36%, $p=0.031$).

Our results suggest improved levels of MC following MCT across different contraction intensities and muscle groups, which may be explained by the reduction in FR variability. These data from young individuals suggest MCT may lead to improvements/maintenance of MC in older adults, a future direction of this work.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Indices of Central Sensitisation can predict effective Self-management in Individuals with Chronic Low Back Pain

Georgopoulos V, Akin-Akinyosoye K, McWilliams DF, Hendrick P, Walsh DA
Contact: vasileios.georgopoulos@nottingham.ac.uk

Background: Guidelines for managing Chronic Low Back Pain (CLBP) prioritise the development of self-management strategies. Central sensitisation (CS) refers to neurophysiological processes that can occur throughout the central nervous system and can lead to amplified pain experience, often at sites distant to the primary area of pathology. It is currently unknown whether CS might be a barrier to self-management in people with CLBP.

Methods: Individuals with CLBP undertaking cognitive behavioural therapy (CBT)-based group physiotherapy interventions provided CS and self-management data at baseline (n=97) and at 3-months (n=87). Pressure pain detection threshold (PPT) at a distant site (forearm), temporal summation (TS) and conditioned pain modulation (CPM), Widespread Pain Index (WPI) classified using a body manikin, and Central Mechanisms Trait (CMT) scores derived as a single factor from 8 self-reported characteristics were used as indices of CS. Self-management was measured by self-report questionnaire in 8 discrete domains; health-directed behaviour (HDB), positive engagement in life (PEL), self-monitoring and insight (SMI), constructive attitudes and approaches (CAA), skill and technique acquisition (STA), social integration and support (SIS), health services navigation (HSN) and emotional distress (ED).

Results: Multiple CS indices predicted worse PEL (PPT, CPM, WPI, CMT: $r=0.54$ to 0.31, $p<0.05$), increased ED (PPT, CPM, CMT: $r=0.21$ to 0.54, $p<0.05$), worse SIS (PPT, CMT: $r=0.28$ and 0.37, $p<0.05$), worse HDB (CMT: $r=0.25$, $p<0.05$) and worse CAA (CMT: $r=0.51$, $p<0.05$) at 3-months. In multivariable regression models (adjusted for baseline depression, catastrophization, pain and fatigue) low PPT, high TS, inefficient CPM and CMT at baseline retained their significant association with SIS, PEL, CAA and ED at 3 months ($R^2=0.23$ to 0.35). Baseline indices of high CS were amongst the strongest independent predictors of worse self-management at 3-months ($\beta=0.32$ to 6.61).

Conclusion: Treatments which specifically target CS might help remove barriers to self-management in people with CLBP.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Deriving a cartilage signature to predict joint replacement in osteoarthritis

Peake E, Pszczolkowski S, Arthofer C, Auer DP
Contact: Edward.Peake@nottingham.ac.uk

Osteoarthritis (OA) is a highly prevalent disease, with knee osteoarthritis affecting nearly 1 in 4 adults. OA has considerable impact on the individual patients. Progressive pain and restricted joint movement are the main symptoms of knee OA, but individual trajectories and response to treatment are highly varied. There are currently no disease modifying drugs for osteoarthritis to prevent, stop or even restrain the progression of OA. Moreover, the current pain medications have a number of risk-benefit considerations. Failure of clinical trial has been linked to the dissonance between structural improvement and demonstrable clinically relevant benefit. In recognition of OA as a serious disease, US drug regulatory authorities have approved the use of surrogate outcome markers in clinical trials provided they are reasonably likely to predict important clinical outcomes.

MRI is used in clinical trials to evaluate knee osteoarthritis. Current practice is to rely on expert knowledge to provide semi-quantitative scores relating to the degenerative changes in the joint. We propose a novel method to use cartilage MRI as a surrogate outcome marker for knee replacement surgery. Our method relies on the use of deep learning to segment knee cartilage, and a the growing 'omics' field to extract feature used to estimate individual risks. Evaluating our model against clinico-demographic features shows the radiomic signature as a robust independent marker for knee replacement surgery, with the potential for future use in OA drug trials.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Systematic review of exercise interventions and functional MRI outcomes in older adults with Dementia or Mild Cognitive Impairment (MCI)

Bajwa RK, Armugam N, Wardt VVD, Harwood R, Dineen R
Contact: rupinder.bajwa@nottingham.ac.uk

Background: The neural mechanisms involved in exercise in people with MCI and Dementia are not well understood. fMRI measures changes in blood oxygenation levels and blood flow which correspond to changes in neuronal activity, thus providing a useful tool to investigate changes in functional connectivity at rest and brain activity during a task. We conducted a systematic review and narrative synthesis of studies investigating effect of exercise interventions on resting state (rs) and task related (ts) fMRI outcomes in older adults with Mild Cognitive Impairment (MCI) or Dementia.

Method: Searches were conducted in relevant database for primary studies on 23rd September 2020. Studies of older adults with MCI or Dementia, aged 65 and over, testing exercise or physical activity intervention and reporting rs/ts fMRI outcome were included. Studies reporting other neuroimaging outcomes or using cognitive training as a comparator were excluded. We assessed quality of the studies using appropriate appraisal tools.

Results: 9 papers from 6 studies were included in the review; 2 RCTs, 4 studies nested within RCTs, 2 case control studies and 1 cross sectional study. n=271, mean age = 70.75 (6.81). 4 studies reporting rs-fMRI outcomes found changes in functional connectivity post intervention. 5 studies reporting ts-fMRI outcomes found changes in task related activation post intervention during cognitive tasks. Intervention duration ranged from 12-24 weeks and included aerobic training, progressive resistance training, treadmill walking, brisk walking, dancing and mind-body exercise.

Discussion: Exercise can elicit changes in functional connectivity and task related activation in older adults with MCI. More research is needed to identify neural mechanisms involved in exercise in people with differing severity of dementia. Future studies should look to develop more realistic paradigms, investigate effect of duration and intensity of exercise on fMRI outcomes and aim to recruit greater number of participants.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Independent and combined effects of immobilisation and systemic and local inflammation on muscle mass regulation and insulin resistance in ankle fracture

Shur NF, Scammell B, Smith K, Atherton P, Ollivere B, Greenhaff PL
Contact: natalie.shur@nottingham.ac.uk

Both immobilisation and inflammation result in muscle mass loss and insulin resistance in humans. In immobilisation, muscle mass loss occurs secondary to a reduction in muscle protein synthesis in the main, whilst muscle insulin resistance is thought to be attributable to the loss of muscle contraction *per se*. Inflammation has also been shown to stimulate muscle mass loss and insulin resistance, but mechanistic insight is limited. Furthermore, as far as we are aware no study has addressed whether the combination of immobilisation and inflammation has summative negative effects on muscle mass loss and insulin resistance, and whether the physiological drivers of metabolic dysregulation are the same. Nevertheless, this has important clinical implications. This presentation will describe a study evaluating the effect of early versus delayed ankle fracture fixation on muscle mass and glucose disposal in patients who will be age matched with healthy volunteers undergoing 2-weeks of unilateral leg immobilisation. Outcome measures include changes in net muscle protein synthesis and protein breakdown, muscle gene expression, *medial gastrocnemius* muscle thickness and whole-body insulin sensitivity using an intravenous glucose tolerance test. The study design allows for differentiation of the relative impact of immobilisation *per se* versus immobilisation plus systemic (non-damaged limb) and local (damaged limb) inflammation on study end points. We also hypothesise end-point measures will be affected to the greatest extent in those undergoing delayed surgery compared to early surgery, due to the additional insult of immobilisation prior to and following surgery in the damaged limb. This important clinically-relevant study will provide insight of the drivers of muscle dysfunction in ankle fracture fixation patients, and will inform the development of advances in the treatment of such patients.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

The association of knee pain with frailty: the Investigating Musculoskeletal Health and Wellbeing Cohort Study

Chaplin WJ, McWilliams DF, Millar B, Gladman JRF, Walsh DA
Contact: wendy.chaplin@nottingham.ac.uk

Introduction: Pain is the prevailing symptom of knee osteoarthritis in which knee pain is common. Frailty is a vulnerability state seen in older people. Pain is associated with developing frailty, understanding, aids and identifying risk factors. We report a cross-sectional analysis of the association between knee pain and frailty.

Methods: A sub-study of 830 participant's baseline data, recruited to the IMH&W cohort study. Inclusion criteria required participants to complete all FRAIL questionnaire components and report Numerical Rating pain Score (NRS) of knee pain ≥1.

The FRAIL questionnaire comprises five self-report items: Fatigue, Resistance, Ambulation, Illnesses and Loss of weight, total score classifies participants into three groups: robust, prefrail and frail.

The NRS scale asked participants: over the past month, how intense was your average pain/aching in your most bothersome joint, where 0 is 'no pain' and 10 is 'pain as bad as could be'?

An ordinal logistic regression (OLR) was performed producing an odds ratio for the risk of increasing FRAIL per unit increase in NRS pain. Model assumptions for consistency of NRS pain across the different thresholds of FRAIL were tested using the proportional odds test.

Results: 830 participants with knee pain rated ≥1/10. 56% female, median age 72 (range 40-95). NRS pain score M=6.0, (SD=2.2). Classified as 31% robust, 41% prefrail and 28% as frail.

Mean pain levels increased with frailty level: robust NRS=4.7 (SD=1.9), prefrail NRS=6.0 (SD=1.9) and frail NRS=7.6 (SD=1.6). Pain NRS and frailty were positively correlated (r_s= 0.52, $p<0.001$).

The unadjusted odds of being allocated to a higher FRAIL category increased by 1.70 (95% CI 1.58,1.83) for each unit increase in NRS pain ($p<0.001$). The proportional odds assumption test was non-significant ($p=0.062$), indicating the OLR assumption was met.

Conclusions: For participants with knee pain, increasing pain levels were associated with increasing levels of frailty.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

The risk of deconditioning in older people with frailty and fragility fractures: a baseline comparison and extent of muscle changes during inactivity

Lunt E, Gordon AL, Greenhaff PL, Gladmam JRF
Contact: Eleanor.Lunt1@nottingham.ac.uk

Introduction: For older people with frailty, disability arising from an acute illness potentially results in a negative cycle of greater inactivity and heightened disability. As a prelude to addressing this challenge, older patients admitted with a fragility fracture, then immobilised for several weeks for their clinical management, were studied in a longitudinal study design.

Methods: Handgrip strength (HGS), knee extensor strength (KES) and Vastus Lateralis muscle thickness (VLMT; ultrasound) were measured in the non-injured limb of 50 patients (88% female) aged ≥70 with a limb fracture. Measurements were performed at hospital admission and 3 weeks later. Additionally, measurements made at hospital admission in female patients (n=36) were compared with data from 11 female healthy, non-frail, non-hospitalised volunteers with comparable BMI, aged ≥70. Values represent mean±SD. Independent and paired t-tests were used to establish differences between and within groups, respectively.

Results: Three weeks immobility had no effect on HGS (10.1±6.3kg week 0, 10.8±7.6kg week 3, p=0.34), KES (4.3±1.6kg week 0, 4.5±1.5kg week 3, p=0.58) or VLMT (1.26±0.35 week 0, 1.19±0.43week 3, p=0.25)

At the time of hospital admission, female patients were older (84±7years vs. 77±6years, p<0.05), weaker (HGS of 9.2±4.7kg vs. 19.9±5.8kg, p<0.001; KES 4.5±1.5kg vs. 7.8±1.3kg, p<0.001) and had lower VLMT (1.38±0.47cm vs. 1.75±0.30cm, p=0.02) than female, non-frail controls.

Discussion: Older patients admitted with fragility fractures were weaker and had a lower VLMT compared to healthy, non-frail older people. Moreover, the lack of further declines in muscle strength and thickness during subsequent immobility suggests muscle resilience is attenuated pre-admission, such that enforced immobility in hospital had no further detrimental effect. Given that the falls leading to hospital admission were likely to be due to pre-existing sarcopenia and weakness, it emphasises the importance of population level community interventions to encourage activity and exercise in those at risk of frailty.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

The Effects of Very Low Energy Diets and Low Energy Diets with Exercise Training on Skeletal Muscle Mass: A Narrative Review

Ardavani A
Contact: Arash.Ardavani@nottingham.ac.uk

In recent years, very low energy diets (VLEDs) have been recognised as a viable strategy for improving the extent of weight loss and cardio-metabolic outcomes in people who are either overweight or obese. However, concerns exist regarding the reductions in lean body mass (LBM) during VLEDs, particularly in vulnerable demographic groups, such as middle-aged and elderly adults. Such populations are already prone to developing sarcopenia, a disease of aging associated with incremental losses in muscle size, function and quality. This disease entity is itself associated with multiple adverse outcomes, including frailty, reduced quality of life, reduced physical fitness and increased mortality. Therefore, a number of studies investigating strategies that reduce this adverse effect in VLEDs have been investigated. This presentation explores the potential benefits and limitations of exercise and/or protein supplementation for LBM retention during VLEDs based on current evidence. Current studies suggest that both protein supplementation and exercise training may result in improved LBM retention (and skeletal muscle function) during VLEDs. However, some uncertainty remains concerning the interactions between different interventions. Additionally, a wide variety of outcomes have been observed in studies assessing the effects of different exercise types and protein supplementation in VLEDs. Consistent outcomes in diabetic patients, alongside the effects of high intensity interval training (HIIT) paired with VLEDs, are yet to be determined. Given the continued pace of the obesity epidemic and the co-association with type 2 diabetes mellitus, understanding the effectiveness and feasibility of these conservative approaches is an important area of development within the literature.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Relationship between Physical Activity and Asthma in Adults

Ahmad AN
Contact: Adeel.Ahmad@nottingham.ac.uk)

Physical inactivity, with a worldwide prevalence of 31%, has become a worldwide epidemic since the technological revolution. Many medical conditions are positively affected by physical activity including depression, obesity, osteoporosis, hypertension, coronary heart disease and stroke.

Asthma is one of the commonest respiratory diseases, reported to be a major social and financial burden. Asthma prevalence is high among elite endurance athletes, but little is known about its prevalence among competitive recreational athletes.

The interaction between asthma and various levels of physical activity is often complex and understanding the association between these interactions in an active population has not been well studied. Many individuals believe that their asthma prevents them from being physically active or that physical activity can have a detrimental effect on their asthma, hence limiting activity.

Better understanding of the association between PA and Asthma can help plan effective strategies to manage Asthma in those who perform physical activity to improve asthma control, quality life and physical activity. It will help promote to the public the importance of Physical Activity and health with particular emphasis on Asthma to improve disease burden and physical activity levels. Some of the following questions will be answered in the abstract presentation.

1. What is the relationship between physical activity and asthma?
    a. Are active people equally likely to have asthma as inactive people?
    b. Are asthmatics equally as active as non- asthmatics?
2. What is the relationship between physical activity, asthma quality of life and asthma control?
3. What is the relationship between types of sports and asthma?
4. What is the perception of PA participation on the participant's asthma?
    a. Does asthma limit ability to be physically active?
    b. Does being physically active improve asthma?
    c. Asthma symptoms experienced during physical activity

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Development and Feasibility Testing of Web Based Intervention for Self-Management of Low Back Pain in Nurses: A Mixed Method Study

Alduraywish R, Hendrick P, Blake H
Contact: Rana.Alduraywish@nottingham.ac.uk

Purpose: Nurses have a higher prevalence of low back pain (LBP) than other occupations globally; this is associated with decreased job productivity, greater work absence and functional limitation. Digital interventions have demonstrated efficacy in supporting self-management of LBP and improvements in self-reported outcome measures of pain, functionality, quality of life. In this study, a theoretically informed web-based intervention programme was designed and tested for the nursing population. The purpose of this study is to test the feasibility and acceptability of a web-based intervention programme for the self-management of LBP (WBI-BACK) among a nursing population in the KSA.

Method: The convergent parallel mixed method research (MMR), feasibility study approach was used to achieve the study' objectives. The research adopts three phases. The first, exploratory phase is the design and development of the WBI-BACK programme. The second, quantitative phase involves the recruitment of the nurses with and without LBP, the implementation of the WBI-BACK programme and collecting feasibility and outcome measures data. The third, qualitative phase includes evaluation of the WBI-BACK programme through semi-structured interviews. Primary outcomes are the feasibility of the study design, recruitment rate, methods, and delivery of the WBI-BACK programme. Secondary outcomes involved exploratory analysis of LBP-related measures including pain, disability, quality of life, physical activity, and exercise self-efficacy.

Results: Fifty-three nurses (35 participants with LBP and 18 participants without LBP) were recruited.

The recruitment process and response rate, retention rate and adherence to the intervention indicated the feasibility of the research processes. Nurses with LBP improved significantly in their physical disability and moderated physical activity exercise after WBI-BACK intervention while there were no significant differences on other secondary measures. Nurses without LBP did not show any significant improvement in secondary outcome measures.

Conclusion: The WBI-BACK programme is feasible and acceptable to be delivered for nurses in Saudi Arabia.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Metabolomics: novel insight of routes and mechanisms of deconditioning and mass loss in human skeletal muscle in ageing and disease

Alldritt I, Greenhaff PL, Wilkinson DJ
Contact: Isabelle.Alldritt@nottingham.ac.uk

Muscle metabolic deconditioning and mass loss in ageing and disease impairs both locomotor function and metabolic health and is associated with reduced quality life and increased mortality rates. Despite an appreciation of the existence of phenomena such as muscle anabolic resistance, mitochondrial loss and insulin resistance with age and disease, little is known about the mechanisms responsible for these negative traits. With the complexities surrounding these unknowns and the lack of progress to date in development of effective interventions, there is a clear need for an alternative approach. Metabolomics is the study of the full set of metabolites within cells or tissues, which collectively makes up the metabolome. As metabolomics allows for the assessment of the cellular state in response to physiological stimuli, any chronic change in the metabolome is likely to reflect change in the physiological phenotype of an organism. This provides a holistic and unbiased approach that can be applied in clinical research to potentially uncover important facets in the pathology of muscle metabolic deconditioning and mass loss in ageing and disease, as well as prognostic markers for those at the greatest risk of decline. This presentation will aim to highlight the current knowledge and potential impact of metabolomics in the study of human muscle deconditioning and mass loss, and key areas for future research.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Changes in the vascular endothelial growth factor A splicing axis in human synovium are related to arthritis pain

Amanitis D, Shahtaheri S, Mcwilliams DF, Walsh DA, Donaldson LF
Contact: Dimitrios.Amanitis@nottingham.ac.uk

Purpose: VEGF-A is a key regulator in osteoarthritis (OA) upregulated during articular inflammation. Two splice variant families, VEGF-A$_{xxx}$a and VEGF-A$_{xxx}$b (xxx represents the number of amino acids), result from alternative splice site selection in exon 8. VEGF-A$_{xxx}$a expression is controlled by Serine/Arginine Protein Kinase 1 (SRPK1), which phosphorylates Serine/Arginine Rich Splicing Factor 1 (SRSF1), resulting in nuclear translocation. VEGF-A$_{xxx}$b predominates in normal tissues, with anti-nociceptive and anti-angiogenic functions. VEGF-A$_{xxx}$a predominates in pathological conditions, exerting pro-nociceptive and pro-angiogenic actions. VEGF-A has been proposed as a therapeutic target in OA. **Hypothesis**: The VEGF-A splicing axis is changed in favour of VEGF-A$_{xxx}$a and contributes to pain in OA. **Methods:** Age, sex and chondropathy matched cases from the Pain Centre VA joint tissue repository of post-mortem (PM) synovial tissue samples with asymptomatic chondropathy (AC) but no reports of knee pain, and arthroplasty derived synovium samples from OA with symptomatic chondropathy (SC). Sections were stained for SRSF1, SRPK1 and VEGF-A (total and isoforms). Fractional area, and SRSF1 activation measured by the degree of nuclear localization were quantified. Statistical analyses were performed using Mann-Whitney U tests. **Results:** Total VEGF-A, SRPK1 and SRSF1 expression, were significantly higher in SC: VEGF-A: SC=0.39(0.27-0.46), AC=0.21(0.17-0.26) ((IQR), U=24, p<0.0001, n=15SC, n=17AC); SRPK1: SC=0.13(0.11 -0.17), AC=0.10(0.06 -0.13), (U=67, p=0.006, n=17SC, n=17AC) and SRSF1: SC=0.22(0.19 -0.27), AC=0.15(0.13 -0.18) (U=25, p=0.0001, n=15SC, n=16AC). SRSF1 activation, was significantly higher in SC: SC=45% (35 -52), AC=28% (16 -39) (U=36, p=0.0005, n=15SC, n=16AC). VEGF-A$_{xxx}$a was significantly higher, (SC=0.16(0.14 -0.2), AC=0.14(0.09 -0.15) (U=63, p=0.048, n=15SC, n=15AC)), and significantly lower for VEGF-A$_{xxx}$b (SC=0.14(0.12 -0.16), AC=0.26(0.21 -0.3), U=15, p<0.0001, n=13SC, n=16AC)) in the SC group. The ratio of VEGF-A$_{xxx}$b/ VEGF-A$_{xxx}$a was significantly higher for the AC group (SC=0.14(0.12 -0.16), AC=0.26(0.21 -0.30), U=15, p<0.0001, n=13SC, n=16SC). **Conclusions:** Symptomatic chondropathy is associated with increased expression of total VEGF-A and SRPK1, activation SRSF1, and altered proportions of VEGF-A$_{xxx}$a and VEGFG-A$_{xxx}$b in synovium. The higher relative expression of VEGF-A$_{xxx}$a isoforms in SC supports our hypothesis.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Implementation of a biopsychosocial physiotherapy programme for patients with chronic low back pain in Ghana: a mixed-methods, feasibility, quasi-experimental study

Ampiah PK, Hendrick P, Moffatt F
Contact: PAAPA.AMPIAH@nottingham.ac.uk

Background: Low back pain (LBP) is a common musculoskeletal condition, affecting populations from both low- and middle-income (LMIC), and high-income countries (HICs). Global point prevalence of LBP is estimated at 9.4%. Prevalence is higher in LMICs especially in Africa (39%). The biopsychosocial approach is recommended by international practice guidelines for managing patients with LBP but predominantly applied in HICs. A recent review established a paucity of high-quality studies applying biopsychosocial approaches in LMICs. Management of patients with LBP in LMICs, like Ghana, appear to be biomedically focused.

Aim: To investigate the feasibility of implementing a biopsychosocial physiotherapy programme (exercise plus education) for the management of patients with CLBP in Ghana.

Methods: Mixed-methods feasibility study

Context: Komfo Anokye Teaching Hospital Physiotherapists (n = 2) were recruited and trained to deliver the biopsychosocial intervention. Thirty patients with CLBP were recruited: outcome measures were collected at baseline, post-intervention, and 3-months. Patient demographics and secondary outcomes were also collected. Descriptive statistics summarized the outcomes data and assessed feasibility against *a priori* feasibility criteria. Qualitative interviews (physiotherapists: n = 2; patients: n = 6) were conducted; analysis followed a thematic approach.

Results: A majority of feasibility criteria were met: including consent rate (100%), recruitment rate (5 participants/week), retention rate (90%), data completion rate (pre-intervention – 99.2%, post-intervention – 99.8%), and treatment fidelity (83%); 80.56% of patients adhered to their treatment schedule, whilst only 16% adhered to the home walking programme which did not meet feasibility criteria. No adverse events were recorded. Post-intervention outcomes showed improved pain, function, catastrophising, kinesiophobia, self-efficacy, and quality of life. Preliminary qualitative analysis suggests themes including patient autonomy, and personnel and professional characteristics as positive facilitators.

Conclusion: These results show that it is feasible to implement a biopsychosocial physiotherapy management approach for patients with CLBP in Ghana and will inform future trials.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Atrophy resistant vs. atrophy susceptible skeletal muscles: a new experimental model to study human disuse atrophy.

Bass JJ, Hardy EJO, Inns TB, Wilkinson DJ, Piasecki M, Morris R, Sale C, Smith K, Atherton PJ, Phillips BE
Contact: joseph.bass2@nottingham.ac.uk

Introduction: Muscle wasting through inactivity-induced disuse atrophy (DA) is not fully understood, and currently a major goal of muscle biology efforts. Interestingly, not all muscles atrophy to the same degree despite similar roles/locations. Here we used a new approach to investigate the mechanisms of DA in humans. We developed an experimental model investigating both atrophy resistant and susceptible muscles in the lower leg, i.e. the *tibialis anterior* (TA) and *medial gastrocnemius* (MG), respectively.

Methods: To investigate this, we recuited seven healthy young men who underwent 15-days single leg immobilisation using a knee and foot brace to prevent movement in the leg. Various methods to assess muscle mass (i.e. MRI, ultrasound and DXA scans) were used before, mid-way (~7d) and after (15d) immobilisation. After 15 days immobilisation, TA/MG muscle biopsies were taken to measure the rate of newly made muscle protein.

Results: After just 7 days immobilisation, lower leg muscle mass decreased, which continued until day 15. Using MRI and ultrasound to study individual muscles, MG size decreased with immobilisation, while TA remained unchanged. There were no changes in muscle size in the non-immobilised leg. Rates of newly made protein decreased in MG and TA compared to the non-immobilised leg, with MG decreasing at a much greater rate.

Conclusion: The use of this new atrophy susceptible vs. atrophy resistant model provides an effective means to study the process of muscle wasting in people. We reveal that the rate of new muscle protein produced decreases to a greater extent in atrophy susceptible muscle. This model may be used to identify the mechanisms responsible for muscle wasting by comparing the changes occurring in each muscle, allowing new insights into muscle mass regulation.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

More than just healthy bones? The importance of the vitamin D axis in the musculoskeletal system.

Bollen SE, Wilkinson DJ, Hewison M, Atherton PJ
Contact: Shelby.Bollen@nottingham.ac.uk

Commonly associated with maintaining skeletal health, it now appears that there is more to vitamin D than just healthy bones. In fact, vitamin D deficiency clinically presents with myopathy, muscle weakness and atrophy. Considering that deficiency is deemed a global public health issue, the exact mechanisms and true role of this hormone in skeletal muscle remain unestablished. Recent studies have indicated that certain key players of the vitamin D system, e.g., the vitamin D receptor (VDR) and the enzyme responsible for conversion of inactive vitamin D to its active form (CYP27B1), are present in skeletal muscle. VDR have further been implicated in regulating the process of muscle formation (myogenesis) and evidence suggests involvement in intracellular signalling, proteostasis, and maintenance of calcium homeostasis. Work using cells and mice lacking VDR has confirmed its physiological importance in muscle function and has provided a solid foundation for future work. Additionally, it is well known that an individual's genetics can have a substantial impact on their physiology, and it seems that certain genetic variants of the VDR are associated with different skeletal muscle phenotypes. Indeed, carriers of the rare genotype of the FokI VDR polymorphism (ff) display improved muscular function and also appear to have reduced risk of sarcopenia. The molecular basis for these differences between genotypes is uncertain but represents a promising area of research for the vitamin D field. When viewed collectively, the evidence is clear – vitamin D is more than just for healthy bones, instead it is a key endocrine factor contributing to normal musculoskeletal functioning. This project aims to clarify the functional role of vitamin D in skeletal muscle by exploring the molecular processes underlying its action within muscle cells, whilst also exploring the molecular consequences of genetic variation within the vitamin D system itself.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

A collagen extraction and deuterium oxide stable isotope tracer method for the quantification of bone collagen synthesis rates *in vivo*

Civil R, Brook MS, Elliott-Sale KJ, Santos L, Varley I, Lensu S, Kainulainen H, Koch LG, Britton SL, Wilkinson DJ, Smith K, Sale C, Atherton PJ
Contact: rita.civil2017@my.ntu.ac.uk

The development of safe and practical strategies to prevent weakening of bone tissue is vital, yet attempts to achieve this have been hindered by a lack of understanding of the short-term (days-weeks) physiology of bone collagen turnover. To address this, we have developed a method to quantify bone collagen turnover *in vivo*, using deuterium oxide (D_2O) tracer incorporation techniques combined with gas chromatography pyrolysis isotope-ratio mass spectrometry (GC-*pyrolysis*-IRMS). Forty-six male and female rats from a selectively bred model, ingested D_2O for 3 weeks. Femur diaphyses (FEM), tibia proximal (T-PRO), and distal (T-DIS) epiphyses-metaphyses and tibia mid-shaft diaphyses (T-MID) were obtained from all rats after necropsy. After demineralisation, collagen proteins were isolated, hydrolysed and collagen synthesis rates (CSR) determined by incorporation of deuterium into protein-bound alanine via GC-*pyrolysis*-IRMS. The CSR for the FEM (0.131 ± 0.078 %/day; 95% CI [0.106-0.156]) was greater than the CSR at T-MID (0.055 ± 0.049 %/day; 95% CI [0.040-0.070]; $P < 0.001$). The T-PRO site had the highest CSR (0.203 ± 0.123 %/day; 95% CI [0.166-0.241]) and T-DIS the lowest (0.027 ± 0.015 %/day; 95% CI [0.022-0.031]). The three tibial sites exhibited different CSRs ($P < 0.001$). Herein we have developed a sensitive method to quantify *in vivo* bone collagen turnover and identified site-specific rates of turnover, which could be applicable to studies of human bone collagen synthesis.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

"Super-whey" = Super-gran? The efficacy of a purified whey protein for improving muscle health in older adults

Ely IA, LarseN MS, Breen L, Wilkinson DJ, Smith K, Phillips BE, Atherton PJ
Contact: isabel.ely@nottingham.ac.uk

Skeletal muscle (SKM) accounts for approximately 45-55% of total body mass in healthy adults and plays a pivotal role in whole-body metabolic health, locomotion and physical independence. Undesirable loss of SKM mass (atrophy) is, however, a common feature of many communicable and non-communicable diseases including ageing, bed-rest/immobilisation, cancer and physical inactivity.

Despite exact mechanisms remaining to be fully elucidated, "anabolic resistance" (blunted anabolic responses to protein feeding and exercise) is a key influence in age-related SKM losses (sarcopenia). Optimal mitigation strategies (e.g., exercise/nutritional interventions), therefore, remain a hot topic amongst researchers to "offset" the detrimental progression of sarcopenia. In particular, fortification of protein with leucine may provide a nutritional avenue for combating anabolic resistance.

Leucine, an essential and branched chain amino acid (EAA/BCAA), is thought to be the most potent EAA for stimulating muscle protein synthesis (MPS). Although, as a stand-alone supplement, leucine is unlikely to provoke a robust and prolonged state of MPS due to the absence of other EAAs, low doses of leucine-enriched EAAs can elicit similar increases in MPS as compared to a large dose of whey protein. In fact, as little as 0.6g of leucine (combined with EAA) was observed to robustly (perhaps maximally) stimulate MPS in older women. Reduced appetite and increased satiety after a meal commonly occurs with advancing age, contributing to reduced energy intake and SKM mass loss. As such, supplementation of low-dose protein (i.e., leucine-enriched and/or purified whey protein) may, therefore, contribute to muscle health maintenance in energy-restricted states and reduce satiation following a meal.

This project aims to examine whether a novel purified whey protein with greater leucine content has superior anabolic properties compared to a regular whey protein, at rest and during acute/chronic exercise, to improve muscle health in older adult.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Associations between DHEA and motor unit function in young and old athletes

Guo Y, Piasecki J, McPhee JS, Phillips BE, Atherton PJ, Piasecki M
Contact: Yuxiao.GUO@nottingham.ac.uk

Ageing is associated with a number of pathophysiological processes, including neuromuscular decrements which are in part attributable to motor unit (MU) remodelling, reductions in firing rate, and changes in circulating hormones. Dehydroepiandrosterone (DHEA), a steroid hormone, influences a number of physiological systems and also contributes to neuroplasticity. We aimed to explore the association between DHEA and MU properties in healthy humans, and to investigate the combined effects of ageing and exercise.

85 males were recruited and divided into sub-groups based on age (young and old) and exercise discipline (control, endurance, and power). Intramuscular electromyography (iEMG) data were collected from vastus lateralis muscles during voluntary contractions at 25% of maximum. DHEA concentrations from venous blood samples were quantified using a validated liquid chromatography-mass spectrometry system. Multi-level mixed effects linear regression models were performed to explore within-individual variability and the effects of exercise discipline on these parameters. Significance was assumed when $p < 0.05$.

Seventy-five subjects had complete data on both iEMG and hormones, consisting of 32 young (mean ± SD: 27 ± 4.4 yrs) and 43 old males (70 ± 4.6 yrs). The mean concentration of DHEA in young was significantly higher than that in old (17.00 ±10.37 vs 5.30 ± 3.01, $p < 0.0001$). Motor unit firing rate was higher in young (9.87 ± 1.56 vs 8.98±1.36, $p < 0.05$). After adjusting for age and exercise discipline, firing rate was positively associated with DHEA levels in both young and old ($p < 0.05$), and the exercise disciplines and inherent ageing did not influence this relationship.

Our findings highlight the association between DHEA and MU properties in humans, which is independent of exercise discipline, suggesting that DHEA may be a potential therapeutic strategy against muscle strength decline in elderly

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

DYNAMO Covid-19: DYNamic Assessment of Multi Organ level dysfunction in patients recovering from Covid-19

Gupta A, Nixon A, Mallinson J, Piasecki M, Nicholas R, McGing J, Serres S, Gowland P, Greenhaff PL, Francis S, Bolton CE
Contact: Ayushman.Gupta@nottingham.ac.uk

The long-term impacts for those surviving Covid-19 are emerging. There is a priority to address the multi-organ dysfunction and develop evidence-based strategies to improve recovery to full health and return to work, particularly for those with significant damage, who are recovering from severe infection. Strength loss and persistent fatigue during recovery are apparent, but the degree to which these symptoms can be attributed to specific organ dysfunction is unknown.

This study aims to characterise the extent of multi-organ dysfunction in patients recovering from severe Covid-19 in an effort to explain whole-body physiological decline and fatigue. Importantly, we systematically assess the dysfunction under conditions of exercise stress.

We aim to recruit up to 30 adults, with severe confirmed Covid-19 infection 5-7 months from hospital discharge. State-of-the-art validated magnetic resonance imaging (MRI) will be used to assess organ volume and structure (brain, lung, heart and muscle) and heart and brain vascular function during low intensity in-scanner exercise. We will assess the extent of calf muscle deconditioning using ^{31}P magnetic resonance spectroscopy and further assess nerve-muscle conduction using intramuscular electrical myography. Finally, we will assess the persons ability to process and metabolise food intake: their metabolic flexibility and if they have built up resistance to the hormone insulin. Historical control data will be used for comparison matched for age, gender and ethnicity.

We anticipate that this multi-faceted and dynamic approach to quantifying organ specific damage and dysregulation in patients recovering from Covid-19 will provide valuable insight into the aetiology of fatigue and inform on exercise rehabilitation strategies to maximise patient recovery.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Fatigue: A prevalent and persistent symptom in early rheumatoid arthritis

Ifesemen OS, McWilliams DF, Kiely PDW, Young A, Walsh DA
Contact: mbxosi@nottingham.ac.uk

Background: Fatigue is associated with poor quality of life in people with rheumatoid arthritis (RA). Evidence shows that fatigue may persist in people with well-controlled inflammatory disease. However, this is based on data from people with long standing or refractory disease. This study aims to examine the course of fatigue in early RA.

Methods: Data from the early Rheumatoid Arthritis Network (ERAN), a multicentre inception cohort of people with <24months disease duration(n=1236) were analysed. ERAN collected demographic, clinical, and laboratory data. Fatigue was measured using the vitality subscale of the Short Form Health Survey questionnaire (SF36VT). Baseline prevalence was standardized to Eurostat 2013 by age and sex. The course of fatigue was examined using linear mixed effect models and group-based trajectory modelling (GBTM).

Results: Baseline characteristics include female=67%, Age=57(±14)yrs. SF36VT=41(±11), disease duration=11(7 – 18)mths. Age and sex standardized prevalence of fatigue was 44%(CI:38-50). 729 (59%) participants were included in the longitudinal analysis. Over 4 years follow up, and after accounting for the effect of age, sex, patient's global assessment of disease activity, BMI, pain and mental health, there was no clinically significant change in vitality levels from baseline, (β: -0.14CI: -0.26 to -0.02, $p \leq 0.001$). GBTM showed 2 sub-groups best fit the data. These groups were 'Fatigue' and 'No-fatigue' groups and comprised 52% and 47% of the population, respectively. Baseline BMI, disability, comorbidities, pain and mental health were collectively associated with fatigue group membership (AUROC=0.81).

Conclusions: Fatigue is a prevalent symptom in early RA. Embedded within the RA population are distinct sub-populations, with or without fatigue. Those with fatigue at baseline were likely to continue to report fatigue over 4 years of follow up. Management of fatigue might require strategies additional to disease modification, and people who require such interventions might be identified at presentation with early RA.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Short-term immobilisation alters neural input to the tibialis anterior in healthy young males

Inns TB, Atherton PJ, Phillips BE, Piasecki M
Contact: Thomas.Inns1@nottingham.ac.uk

Short-term immobilisation has a detrimental effect on muscle size and strength; however, little is known of the effects on motor nerves. The lower limbs are of particular interest as their functional relevance cannot be understated for tasks as simple as standing up. Motor unit potential (MUP) area can be used as an indicator of the size and number of muscle fibres in a single motor unit (MU), which in turn determines aspects of muscle function. Similarly, MU firing rate also influences muscle function but in terms of central, i.e., spinal, control.

In this study, five young, healthy males underwent single leg immobilisation for 15 days. Before and after immobilisation, needle electrodes were inserted into the tibialis anterior muscle (shin) of the immobilised and non-immobilised legs, to record MUP area and MU firing rate during submaximal voluntary contractions (25% of maximal voluntary force).

Analysis of MUP area revealed different responses between the legs, with area decreasing in the immobilised limb (−40%) but not changing in the non-immobilised limb. This was also true of MU firing rate, which decreased in the immobilised limb (−11%), yet interestingly, increased in the non-immobilised limb (+6%).

These findings suggest that 15 days of immobilisation has considerable effects on motor nerve properties. The reduced MUP area in the immobilised leg likely indicates a reduction in muscle fibre size and/or muscle fibre number, which was not observed in the non-immobilised leg. Furthermore, the reduction in MU firing rate in the immobilised leg and concurrent increase in the non-immobilised leg likely reflects changes in the central nervous system, where each limb has responded to reduced activity, and preferential loading, respectively. These findings may help us better understand the changes in neuromuscular mechanisms with muscle loss.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

The Impact of Surgical Trauma on Protein Turnover: A Meta-Analysis of Stable Isotope Techniques to Investigate Post-Operative Catabolism

Jaconelli M, Lord JM, Greenhaff PL, Atherton PJ, Lobo DN, Brook MS
Contact: Matthew.Jaconelli@nottingham.ac.uk

Rationale: Routine surgery induces skeletal muscle wasting that must occur through an imbalance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). However, due to variation between stable isotope tracer methods that measure whole body protein kinetics in the blood and those that directly assess tracer kinetics within muscle; our understanding of the dynamic processes that lead to this imbalance are currently lacking.

Methods: A meta-analysis was conducted of studies investigating perioperative protein turnover between 01/01/1990-08/11/2020. Articles with human studies containing pre- and post-operative stable isotope measures of muscle or whole body protein turnover during conventional perioperative care were deemed eligible. The primary outcome was relative changes in protein turnover post-surgery.

Results: Eligible studies predominantly contained patients who had undergone elective abdominal surgery. Tracer methods included arterio-venous whole body protein measures and direct stable isotope incorporation techniques assessed via *rectus femoris* muscle biopsy. Analyses via a random effects model illustrated whole body protein turnover responses to be variant, with mixed changes occurring following surgery. However, direct measures of MPS within muscle illustrated marked suppressions as a result of surgical trauma.

Conclusion: Current evidence suggests a role for suppressed skeletal MPS during post-operative muscle catabolism, providing a target for future interventions aimed at alleviating surgical insult. The absence of uniform changes in whole body PS/PB likely reflects metabolic changes in all organs, in addition to muscle. This highlights the requirement for direct incorporation methods, which may benefit from advances in D2O tracer techniques capable of defining the time-course of these perioperative changes. However, potent limitations remain in the accurate assessment of protein breakdown within skeletal muscle using current methodology, largely due to underlying kinetic assumptions inherent to the models employed.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Nerve-muscle communication differs with different types of muscle contraction when performed to fatigue

Jones EJ, Martinez-Valdes E, Negro F, McCormick D, Atherton PJ, Phillips BE, Piasecki M.
Contact: eleanor.jones@nottingham.ac.uk

For muscles to contract and facilitate movement, nerves and muscle must interact, with motor units ((MU's); a nerve and all the muscle fibres it is connected to) essential for this communication. Just as increases in muscle force are partly attributable to changes in MU firing, muscle fatigue (described by a reduction in force output) may also be related to this. However, previous research has found mixed results on what happens to MU firing with fatigue. These mixed findings may be related to different muscle contraction types being used in previous work, as concentric (muscle shortening) and eccentric (muscle lengthening) contractions are known to elicit different physiological responses to fatigue. In this study, we aimed to assess the effect of fatigue, when caused by two different types of muscle contraction, on MU firing properties.

High-density surface electromyography (HD-EMG) was used to identify individual MU electrical activity from the quadriceps muscles of 8 young volunteers. MU activity was recorded during 4 repeat contractions held at 25% and 40% of the volunteers' maximal voluntary contraction (MVC) force, before and after fatiguing exercise. Wearing a weighted vest, volunteers 'stepped up' with one leg (concentric) and 'stepped down' on the other leg (eccentric), so both types of muscle contraction could be compared.

MVC decreased after both concentric and eccentric exercise (-10.6% and -19.2% respectively). MU firing was slower following concentric exercise (-7.7%) but faster after eccentric exercise (+8.0%). The variability in MU firing was greater only after eccentric exercise (+11.4%).

These findings show that MU firing properties following fatiguing exercise differ according to the type of muscle contraction performed. These differences may explain the greater degree of muscle damage (i.e. muscle soreness) seen after eccentric exercise, and may be important when prescribing exercise to improve muscle strength in older individuals and/or those with neuromuscular conditions.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Spaceflight, Inactivity and Exercise: a cell culture model to investigate skeletal muscle glucose uptake.

Kirkpatrick E, Wilkinson DJ, Drory A, Williams P, Greenhaff PLG, Atherton PJ, Brook MS
Contact: euan.kirkpatrick@nottingham.ac.uk

Background: Skeletal muscle is essential for the completion of everyday activities and has crucial roles in maintaining whole body health. For instance, the majority of the carbohydrate we eat is taken up and stored by muscle, and this process is essential in regulating blood glucose levels. The inability of insulin to stimulate muscle glucose uptake in response to feeding is known as insulin resistance and is associated with poor health outcomes and the development of type II diabetes. Skeletal muscle contraction during exercise is a stimulator of muscle glucose uptake independent of insulin, whilst inactivity quickly induces insulin resistance that persists whilst in an inactive state. Inactivity induced insulin resistance therefore represents a significant barrier to healthy ageing, long-term hospitalized patients and long-term space exploration.

Aims & Methods: The frequency of muscle contraction required to prevent the development of insulin resistance during periods of space flight or immobilization remains unresolved. Furthermore, undertaking longitudinal long-term studies in immobilised humans is challenging (i.e bed rest or single-limb immobilisation). As such, models to investigate the interplay between inactivity, contraction and glucose uptake would be advantageous to scientific progress. Our aim is to use a skeletal muscle cell model in which muscle contraction can be induced through electrical pulse stimulation (EPS) to simulate exercise. Cellular glucose uptake will be determined using traceable glucose analogues such as 2-deoxyglucose and mass-spectrometry, and fluorescent 2-deoxyglucose and microscopy. An initial aim is to quantify cellular glucose uptake over 24hrs using a validated EPS (2ms, 11.5V, 1Hz) model, which we will use to compare to different contraction/inactivity paradigms. Further work involving sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase-modulators will help elucidate the interplay between contraction induced calcium release and cellular glucose uptake, which will hopefully provide mechanistic insight of the impact of inactivity of glucose homeostasis.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

The clinical impact of chronic mTOR inhibition upon aged human skeletal muscle

Liu HT, Jones E, Phillips BE, Smith K, Piasecki M, Wilkinson DJ & Atherton PJ
Contact; alyhl13@nottingham.ac.uk

Skeletal muscle is the largest organ of the human body, with established roles in structurally supporting the skeleton, driving locomotion, in addition to regulating core metabolic processes such as glycemic control and energy flux. Loss of skeletal muscle mass (i.e. muscle atrophy) occurs in the ageing process and in common diseases such as cancers, infections and neuromuscular disorders. In particular, muscle atrophy associated with ageing (engendering frailty) remains a major public health problem for which there remains a poor mechanistic understanding and no pharmaceuticals.

The mechanistic target of rapamycin complex 1 (mTORc1) pathway is deemed to be a cell-type agnostic master regulator of metabolism, and in skeletal muscle, regulates core processes such as protein synthesis and breakdown. Despite the apparent positive role of mTOR, recent research in pre-clinical and clinical studies, show that mTOR signalling is hyper-active in aged muscle, and that this is considered a potential cause of sarcopenia via inducing an imbalance between protein synthesis and degradation. Reflecting this, mTOR inhibition extends lifespan and spares muscle in both invertebrate and vertebrate species e.g. treatment of aged mice with rapamycin ameliorates sarcopenia, via attenuating fibre atrophy and satellite cell senescence. Notably, inflammation, mitochondrial dysfunction and impaired autophagy caused by over-active mTOR signaling are also dampened by rapamycin treatment. We therefore hypothesize inhibition of mTOR could mitigate aspects of muscle ageing, in humans.

In a project funded by the UK SPINE (https://www.kespine.org.uk) we will investigate the impacts of Rapamune (an mTOR inhibitor) administration in relation to muscle metabolism and physiology of older volunteers. The translational potential of this project is significant, since a recent phase II trial of Rapamune showed safety in older people, and since these drugs are already deployed clinically (e.g. for organ rejection).

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Development of the CORE-Kids international core outcome set for childhood fractures

Marson BA, Manning JC, James M, Craxford S, Deshmukh SR, Perry D, Ollivere BJ and the CORE-Kids collaborative group
Contact: ben.marson@nottingham.ac.uk

A third of children will experience a limb fracture before their 17th birthday. However, there are only a few studies to help us decide on the best treatments for these injuries. One of the reasons for this is a lack of a core outcome set to prevent research wastage and ensure research outcomes are consistent and relevant.

A core outcome set is a minimum standard set of outcomes that are to be measured in every research study. The need for a core outcome set was scoped with the NIHR trauma trials network and was designed in accordance with COMET guidelines.

A four-phase study was conducted to agree the core outcome set. Outcomes relevant to professionals were identified through systematic review of trials and outcomes relevant to families were identified through semi-structured interviews with 20 families. Outcomes were prioritised using a three round Delphi survey with 205 panellists from 23 countries followed by a multidisciplinary consensus workshop.

The systematic review and interviews identified 85 relevant outcome domains. The Delphi survey identified 51 upper and 51 lower limb outcomes as important outcomes.

At the consensus workshop, the core outcome domains was agreed to be: Pain, Return to physical & recreational activities, Emotional & psychosocial wellbeing, Complications, Return to baseline activities, Participation in learning, Appearance & deformity, Time to union. Agreement was reached that mobility and manual dexterity should be included for lower and upper limb fractures.

This core outcome set has been endorsed by three national societies as the reporting standard for these injuries. It is not an exhaustive set and further work is required to identify what outcome tools should be used to measure each of these outcomes. Adoption of this outcome set will ensure research for these children remains relevant and can be combined in treatment guidelines.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Early Motion And Directed Exercise (EMADE) versus usual-care, post ankle fracture fixation: 12 to 52-week results from a pragmatic-RCT suggest accelerated recovery

Matthews PA, Scammell BE, Ali A, Nightingale J, Coughlin T, Khan T, Ollivere BJ
Contact; Paul.Matthews1@nottingham.ac.uk

Introduction: Ankle fractures are extremely common, accounting for over 20% of all lower limb fractures. For those ankle fractures requiring surgical fixation, usual-care post-surgery has included 6-weeks cast immobilisation and non-weightbearing. Disuse atrophy, stiffness and pain are detrimental sequelae of this management. Our objectives were to determine if following surgical fixation of Weber-B ankle fractures, the physiotherapy intervention; Early Motion And Directed Exercise (EMADE), was superior to the usual-care.

Method: A pragmatic randomised controlled trial (RCT) was conducted in an NHS fracture clinic, recruiting 157 individuals with surgical fixed Weber-B ankle fractures. Allocation at week-2 post-surgery was to either EMADE, which utilised a removable cast, progressive home exercises, manual therapy, advice and education, or to the usual-care of cast immobilisation. Both groups were non-weightbearing until their intervention finished at week-6.

Results: At week-12, 130 participants returned their OMAS questionnaires, exceeding the 60 per group threshold set by the a-priory power calculation. The week-12 results favoured the EMADE group (62.0 (SD 20.88) versus 48.8 (SD 22.52) $p<0.001$) by a difference in means of 13.2 (95% CI 5.7 to 20.7), exceeding the accepted minimal clinically important difference of 10 points on the OMAS. Significant and clinically meaningful results were maintained at week-24, with results converging by week-52. No intervention related or unexpected adverse events were identified.

Discussion/conclusion: This pragmatic-RCT yielded both significant and clinically meaningful outcomes, at week-12 favouring EMADE over the usual-care of 6-weeks immobilisation. While these benefits were not long-term, the favourable results at week-12 and 24 suggest that, following surgical fixation of Weber-B ankle fracture, EMADE physiotherapy provides patients with an accelerated recovery.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Development and application of MRI methods to physiologically phenotype ageing in humans

Nicholas R, McGing J, Gupta A, Greenhaff PL, Francis S
Contact: Rosemary.Nicholas@nottingham.ac.uk

We live in an increasingly ageing population, understanding the mechanisms of the ageing process and the role of environmental factors, such as physical activity levels, in modulating age related decline is key. Despite this, the most widely used tool to quantify age related decline is currently hand-grip strength. The overarching aim of this study is to combine MRI and human physiology approaches to understand the effects of life-long physical activity on the age-related decline and attempt to isolate those physiological traits driven by habitual physical activity levels. To do this, sedentary, healthy older male volunteers and age-matched high-level male cyclists(capable of doing ~100 km)are undergoing MRI scans at rest, during an acute exercise challenge (Trispect, Ergospect), and during post-exercise recovery. This allows us to investigate brain anatomical structures, brain function (systemic and regional blood flow, and the amount of oxygen extracted), heart function and muscle composition and metabolism. Importantly, method development has established techniques to quantify muscle volumes and the fat composition of the lower leg that are extracted from whole body scans through a semi-automated pipeline. This delivers robust and impactful end-point measurements at speed, and without the need to manually delineate muscle groups on selected MRI slices. This methodology is currently also being applied to other muscle groups. This comprehensive battery of MRI measures will be correlated with brain structural scans, muscle strength and fatigue measures, and cognitive tests to bring detailed physiological insight of the older individual. Moreover, the same whole-body scans are being collected in other participant groups, including age-related disease where weakness and fatigue are prevalent, such as COPD. Interim results reveal age-matched patients with COPD present with the lowest muscle volumes and highest fat fraction, whilst the older cyclists have the highest muscle volumes and lowest fat fraction.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Neuromuscular Electrical Stimulation (NMES) for hospitalised older patients

Obasi AA

Contact: Akanu.OBASI@nottingham.ac.uk

Older adults with frailty commonly present to hospital with conditions that render them immobile – such as a fragility fracture (FF).

Many are likely sarcopenic before presentation, and disuse atrophy may further exacerbate their muscular function. This may result in delayed or incomplete recovery, and a prolonged period of risk of the complications of immobility.

Early mobilisation and progressive resistance exercise training (RET), in the nourished, are the best treatment to avoid the complications of immobility and restore muscular function. But pain and the systemic effects of injury means that patients often cannot mobilise or do sufficient RET.

NMES is an intervention that could address this problem. NMES involves placing a skin electrode over the femoral and/or tibial nerves and using this to stimulate the muscles of the thigh and calf. It can be done while the patient is lying on the bed. It has been used by athletes, and there have been studies in medical conditions in ITU patients, patients undergoing knee surgery, and in the sarcopenia associated with COPD. This treatment could also be applied to attempt to maintain muscle function during periods of immobility after FF until the patient is able to undertake RET. This may shorten the period of immobility and risks associated with it, and hence speed up and improve ultimate outcomes.

In my PhD, during 2021 I will conduct a feasibility study of the use of NMES (with or without protein supplementation) in older patients admitted to hospital with FF. Key questions to answer will be whether patients tolerate NMES, and whether leg strength is maintained. If NMES is feasible and acceptable and has early evidence of effectiveness we will proceed to conduct a large scale RCT with clinical outcomes.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Investigating the role of blood vessels on cartilage health

Sohail R, Beazley-Long N, Vitterso E, Bates DO and Donaldson LF
Contact: Roheena.Sohail@nottingham.ac.uk

Background: Inflammatory arthritis is a chronic progressive autoimmune disease caused by multiple factors that result in the inflammation of one or more joints. Inflammation and angiogenesis are closely integrated processes that can stimulate each other. Angiogenesis plays an important role in the development and progression of arthritis. Angiogenesis inhibition might be a potential therapeutic option for management of arthritis as it tends to improve symptoms by retarding joint damage. The binding of vascular endothelial growth factor A (VEGF-A) to VEGF receptor 2 (VEGFR2) is considered to be the main stimulatory signal of angiogenesis. We have previously found that knockout of endothelial VEGFR2 ($VEGFR2^{ECKO}$) delayed both the onset and distant spread of pain in a mouse model of inflammatory arthritis. Our next finding suggested that endothelial VEGFR2 KO was detrimental to tibiotalar cartilage integrity during inflammatory arthritis.

Hypothesis: Knockout of VEGFR2 in endothelial cells ($Tie2^{+}$ cells) may result in damage to cartilage through increased hypoxia.

Methods: Transgenic mice experienced unilateral sub-cutaneous, peri-articular (tibiotarsal) injection of Complete Freund's Adjuvant (CFA) [2 - 80 µg CFA in 40 µL oil, on either side of the joint under isoflurane anaesthesia (2–3% in oxygen) two weeks after tamoxifen induction (1 mg/100 µL i.p.). Sham mice underwent anaesthesia and injection site preparation without CFA injection. Inflammation was confirmed with behavioural tests as well as measured via increased ankle joint diameter. CD31- endothelial marker was used to stain 10µm sections by using immunohistochemistry protocol in order to quantify the blood vessel density in synovium and subchondral bone.

Results: Significant reduction in synovial blood vessel density ($p < 0.05$) and subchondral blood vessels regression ($p < 0.05$) was observed in VEGFR2 KO mice with CFA inflammation as compared to other experimental groups.

Conclusion: Decrease in vascular density in synovium and vascular regression in subchondral bone suggests that loss of vascular function exacerbates arthritis. Subchondral bone has a very important role in maintaining cartilage integrity.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Multimorbidity prevalence and clusters in people with osteoarthritis and associations with all-cause mortality compared to controls in the UK

Swain S, Coupland C, Strauss V, Mallen C, Kuo CF, Sarmanova A, Bierma-Zeinstra SMA, Englund M, Prieto-Alhambra D, Doherty M, Zhang W
Contact: Subhashisa.Swain@nottingham.ac.uk

Objective: To examine the prevalence and clusters of multiple chronic conditions present in people with osteoarthritis (OA) and the association with the all-cause mortality compared with people without OA.

Methods: The Clinical Practice Research Datalink (CPRD) GOLD was used to identify people with incident OA and age, gender, and practice matched controls without OA from UK primary care. Controls were assigned the same index date as their matched cases (date of osteoarthritis diagnosis). Multimorbidity was defined as having 2 or more chronic conditions. Clustering of 49 individual comorbidities was examined using latent class analysis in both the cases and controls. The association of all-cause mortality with the clusters was estimated using time varying Cox regression adjusting for the covariates. Multiplicative interaction between OA and clusters were examined.

Results: During 1997-2017, we identified 221,807 incident OA cases and 221,807 matched controls. The prevalence of multimorbidity among people with OA was 53.2% and 42% among the controls ($p<0.05$). Five multimorbidity clusters were identified in both OA cases and controls: relatively healthy; cardiovascular (CV), CV and musculoskeletal (MSK); MSK and mental health (MH) and metabolic clusters. The cluster sizes of CV (30.5%), CV and MSK (11%), and MSK and MH (21%) were greater in the OA group compared to controls. OA significantly interacted with any of the identified clusters to increase the risk of all- cause mortality.

Conclusions: The identified clusters were centred around cardiovascular, mental health, musculoskeletal and metabolic conditions. Further research is warranted to better understand the causes and patterns in detail.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Monitoring muscle metabolism non-invasively with Dynamic Nuclear Polarisation

Torchi A, Serres S, Mallinson J, McGing J, Lobo D, Cooper A, Awais R, Årstad E, Glaser M, Twyman F, Gowland P, Auer D, Greenhaff PL, Faas H, Morris P
Contact: andrea.torchi@nottingham.ac.uk

Dynamic Nuclear Polarisation (DNP) applied to Magnetic Resonance Imaging (MRI) enables to probe metabolism in humans with unprecedented sensitivity, with many potential applications in clinical diagnostics and research because of the possibility to quantify and localise different downstream metabolites in-vivo and in real time with a sensitivity and a resolution that are not obtainable without DNP hyperpolarisation. For instance, the ability of DNP to detect local lactate levels could potentially offer a radiation-free alternative to PET scans for some types of cancer therapy monitoring. In the last few years, DNP experiments have been successfully carried out in both preclinical and clinical models. The human studies so far have mainly focused on prostate, brain and breast cancer, as well as on cardiac function and healthy volunteers. In this work we present a non-invasive MRI measurement of the enzymatic conversion of pyruvate to lactate, alanine and bicarbonate in healthy human calf muscle under exercise. To the best of our knowledge, our DNP study is the first on human skeletal muscle. Three healthy volunteers (of ten planned in total) were scanned on a 3 Tesla MRI system by using a surface coil placed on their calf muscle, after injection of a 35 ml volume of hyperpolarised [1-13C] pyruvate solution in the antecubital vein. The volunteers exercised during the scan with an ergometer pedal. To derive the enzymatic conversion rates of pyruvate to lactate, alanine and bicarbonate from the measured signals, a metabolic model was fitted to the experimental data. This preliminary study demonstrates that in-vivo DNP enables the measurement of exchange dynamics in human skeletal muscle. The differences in enzymatic kinetics are potentially linked to the degree of endurance training of the volunteers and the intensity of the exercise.

ISSN: 2059-3341
BRC MSK Conference 27 January 2021
www.nottingham.ac.uk/emran

Changes in serum levels of Omega-3 fatty acids and their metabolites in hospitalised COVID-19 patients

Turnbull J, Jha RR, Ortori C, Lunt E, Tighe PJ, Irving WL, Gohir S, Kim DH, Valdes AM, Tarr AW, Barrett DA, Chapman V
Contact: jamies.turnbull@nottingham.ac.uk

The COVID-19 global pandemic is an on-going health crisis. Severe cases of the disease are characterised by uncontrolled inflammatory response, with potential long-lasting health complications and death. Bioactive lipids are small molecules which have diverse functions within the body, including the initiation, propagation, and resolution of inflammation.

We measured levels of several classes of bioactive lipids including omega-3 fatty acids (ω-3 FA) in serum samples taken from 50 patients infected with SARS-CoV-2 soon after hospitalisation, using our in house liquid chromatography-mass spectrometry (LC-MS/MS) method. As a control, samples from 94 aged-matched non-infected people with osteoarthritis were used. Anti-nucleocapsid antibodies, a measure the adaptive immune response to the virus, was quantified.

Participants were separated into three age groups (<60, 61-74, & >75yr). Levels of eicosapentaenoic acid (EPA) were stable across all groups with the exception of the COVID-19 >75 yr group, where they were significantly lower (P = <0.0001). The EPA metabolite, 18-hydroxy-eicosapentanoic acid (18-HEPE), was significantly increased in all patients with COVID-19, compared to the non-infected groups. Levels of DHA were also lower in the COVID-19 >75 compared to control (P = 0.01). Despite this, DHA metabolites 17-hydroxy-docosahexaenoic acid (17-HDHA), maresin 2, and resolvin D4 (RvD4) were all significantly higher in all COVID-19 groups, compared to non-infected group. Serum levels of DHA, EPA, 14-HDHA, and 18-HEPE were positively correlated with anti-nucleocapsid levels.

These data show levels of ω-3 FA metabolites are elevated during COVID-19, despite levels of EPA and DHA remaining stable across groups – with the exception of the COVID-19 >75 yr group. Correlation of ω-3 FAs with anti-nucleocapsid antibody levels indicates that ω -3 FAs may be associated with the production of the adaptive immune response to SARS-CoV-2.