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Improving the outcomes of elective surgery for older adults: a research impact case study

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ABBREVIATIONS

CRF: cardiorespiratory fitness
CPET: cardiopulmonary exercise test
HMB: β-hydroxy-β-methylbutyrate
MCID: minimal clinically important difference
MDT: multidisciplinary team
ABSTRACT

Introduction
The ultimate purpose of bio-scientific research is to produce societal benefit – "research impact". Demonstration of the impact of bio-scientific research is difficult. It is, however, vitally important for researchers to try to do this, to ensure that research is directed towards this purpose.

Method
We wished to examine the impact our research has made, or might make in the future. We collated and summarised a body of our bio-scientific research studies on a related topic, our review articles on that topic, and then described the subsequent body of our applied research studies that mobilised that bio-scientific knowledge along the translational pipeline towards eventual impact. We proposed what ultimate impact of this research knowledge is possible, and the steps that are needed for that impact to be realised.

Results
We present the impact of our work with respect to the clinical problem of adverse outcomes of elective surgery driven by underlying poor muscle health and cardiorespiratory fitness in older adults. We presented 32 bio-scientific research papers reporting the results of studies we have conducted over the last decade on skeletal muscle physiology and metabolism and summarised their key academic impact. We presented a further 16 review articles demonstrating knowledge synthesis and mobilisation, and a further 22 early translational studies where this bio-science knowledge has been applied to develop and evaluate nutritional and exercise “prehabilitation” interventions and associated imaging-based assessment tools.

Discussion
This case study illustrates the actual academic impact and potential health impact of our work. We describe the next steps along the translational research pipeline needed to realise the potential clinical impact of our research.
INTRODUCTION

Impact: knowledge mobilisation and translation

The purpose of research is to acquire new knowledge. Research is seen as investment rather than mere speculation or the acquisition of knowledge for its own sake. It is important to direct the vast sums of investment involved in research towards the production of the most valuable new knowledge. The concept of research impact characterises this value. Research impact is 'the demonstrable contribution that excellent research makes to society and the economy' [1]. The impact of bio-scientific research can be academic, or health-related. Academic impact is where research makes major shifts in understanding, methods or theories. Health-related impact includes contributions to policy, services, health outcomes and broader societal effects.

The means by which a new piece of research knowledge produces impact is complex. First, the potential value of new knowledge has to be recognised (“knowledge mobilisation”) and then it has to be applied elsewhere (“knowledge transfer”). Knowledge mobilisation refers not only to its publication but also its dissemination to potential users of that new knowledge. New bio-scientific knowledge can rarely be applied in one jump to produce impact: usually several steps are required. The translational research pipeline provides a simplified model of those steps (Figure 1)[2]. “Early translational research” refers to that research where bio-scientific knowledge- such as that acquired from studies involving modelling, or laboratory studies of molecules, cells, tissues organs or animal studies, is applied in human volunteers and, increasingly along the pipeline, in patients and clinical settings. The further along this pipeline, the more the term "applied health research" is used. “Implementation research” refers to the final part of the research process, where the products of research such as clinical interventions or policies are applied and ultimately deliver improved societal, health or economic impacts. Figure 1 illustrates this pipeline, referred to here as the “critical path”, as it could be applied to the development and application of a new drug. The figure also illustrates particular challenges to knowledge transfer along this pipeline referred to as “gaps in translation”: the first being in early translational research and the second being in implementation research. The figure also illustrates how funding bodies- the Medical Research Council and the various funding streams of the NHS’s National Institute for Health Research (NIHR), support research at different stages along this pipeline.
This model is clearly highly simplified, and does not take account of the ways in which different types of knowledge may be translated, and implies a more unidimensional and linear process than is the case in reality. Nevertheless, it is sufficient to illustrate the long and complex journey that basic bio-scientific knowledge has to make before impact is achieved. No single research group is ever likely to be able to manage all steps of this pathway, and so those working in bioscience need to take what steps they can to mobilise and transfer their newly acquired knowledge. In the first instance this means publication of their research findings and their dissemination. A further part of the process of mobilisation of new knowledge to make it useful to potential users of that knowledge is to set it in the context of what is already known. This is achieved by producing and publishing knowledge syntheses, usually referred to as review articles. The next step along the translational pathway that bio-scientific researchers can take is to work with other researchers wishing to apply these research findings. Historically, the absence of funding and opportunities for this produced the first gap in translation: NIHR Biomedical Research Centres such as ours in Nottingham (https://nottinghambrc.nihr.ac.uk/) are aimed specifically at closing that gap.

The above diagram provides the basis for our approach to demonstrating the impact or potential impact of our research. We start by describing a clinical problem and elucidate a knowledge deficiency and hence a potential research-based solution to the problem. Next, we show that we have conducted a substantial volume of high-quality bio-scientific research related to that knowledge gap. We show that we have also produced a steady...
output of review articles. We then illustrate what we have done to set this body of knowledge on its way along the translational research pipeline by showing what early translational research we have contributed to. Finally, we need to make clear what steps we think are next required to address the clinical problem, and achieve impact. Using this approach, whilst we cannot claim that the research journey is complete and that societal impacts have been achieved, we can illustrate that we have set off productively along this journey. Here, we refer to this journey as the “pathway to impact”.

The clinical problem

Across the Western world people are living longer. For example, in the UK alone between 2001 and 2011 there was an 11% increase in the population aged over 65 years. Similarly, the median age in the UK increased from 33.9 in 1974 to 40.0 years in 2014, with future predictions estimating a median age of 43 years by 2037 [3]. These predictions may actually be under-estimations given the increasing population size that is also occurring across the Western world.

It is largely inevitable that a sizeable, ageing population will have significant social and clinical needs with economic consequences. For example, many older adults will lose physical function to the extent that they will be unable to maintain independence, and if adequate at-home support is not available, may need supportive accommodation. In 2016, provision of supportive accommodation was estimated to cost the UK economy £4.12 billion [4]. A large, ageing population also brings an increased proportion of people living with chronic disease and increasing levels of co-morbidity and patient complexity, all of which have independent and inter-related socioeconomic effects.

Older individuals living with co-morbidity often have reduced functional reserve across a range of organ systems limiting numerous aspects of physical function, including skeletal muscle, cardiovascular and respiratory function [5]. All of these limitations make these individuals susceptible to a disproportionate impairment in global physical function should any physiological insult occur. Surgery is a prime example of a significant physiological insult [6], posing a unique challenge to older adults whose ability to respond is dependent upon the interaction of comorbidities and the ageing process.

Two specific yet interlinked aspects of physical function which are known to be negatively affected by advancing age per se and further impaired by age-associated comorbidities
(i.e., diabetes, COPD) are i) muscle mass and function (in a deleterious condition known as sarcopenia [7]), and ii) cardiorespiratory fitness (CRF) [8]; both of which have been shown to be associated with detrimental health outcomes [9,10], yet able to be enhanced across the life-course by exercise training [11,12].

In relation to the challenge of surgery, the prevalence of many conditions requiring major surgery increases with advancing age. This, in conjunction with improved perioperative care, surgical techniques, and the aforementioned ageing population has led to increased numbers of older patients undergoing major surgery in recent years [13]. However, despite this, a disproportionate reduction in in access to surgery for older individuals still exists, as highlighted in the National Cancer Intelligence Network report: Major surgical resections England, 2004-2006 [14] and more recently in the Dunhill Medical Trust & Royal College of Surgeons joint report: Access all Ages and Access all Ages II [15]; with both these reports highlighting a stark decline in access to surgical procedures after the age of 65 years.

For older surgical patients, muscle mass and CRF have both been shown to have an important role to play in post-operative outcomes, with current clinical recommendations to objectify the fitness for surgery of older adults. For example, poor CRF has been linked to both perioperative mortality and morbidity in a number of surgical cohorts, including those with cancer [16-18]. In support of the importance of CRF in relation to surgical outcomes, retrospective analysis of cardiopulmonary exercise test (CPET) data in patients undergoing major intra-abdominal surgery led to the notion that there is a minimum CRF required to avoid an increased risk of perioperative cardiac mortality [19]. This work was subsequently supported by a number of studies showing increased risk of post-operative complications in those patients with low peri-operative CRF [18,20,21]. Similarly, increases in CRF have been shown to reduce post-operative complication risk, with studies in general surgery patients suggesting the minimal clinically important difference (MCID) to be a pre-operative increase in VO\text{\textsubscript{2AT}} (anaerobic threshold) of 1.5 – 2.0 ml/kg/min [18,22]. Indeed, achieving this MCID was associated with a 40% reduction in the odds of post-surgical complications in colorectal surgery patients [18], which may also hold true in other surgical populations.

Whilst traditional aerobic exercise training has been proven an efficacious modality to increase the CRF of older (as well as younger) adults [12], the time-frame commonly...
reported to achieve this is not conducive to the surgical pathway of a major age-associated condition, cancer. In the UK, the National Institute of Health and Care Excellence (NICE) imposes a timeline of 31-days for initiation of first treatment (from multidisciplinary team (MDT) decision) for cancers [22], leaving only a 31-day ‘window’ in which to implement any ‘prehabilitation’ regime designed to improve surgical outcomes.

The need to improve surgical outcomes was clearly exemplified in our work which showed that only one-third of patients return to work 1 year after elective surgery for colorectal cancer, with obvious implications for both the individual and society [24]. As low CRF has been shown by us, and others, to be strongly related to low muscle mass [25] in both health and disease, and that both of these factors are independently related to poor post-operative outcomes (including morbidity, mortality, and clinical-care issues such as prolonged length of hospital stay), methods to improve these physiological facets prior to surgery would provide a plausible means to improve elective surgical outcomes in our ageing population.

METHOD

The way we chose to present our research to demonstrate how it will have impact was by outlining a “pathway to impact” as justified in the Introduction.

In the first section we chose a sample of our research papers presenting findings from work conducted at the University of Nottingham over the last decade on skeletal muscle physiology and metabolism, with a brief summation of the principal new bio-scientific knowledge that this body of work as a whole produced. In the second section we list the related review articles we have produced. In the third section, we summarise a further sample of our research papers, in which the new knowledge generated from the work in section one was mobilised along the translational pipeline in early translational research. In this section we included studies where interventions had been developed and evaluated, where we collaborated with clinicians as the professional group likely to apply our knowledge to produce impact, and where we involved clinical settings (i.e. patients rather than ‘healthy’ volunteers). In the Discussion section of this report we speculated briefly on the steps needed to achieve our desired impact and the possible extent of this.
RESULTS

Skeletal muscle physiology and metabolism bio-scientific research

We have elucidated a number of mechanisms by which exercise and nutrition, independently and collectively change cellular, organ and whole-body level functions, and determined limitations (i.e., ageing and disease) to these adaptive responses. These findings include the discovery of two key concepts related to skeletal muscle mass maintenance: the “muscle-full” phenomenon whereby muscle protein synthesis “switches off” despite continued availability of amino acids; and anabolic resistance, the diminished response of skeletal muscle to the anabolic stimuli of exercise and nutrition with advancing age and in some disease states. This body of work also demonstrates acute anabolic responses to different doses and temporal feeding regimes, and the potential role of vascular delivery in this. Additionally, these findings offer new insight into the molecular and metabolomic transducers of skeletal muscle remodelling, with state-of-the-art method platforms (primarily, but not limited to mass-spectrometry based techniques) and diverse models (i.e. rodents through to masters athletes) developed and used to uncover these findings. Table 1 lists 32 papers which demonstrate the breadth and extent of this work.

Table 1. Musculoskeletal bio-scientific research papers

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## Bio-scientific Articles

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Bio-scientific Articles


Knowledge synthesis activity

In Table 2 we list 16 of our review articles in the last 5 years that have synthesised our bio-scientific research findings with those of others from across the globe, to offer insight to the scientific community in this sphere, and to enable us and others to apply this knowledge along the research pipeline.

Table 2. Musculoskeletal peer-reviewed research articles

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Early translation research

In parallel with our largely mechanistic bio-science research, we have used our techniques and understanding of skeletal muscle physiology and metabolism to explore the effect of evidence-based environmental and surgical interventions on parameters related to muscle health and cardiorespiratory fitness (CRF) in older adults and surgical patients. This work demonstrated that the ‘anabolic resistance’ of advancing age discovered through our biobehavioral research was also present in the muscle of colorectal cancer patients while the tumour burden was in situ; yet largely alleviated by surgical resection. This anabolic resistance was associated with muscle inflammation, and also impaired muscle mitochondrial enzyme activity - a parameter not restored by surgical resection and, as such, a potential mechanism for the reduced CRF seen for some time after cancer surgery.
Further, we have undertaken early clinical intervention trials of (primarily) exercise and nutrition (but also pharmacological) interventions in older adults age-matched to those most commonly presenting for major abdominal surgery, and in cancer patients prior to surgery (i.e. as ‘prehabilitation’). In addition to work showing potential benefits of both testosterone and HMB (β-hydroxy-β-methylbutyrate, a metabolite of the amino acid leucine) supplementation for muscle health in older adults, these intervention trials have allowed us to identify an exercise training regime that is feasible and effective at improving CRF and aspects of muscle health in older adults in a clinically dictated pre-surgical window. These trials have also illustrated the heterogeneous adaptive responses of patients with different types of cancer, highlighting the need for this to be considered in both future research and research translation. Table 3 lists 22 papers that illustrate our progress in this sphere.

Table 3. Early translational research papers

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## Knowledge Translation Articles

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<td>Quick and simple; psoas density measurement is an independent predictor of anastomotic leak and other complications after colorectal resection</td>
<td><em>Tech Coloproctol.</em> 2019; Feb;23(2):129-134.</td>
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<td>Does the phase of the scan matter?</td>
<td><em>Nutrition.</em> 2017 Sep;41:37-44.</td>
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<td>Physiological adaptations to resistance exercise as a function of age.</td>
<td><em>JCI Insight.</em> 2017; Sep 7;2(17):e95581.</td>
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<td>A Practical and Time-Efficient High-Intensity Interval Training Program Modifies Cardio-Metabolic Risk Factors in Adults with Risk Factors for Type II Diabetes.</td>
<td><em>Front Endocrinol (Lausanne).</em> 2017; Sep 8;8:229.</td>
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<td>A 31-day time to surgery compliant exercise training programme improves aerobic health in the elderly</td>
<td><em>Tech Coloproctol.</em> 2016; 20(6), 375-382.</td>
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<td>Preoperative carbohydrate supplementation attenuates post-surgery insulin resistance via reduced inflammatory inhibition of the insulin-mediated</td>
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DISCUSSION

We have presented a case that illustrates the pathway to impact of our research relevant to improving the outcomes of elective surgery, particularly in the growing population of older and frailer patients who are most at risk of adverse surgical outcomes. We have presented a coherent set of 70 research outputs: 32 primary research papers, 16 review articles and 22 early translational research papers. We believe that this body of literature not only demonstrates academic impact (such as the theories of ‘full muscle’ and anabolic blunting) but demonstrates that we have directed our new knowledge in a manner most likely to be impactful at a societal level.

The full extent of the potential benefits from exercise and nutrition ‘prehabilitation’ in improving outcomes after elective surgery are, of course, yet to be realised. We recognise that it would be foolhardy to assume that challenges as complex as that posed by ageing will be solved simply and swiftly. However, we show that addressing these challenges is possible, and the effects of ageing are not simply something that has to be accepted as an unalterable fact. Achieving improved outcomes in elective surgery through prehabilitation will require further research along the translational pipeline, including:

- Research to identify the factors responsible for anabolic (and adaptive) blunting in ageing and age-associated disease states such as cancer
- Feasibility research to apply existing knowledge to those likely to benefit
- Further and larger clinical- and cost-effectiveness studies of the application of different prehabilitation regimes and programmes for their delivery
- Research surrounding the implementation of those programmes
Illustrating the complex relationship between bio-scientific knowledge and impact, the potential impact of our research in muscle metabolism and physiology is not limited solely to application in pre-surgical prehabilitation: we chose this clinical problem simply as an example of potential clinical impact. This basic knowledge could be applied to produce exercise and nutritional interventions in a wide range of disease states (for example in emergency surgical patients, or in preparation for cancer chemotherapy), or as part of responses to defer or reverse sarcopenia and frailty.
REFERENCES


