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EDITORIAL

UKRI MRC National Musculoskeletal Ageing Network: strategic prioritisation to increase healthy lifespan and minimise physical frailty

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Introduction

The UKRI Medical Research Council National Musculoskeletal Ageing Network (Director: Professor Cyrus Cooper and Deputy-Director: Professor Nicholas Harvey) brings together, over a 2-year period, key UKRI MRC investments in musculoskeletal research: the MRC Lifecourse Epidemiology Centre, MRC-Versus Arthritis Centre for Integrated Research in Musculoskeletal Ageing (CIMA), MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research (CMAR), MRC Epidemiology Unit, MRC Integrative Epidemiology Unit, and MRC Unit for Lifelong Health and Ageing. Together, these span the Universities of Southampton, Sheffield, Liverpool, Newcastle, Nottingham, Birmingham, Oxford, Bristol, Cambridge, and UCL, with further links to associated NIHR Biomedical Research Centres. This multidisciplinary collaboration will underpin a step change in musculoskeletal ageing research capacity and strategy (principally across the diseases osteoporosis, osteoarthritis, sarcopenia, and rheumatoid arthritis) by identifying key tractable research priorities; developing an integrated multidisciplinary and diversified technology partnership to address the identified research gaps; providing a platform to disseminate best practice; supporting early and mid-career researchers to build research capacity and develop technical expertise to ensure longevity to current UKRI investments; prosecuting an ongoing programme of innovative studies from discovery science to clinical impact.

In this editorial, we briefly set out perspectives on the current landscape and identify research priorities fundamental to achieving healthy musculoskeletal ageing, as articulated and agreed at a scoping workshop of the Network held at the Academy of Medical Sciences, London, UK, on June 17, 2022.

We are all getting older

Prior to the finality of death, ageing is an inevitability for us all. Increasing age is inextricably linked to a wide range of chronic disorders, with every organ system affected in some way [1]. A consequence is that increases in life expectancy are not automatically associated with increases in the number of years lived in health. In fact, the converse is often true, placing a massive burden upon health and social care [1, 2]. Populations around the world have become, on average, older in recent decades, and are projected to grow older still in coming years [1, 3]. It is clear that unless we can achieve a step change in years lived in good health across a longer lifespan, we will face the prospect of ever-increasing

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health and social care demands. This imperative is recognised through the UK Government's Grand Challenge of achieving 5 years of additional healthy life by 2035 [4] and through the current United Nations Decade of Healthy Ageing (2021–2030) [5].

The rather gloomy forecast of functional decline with age applies across organ systems, including components of the musculoskeletal system. Indeed, musculoskeletal disorders constitute a major public health problem: the Global Burden of Disease study estimates that they impose amongst the highest impact worldwide of any disease group on years of life lived with disability, an impact that is set to rise by over 40% by 2050 [6]. The costs associated with musculoskeletal conditions are equivalent to 3% of the gross national product globally each year. Osteoporosis and osteoarthritis (the most common metabolic bone and joint disorders, respectively) account for 6.8% of this total disability. The remaining lifetime risk of osteoporotic fractures at the hip, wrist, or spine is 39% among women and 13% among men at the age of 50 years, [7, 8] and the annual NHS cost of managing osteoporotic fractures is estimated at £5 billion, half of which is attributable to hip fracture [9, 10]. From age 50 years, lifetime risks of total knee arthroplasty (representing end-stage osteoarthritis) are 10.8% for women and 8.1% for men [11]. Furthermore, sarcopenia (accelerated loss of muscle strength, mass, and function [12]), the commonest muscle disorder worldwide, is estimated to cost £2.2 billion in the UK each year [13]. As populations age, this burden is set to increase markedly. For example, the number of individuals at high fracture risk worldwide, estimated at around 150 million in 2010, is expected to double to over 300 million by 2040 [3].

The whole system/person approach

Importantly, components of the musculoskeletal system do not act in isolation from each other. For example, reduced mobility as a result of knee osteoarthritis may lead to muscle wasting and consequent bone loss, along with impaired cardiometabolic health and increased mortality [14]. This linkage is also relevant across non-musculoskeletal organs and systems [1], such that collectively these associations may dictate the development of the frailty phenotype [15]. For example, conditions such as dementia and chronic obstructive pulmonary disease may lead to bone and muscle loss, with an increased risk of falls and fractures via reduced mobility, poor nutritional intake, and side effects of medication [16, 17]. A further example is the increasing evidence of associations between low bone mineral density and greater cardiovascular risk [18, 19]. The age-related cross-talk between systems, and their associated outcomes, reflect a mixture of shared risk factors, shared common underlying mechanisms, and in some cases direct, causal links [20–22]. Furthermore, age is the biggest risk factor for musculoskeletal disease. The biological processes that drive the ageing phenotype, including inflammation, may represent shared pathogenic factors and therapeutic targets [23].

Attempts have been made to integrate various measures into a more general construct that reflects the ageing phenotype. An example is a frailty, which has been proposed as a "biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiological systems, and causing vulnerability to adverse outcomes" [24]. A corresponding clinical algorithm incorporating information on unintentional weight loss, exhaustion, reduced gait speed, reduced grip strength, and reduced physical activity has been frequently used [24]. This "biological syndrome" characterises frailty as a specific clinical entity. Alternative proposals such as the clinical frailty scale [25] and the more recent electronic frailty index [26] approach frailty via the accumulation of deficits across multiple organ systems. Explicit recognition of the importance of musculoskeletal impairment in the context of a whole person paradigm is core to the World Health Organisation's work on healthy ageing, incorporating the concept of maintaining "functional ability" as a key component of achieving this goal [1]. Core to this approach is the concept of "intrinsic capacity", which reflects the mental and physical capacities on which an individual can draw to achieve functional ability [27, 28]. Overall functional ability is thus determined by intrinsic capacity together with extrinsic factors (e.g. social and physical environment) and the interaction between the two [1]. This latter point encapsulates a key further consideration; the elucidation of the specific effect of ageing from the consequences of cumulative extrinsic insults and the inherent resilience of the system that facilitates subsequent recovery.

A final consideration is increasing evidence for the role of the early environment in determining trajectories of gain in functional ability through development and growth. For example, achievement of maximum peak bone and muscle mass in early adulthood are both important determinants of fracture risk in older age [29]. Studies of older adult cohorts for which birth records exist, [30–33] mother–offspring cohorts detailing characterisation in early development, [34, 35] recent trials of pregnancy interventions [36], and our increasing mechanistic understanding [37, 38] support the need for a whole lifecourse approach. An indeed greater understanding of interrelationships between fat mass, physical activity, musculoskeletal, and cardiometabolic health (for example, obesity is the major risk factor for knee osteoarthritis as well as for type II diabetes mellitus [39]) further emphasises the imperative to consider multiple systems across the whole of life.

Strategic research priorities

So where does this lead in terms of priorities via which to understand healthy musculoskeletal ageing? It is absolutely clear that components of the musculoskeletal system should not be viewed in isolation and that the musculoskeletal system should not be viewed apart from other systems when considering the drivers of frailty: Thus, a whole person, or at least a whole system, approach would ideally be employed [15]. Within this construct, there should be an understanding of whether trajectories of ageing apply similarly across systems, whether systems age independently, and whether such trajectories vary by population globally. This of course, leads to the further question of whether underlying mechanisms are system specific or if there are common mechanisms of ageing, for example, cell senescence and chronic inflammation, [40] which contribute to organ compromise across the board. There needs to be an investigation of trajectories, not just of absolute values but of the magnitude of resilience to external insults and other morbidities, together with differentiation between pure intrinsic ageing effects and those consequent to external influences such as physical inactivity and malnutrition [41]. Given the increasing evidence for the importance of the early environment and the contribution of peak mass/function and metabolic resilience to later health, the approach should encompass the entire lifecourse.

The UKRI MRC National Musculoskeletal Ageing Network provides a world-leading multidisciplinary grouping, with expertise, facilities, and infrastructure spanning the full breadth of biomedical investigation, from molecular biology, integrative physiology, experimental medicine, to trials, causal inference, and genetic/nongenetic epidemiology. This unique collaboration will facilitate truly novel bench-to-bedside-to-policy research. Using preclinical and clinical cohort resources, experimental approaches, technological platforms, and national/international databases, we aim to address the following key questions:

1. What are the patterns and determinants of lifecourse trajectories of gain, maintenance, and loss of key musculoskeletal tissues/systems/pathways, both in terms of absolute values and resilience to the impact of environment and disease?
2. Are these trajectories interdependent, and to what extent are they reversible?
3. Can we differentiate between organ-specific and pan-system mechanisms and the consequences of pure ageing versus those of cumulative extrinsic or morbidity-related insults?
4. Using this understanding, together with national/international resources, can we identify in-depth phenotypes of ageing to discern novel targets for intervention (across nutrition, physical activity, health behaviour as well as pharmacological) at either tissue/system or pan-system level?

Conclusion

Building on established collaborations, the UKRI MRC National Musculoskeletal Ageing Network will develop novel interdisciplinary cross-institution initiatives addressing these questions. Through integrated team science, capacity building, and collaborative working, we are determined that the network will achieve the step changes necessary to enable novel investigations and development of therapeutic interventions to optimise healthy ageing in future generations.

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Declarations

Ethics approval and consent to participate This narrative article contains no original data and thus issues of ethics, informed consent and patient confidentiality do not apply.

Conflict of interest None.

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