ISSN 2059-3341

EMRAN: Elective Surgery Outcomes: Impact study
www.nottingham.ac.uk/emran


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

**ISSN 2059-3341**

Issue 36, 28th January 2021

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

Phillips BE[1,2,3], Lund JN[3,4], Williams JP[3,4], Lobo DN[1,3,5], Greenhaff PL[1,2,3], Smith K[1,2,3], Gladman JRF[1,2,3,5,6] and Atherton PJ[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: Dr Bethan E Phillips, University of Nottingham, Royal Derby Hospital Centre, Derby, DE22 3DT.
Email: beth.phillips@nottingham.ac.uk

**Affiliations**

1. National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre (BRC)
2. MRC-Versus Arthritis Centre for Musculoskeletal Ageing Research
3. University of Nottingham, Schools of Medicine and Life Sciences
4. University Hospitals of Derby and Burton NHS Trust
5. Nottingham University Hospitals NHS Trust
6. NIHR Applied Research Collaboration (ARC) East Midlands

## ORCID

Phillips BE: 0000-0002-1430-1870

Lund JN: 0000-0001-5195-2181

Williams JP: 0000-0001-7156-117X

Lobo DN: 0000-0003-1187-5796

Greenhaff PL: 0000-0003-4403-0490

Smith K: 0000-0001-8971-6635

Gladman JRF: 0000-0002-8506-7786

Atherton PJ: 0000-0002-7286-046X

## 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.

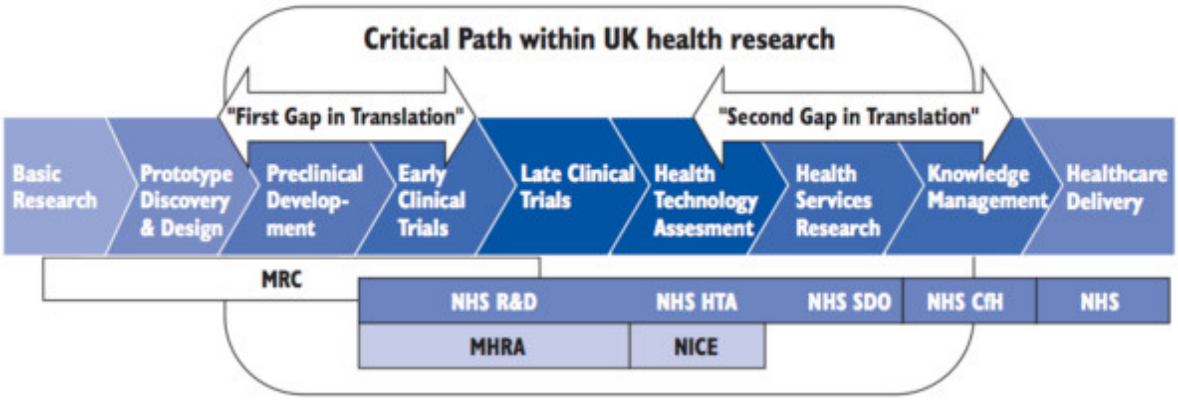


**Figure 1.** The research pipeline ([2] Chart 7.1 p99, Crown copyright)

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 $VO_{2AT}$ (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

| **Bio-scientific Articles** |
|---|
| BASS JJ, NAKHUDA A, DEANE CS, BROOK MS, WILKINSON DJ, PHILLIPS BE, PHILP A, TARUM J, KADI F, ANDERSEN D, GARCIA AM, SMITH K, GALLAGHER IJ, SZEWCZYK NJ, CLEASBY ME, ATHERTON PJ. Overexpression of the vitamin D receptor (VDR) induces skeletal muscle hypertrophy. *Mol Metab*. 2020; Aug 7:101059. |
| STOKES T, TIMMONS JA, CROSSLAND H, TRIPP TR, MURPHY K, MCGLORY C, MITCHELL CJ, OIKAWA SY, MORTON RW, PHILLIPS BE, BAKER SK, ATHERTON PJ, WAHLESTEDT C, PHILLIPS SM. Molecular Transducers of Human Skeletal Muscle Remodelling under Different Loading States. *Cell Rep*. 2020; Aug 4;32(5):107980. |
| ABDULLA H, PHILLIPS BE, WILKINSON DJ, LIMB M, JANDOVA T, BASS JJ, RANKIN D, CEGIELSKI J, SAYDA M, CROSSLAND H, WILLIAMS JP, SMITH K, IDRIS I, ATHERTON PJ. Glucagon-like peptide 1 infusions overcome anabolic resistance to feeding in older human muscle. *Aging Cell*. 2020; Aug 3:e13202. |
| WILKINSON DJ, RODRIGUEZ-BLANCO G, DUNN WB, PHILLIPS BE, WILLIAMS JP, GREENHAFF PL, SMITH K, GALLAGHER IJ, ATHERTON PJ. Untargeted metabolomics for uncovering biological markers of human skeletal muscle ageing. *Aging* (Albany NY). 2020; Jun 24;12(13):12517-12533. |
| CROSSLAND H, PIASECKI J, MCCORMICK D, PHILLIPS BE, WILKINSON DJ, SMITH K, MCPHEE JS, PIASECKI M, ATHERTON PJ. Targeted genotype analyses of GWAS-derived lean body mass and handgrip strength-associated single-nucleotide polymorphisms in elite master athletes. *Am J Physiol Regul Integr Comp Physiol*. 2020; Aug 1;319(2):R184-R194. |

| Bio-scientific Articles |
| --- |
| FARRASH W, BROOK M, CROSSLAND H, PHILLIPS BE, CEGIELSKI J, WILKINSON DJ, CONSTANTIN-TEODOSIU D, GREENHAFF PL, SMITH K, CLEASBY M, and ATHERTON PJ. Impacts of rat hindlimb Fndc5/irisin overexpression on muscle and adipose tissue metabolism. *Am J Physiol Endocrinol Metab*. 2020; Jun 1;318(6):E943-E955. |
| WILLIS CRG, AMES RM, DEANE CS, PHILLIPS BE, BOEREBOOM CL, ABDULLA H, BUKHARI SSI, LUND JN, WILLIAMS JP, WILKINSON DJ, SMITH K, KADI F, SZEWCZYK NJ, ATHERTON PJ and ETHERIDGE T. Network analysis of human muscle adaptation to aging and contraction. *Aging* (Albany NY). 2020; 12(1):740-755. |
| CROSSLAND H, SMITH K, ATHERTON PJ, WILKINSON DJ. A novel stable isotope tracer method to simultaneously quantify skeletal muscle protein synthesis and breakdown. *Metabol Open.* 2020; Mar;5:100022. |
| DEANE CS, AMES RM, PHILLIPS BE, WEEDON MN, WILLIS CRG, BOEREBOOM C, ABDULLA H, BUKHARI SSI, LUND JN, WILLIAMS JP, WILKINSON DJ, SMITH K, GALLAGHER IJ, KADI F, SZEWCZYK NJ, ATHERTON PJ and ETHERIDGE T. The acute transcriptional response to resistance exercise: impact of age and contraction mode. *Aging* (Albany NY). 2019; 11(7), 2111-2126. |
| CROSSLAND H, PEREIRA SL, SMITH K, PHILLIPS BE and ATHERTON PJ. Gene-based analysis of angiogenesis, mitochondrial and insulin-related pathways in skeletal muscle of older individuals following nutraceutical supplementation. *J Funct Foods*. 2019; 56, 216-223. |
| ABDULLA H, BASS JJ, STOKES T, GORISSEN SHM, MCGLORY C, PHILLIPS BE, PHILLIPS SM, SMITH K, IDRIS I, ATHERTON PJ. The effect of oral essential amino acids on incretin hormone production in youth and ageing. *Endocrinol Diabetes Metab*. 2019; Jul 26;2(4):e00085. |
| WILKINSON DJ, BUKHARI SSI, PHILLIPS BE, LIMB MC, CEGIELSKI J, BROOK MS, RANKIN D, MITCHELL WK, KOBAYASHI H, WILLIAMS JP, LUND J, GREENHAFF PL, SMITH K, ATHERTON PJ. Effects of leucine-enriched essential amino acid and whey protein bolus dosing upon skeletal muscle protein synthesis at rest and after exercise in older women. *Clin Nutr*. 2018; Dec;37(6 Pt A):2011-2021. |
| CROSSLAND H, SMITH K, ATHERTON PJ, WILKINSON DJ. The metabolic and molecular mechanisms of hyperammonaemia- and hyperethanolaemia-induced protein catabolism in skeletal muscle cells. *J Cell Physiol*. 2018; Dec;233(12):9663-9673. |
| MITCHELL WK, PHILLIPS BE, HILL I, GREENHAFF P, LUND JN, WILLIAMS JP, RANKIN D, WILKINSON DJ, SMITH K, ATHERTON PJ. Human skeletal muscle is refractory to the anabolic effects of leucine during the postprandial muscle-full period in older men. *Clin Sci* (Lond). 2017; Oct 27;131(21):2643-2653. |
| BROOK MS, WILKINSON DJ, MITCHELL WK, LUND JL, PHILLIPS BE, SWECZYK NJ, KAINULAINEN H, LENSU S, KOCH LG, BRITTON SL, GREENHAFF PL, SMITH K, ATHERTON PJ. A novel $D_2O$ tracer method to quantify RNA turnover as a biomarker of de novo ribosomal biogenesis, in vitro, in animal models, and in human skeletal muscle. *Am J Physiol Endocrinol Metab*. 2017; 313(6):E681-E689. |
| ATHERTON PJ, KUMAR V, SELBY AL, RANKIN D, HILDEBRANDT W, PHILLIPS BE, WILLIAMS JP, HISCOCK N, SMITH K. Enriching a protein drink with leucine augments muscle protein synthesis after resistance exercise in young and older men. *Clin Nutr*. 2017; 36(3):888-895. |

| Bio-scientific Articles |
| --- |
| CROSSLAND H, SMITH K, ATHERTON PJ, WILKINSON DJ. A novel puromycin decorporation method to quantify skeletal muscle protein breakdown: A proof-of-concept study. *Biochem Biophys Res Commun*. 2017; Dec 16;494(3-4):608-614. |
| PHILLIPS BE, ATHERTON PJ, VARADHAN K, LIMB MC, WILLIAMS JP, SMITH K. Acute cocoa flavanol supplementation improves muscle macro- and microvascular but not anabolic responses to amino acids in older men. *Appl Physiol Nutr Metab*. 2016; 41(5), 548-56. |
| MITCHELL WK, PHILLIPS BE, WILKINSON DJ, WILLIAMS JP, RANKIN D, LUND JN, SMITH K, ATHERTON PJ. Supplementing essential amino acids with the nitric oxide precursor, l-arginine, enhances skeletal muscle perfusion without impacting anabolism in older men. *Clin Nutr*. 2016; 36(6):1573-1579. |
| BROOK MS, WILKINSON DJ, MITCHELL WK, LUND JN, PHILLIPS BE, SZEWCZYK NJ, GREENHAFF PL, SMITH K, ATHERTON PJ. Synchronous deficits in cumulative muscle protein synthesis and ribosomal biogenesis underlie age-related anabolic resistance to exercise in humans. *J Physiol*. 2016; 594(24), 7399-741. |
| BELTRAN VALLS MR, WILKINSON DJ, NARICI MV, SMITH K, PHILLIPS BE, CAPOROSSI D, ATHERTON PJ. Protein Carbonylation and Heat Shock Proteins in Human Skeletal Muscle: Relationships to Age and Sarcopenia. *J Gerontol, Series A*. 2015; 70(2), 174-81. |
| PHILLIPS BE, ATHERTON PJ, VARADHAN K, LIMB MC, WILKINSON DJ, SJØBERG KA, SMITH K, WILLIAMS JP. The effects of resistance exercise training on macro- and micro-circulatory responses to feeding and skeletal muscle protein anabolism in older men. *J Physiol*. 2015; 593(12), 2721-34. |
| BUKHARI SS, PHILLIPS BE, WILKINSON DJ, LIMB MC, RANKIN D, MITCHELL WK, KOBAYASHI H, GREENHAFF PL, SMITH K, ATHERTON PJ. Intake of low-dose leucine-rich essential amino acids stimulates muscle anabolism equivalently to bolus whey protein in older women at rest and after exercise. *Am J Physiol Endocrinol Metab*. 2015; 308(12), E1056-65. |
| WILKINSON DJ, CEGIELSKI J, PHILLIPS BE, BOEREBOOM C, LUND JN, ATHERTON PJ, SMITH K. Internal comparison between deuterium oxide ($D_2O$) and L-[ring-$^{13}C_6$] phenylalanine for acute measurement of muscle protein synthesis in humans. *Physiol Rep*. 2015; 3(7). |
| MITCHELL WK, PHILLIPS BE, WILLIAMS JP, RANKIN D, LUND JN, SMITH K, ATHERTON PJ. A dose- rather than delivery profile-dependent mechanism regulates the "muscle-full" effect in response to oral essential amino acid intake in young men. *J Nutr*. 2015; 145(2), 207-14. |
| MITCHELL WK, PHILLIPS BE, WILLIAMS JP, RANKIN D, LUND JN, WILKINSON DJ, SMITH K, ATHERTON PJ. The impact of delivery profile of essential amino acids upon skeletal muscle protein synthesis in older men: clinical efficacy of pulse vs. bolus supply. *Am J Physiol Endocrinol Metab*. 2015; 309(5):E450-7. |
| PHILLIPS BE, ATHERTON PJ, VARADHAN K, WILKINSON DJ, LIMB M, SELBY AL, RENNIE MJ, SMITH K, WILLIAMS JP. Pharmacological enhancement of leg and muscle microvascular blood flow does not augment anabolic responses in skeletal muscle of young men under fed conditions. *Am J Physiol Endocrinol Metab*. 2014; 306(2), E168-76. |
| WILKINSON DJ, HOSSAIN T, HILL DS, PHILLIPS BE, CROSSLAND H, WILLIAMS J, LOUGHNA P, CHURCHWARD-VENNE TA, BREEN L, PHILLIPS SM, ETHERIDGE T, RATHMACHER JA, SMITH K, SZEWCZYK NJ, ATHERTON PJ. Effects of leucine and its metabolite β-hydroxy-β-methylbutyrate on human skeletal muscle protein metabolism. *J Physiol*. 2013; 591(Pt 11), 2911-23. |

| Bio-scientific Articles |
|---|
| MITCHELL WK, PHILLIPS BE, WILLIAMS JP, RANKIN D, SMITH K, LUND JN, ATHERTON PJ. Development of a new Sonovue™ contrast-enhanced ultrasound approach reveals temporal and age-related features of muscle microvascular responses to feeding. *Physiol Rep*. 2013; Oct;1(5):e00119. |
| AWAD S, STEPHENS F, SHANNON C, LOBO DN. Perioperative perturbations in carnitine metabolism are attenuated by preoperative carbohydrate treatment: Another mechanism by which preoperative feeding may attenuate development of postoperative insulin resistance. *Clin Nutr.* 2012 Oct;31(5):717-20. |
| AWAD S, CONSTANTIN-TEODOSIU D, CONSTANTIN D, ROWLANDS BJ, FEARON KC, MACDONALD IA, LOBO DN. Cellular mechanisms underlying the protective effects of preoperative feeding: a randomized study investigating muscle and liver glycogen content, mitochondrial function, gene and protein expression. *Ann Surg.* 2010 Aug;252(2):247-53. |
| ATHERTON PJ, ETHERIDGE T, WATT PW, WILKINSON D, SELBY A, RANKIN D, SMITH K, RENNIE MJ. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signalling. *Am J Clin Nutr*. 2010; Nov;92(5):1080-8. |

**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

| Review Articles |
|---|
| DEANE CS, BASS JJ, CROSSLAND H, PHILLIPS BE, ATHERTON PJ. Animal, Plant, Collagen and Blended Dietary Proteins: Effects on Musculoskeletal Outcomes. *Nutrients*. 2020; Sep 1;12(9):E2670. |
| BROOK MS, WILKINSON DJ, ATHERTON PJ. An update on nutrient modulation in the management of disease-induced muscle wasting: evidence from human studies. *Curr Opin Clin Nutr Metab Care*. 2020; May;23(3):174-180. |
| DVORETSKIY S, LIEBLEIN-BOFF JC, JONNALAGADDA S, ATHERTON PJ, PHILLIPS BE, PEREIRA SL. Exploring the Association between Vascular Dysfunction and Skeletal Muscle Mass, Strength and Function in Healthy Adults: A Systematic Review. *Nutrients.* 2020; Mar 7;12(3):715. |
| LEVY N, GROCOTT MPW, LOBO DN. Restoration of function: the holy grail of peri-operative care. *Anaesthesia.* 2020 Jan;75 Suppl 1:e14-e17. |
| BROOK MS, WILKINSON DJ, SMITH K, ATHERTON PJ. It's not just about protein turnover: the role of ribosomal biogenesis and satellite cells in the regulation of skeletal muscle hypertrophy. *Eur J Sport Sci.* 2019; Aug;19(7):952-963. |
| WILKINSON DJ, PIASECKI M, ATHERTON PJ. The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. *Ageing Res Rev*. 2018; Nov;47:123-132. |

| Review Articles |
|---|
| BLACKWELL JEM, DOLEMAN B, HERROD PJJ, RICKETTS S, PHILLIPS BE, LUND JN, WILLIAMS JP. Short-Term (<8 wk) High-Intensity Interval Training in Diseased Cohorts. *Med Sci Sports Exerc*. 2018; Sep;50(9):1740-1749. |
| BROOK MS, WILKINSON DJ, ATHERTON PJ, SMITH K. Recent developments in deuterium oxide tracer approaches to measure rates of substrate turnover: implications for protein, lipid, and nucleic acid research. *Curr Opin Clin Nutr Metab Care*. 2017; Sep;20(5):375-381. |
| DEANE CS, WILKINSON DJ, PHILLIPS BE, SMITH K, ETHERIDGE T, ATHERTON PJ. "Nutraceuticals" in relation to human skeletal muscle and exercise. *Am J Physiol Endocrinol Metab.* 2017; Apr 1;312(4):E282-E299. |
| WILKINSON DJ, BROOK MS, SMITH K, ATHERTON PJ. Stable isotope tracers and exercise physiology: past, present and future. *J Physiol.* 2017; May 1;595(9):2873-2882. |
| RUDRAPPA SS, WILKINSON DJ, GREENHAFF PL, SMITH K, IDRIS I, ATHERTON PJ. Human Skeletal Muscle Disuse Atrophy: Effects on Muscle Protein Synthesis, Breakdown, and Insulin Resistance-A Qualitative Review. *Front Physiol*. 2016; Aug 25;7:361. |
| MITCHELL WK, WILKINSON DJ, PHILLIPS BE, LUND JN, SMITH K, ATHERTON PJ. Human Skeletal Muscle Protein Metabolism Responses to Amino Acid Nutrition. *Adv Nutr.* 2016; Jul 15;7(4):828S-38S. |
| CLEASBY ME, JAMIESON PM, ATHERTON PJ. Insulin resistance and sarcopenia: mechanistic links between common co-morbidities. *J Endocrinol*. 2016; May;229(2):R67-81. |
| ABDULLA H, SMITH K, ATHERTON PJ, IDRIS I. Role of insulin in the regulation of human skeletal muscle protein synthesis and breakdown: a systematic review and meta-analysis. *Diabetologia*. 2016; Jan;59(1):44-55. |
| BROOK MS, WILKINSON DJ, PHILLIPS BE, PEREZ-SCHINDLER J, PHILP A, SMITH K, ATHERTON PJ. Skeletal muscle homeostasis and plasticity in youth and ageing: impact of nutrition and exercise. *Acta Physiol* (Oxf). 2016; Jan;216(1):15-41. |
| TEWARI N, AWAD S, MACDONALD IA, LOBO DN. Obesity-related insulin resistance: implications for the surgical patient. *Int J Obes* (Lond). 2015; Nov;39(11):1575-88. |

**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 bio-scientific 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

| **Knowledge Translation Articles** |
|---|
| HERROD PJJ, BLACKWELL JEM, BOEREBOOM CL, ATHERTON PJ, WILLIAMS JP, LUND JN, PHILLIPS BE. The time-course of physiological adaptations to high intensity interval training in older adults. *Aging Medicine*. 2020; in Press. |
| BLACKWELL JEM, DOLEMAN B, BOEREBOOM CL, MORTON A, WILLIAMS S, ATHERTON P, SMITH K, WILLIAMS JP, PHILLIPS BE, LUND JN. High-intensity interval training produces a significant improvement in fitness in less than 31 days before surgery for urological cancer: a randomised control trial. *Prostate Cancer Prostatic Dis.* 2020; epub ahead of print. |
| T HOSSAIN, BE PHILLIPS, B DOLEMAN, JN LUND, JP WILLIAMS. A double-blind randomized controlled trial of the effects of eicosapentaenoic acid supplementation on muscle inflammation and physical function in patients undergoing colorectal cancer resection. *Clin Nutr*. 2020; 39(7):2055-2061. |
| ROLLINS KE, GOPINATH A, AWWAD A, MACDONALD IA, LOBO DN. Computed tomography-based psoas skeletal muscle area and radiodensity are poor sentinels for whole L3 skeletal muscle values. *Clin Nutr.* 2020; Jul;39(7):2227-2232. |
| ATKINS R, CONSTANTIN-TEODOSIU D, VARADHAN KK, CONSTANTIN D, LOBO DN, GREENHAFF PL. Major elective abdominal surgery acutely impairs lower limb muscle pyruvate dehydrogenase complex activity and mitochondrial function. *Clin Nutr.* 2020; Jul 14:S0261-5614(20)30353-8. |
| BOEREBOOM CL, BLACKWELL JEM, WILLIAMS JP, PHILLIPS BE, LUND JN. Short-term pre-operative high-intensity interval training does not improve fitness of colorectal cancer patients. *Scand J Med Sci Sports*. 2019; 29(9), 1383-1391. |

| Knowledge Translation Articles |
|---|
| HERROD PJJ, BOYD-CARSON H, DOLEMAN B, TROTTER J, SCHLICHTEMEIER S, SATHANAPALLY G, SOMERVILLE J, WILLIAMS JP, LUND JN. Quick and simple; psoas density measurement is an independent predictor of anastomotic leak and other complications after colorectal resection. *Tech Coloproctol*. 2019; Feb;23(2):129-134. |
| GHARAHDAGHI N, RUDRAPPA S, BROOK MS, IDRIS I, CROSSLAND H, HAMROCK C, ABDUL AZIZ MH, KADI F, TARUM J, GREENHAFF PL, CONSTANTIN-TEODOSIU D, CEGIELSKI J, PHILLIPS BE, WILKINSON DJ, SZEWCZYK NJ, SMITH K, ATHERTON PJ. Testosterone therapy induces molecular programming augmenting physiological adaptations to resistance exercise in older men. *J Cachexia Sarcopenia Muscle*. 2019; 10(6), 1276-1294. |
| DIN USU, BROOK MS, SELBY A, QUINLAN J, BOEREBOOM C, ABDULLA H, FRANCHI M, NARICI MV, PHILLIPS BE, WILLIAMS JW, RATHMACHER JA, WILKINSON DJ, ATHERTON PJ, SMITH K. A double-blind placebo-controlled trial into the impacts of HMB supplementation and exercise on free-living muscle protein synthesis, muscle mass and function, in older adults. *Clin Nutr.* 2019; Oct;38(5):2071-2078. |
| TEWARI N, AWAD S, DUŠKA F, WILLIAMS JP, BENNETT A, MACDONALD IA, LOBO DN. Postoperative inflammation and insulin resistance in relation to body composition, adiposity and carbohydrate treatment: A randomised controlled study. *Clin Nutr.* 2019; Feb;38(1):204-212. |
| VARADHAN KK, CONSTANTIN-TEODOSIU D, CONSTANTIN D, GREENHAFF PL, LOBO DN. Inflammation-mediated muscle metabolic dysregulation local and remote to the site of major abdominal surgery. *Clin Nutr*. 2018; Dec;37(6 Pt A):2178-2185. |
| TEWARI N, AWAD S, MACDONALD IA, LOBO DN. A comparison of three methods to assess body composition. *Nutrition.* 2018 Mar;47:1-5. |
| ROLLINS KE, JAVANMARD-EMAMGHISSI H, AWWAD A, MACDONALD IA, FEARON KCH, LOBO DN. Body composition measurement using computed tomography: Does the phase of the scan matter? *Nutrition.* 2017 Sep;41:37-44. |
| CEGIELSKI J, BROOK MS, QUINLAN JI, WILKINSON DJ, SMITH K, ATHERTON PJ, PHILLIPS BE. A 4-week, lifestyle-integrated, home-based exercise training programme elicits improvements in physical function and lean mass in older men and women: a pilot study. *F1000Res*. 2017; Jul 26;6:1235. |
| PHILLIPS BE, WILLIAMS JP, GREENHAFF PL, SMITH K, ATHERTON PJ. Physiological adaptations to resistance exercise as a function of age. *JCI Insight*. 2017; Sep 7;2(17):e95581. |
| PHILLIPS BE, KELLY BM, LILJA M, PONCE-GONZÁLEZ JG, BROGAN RJ, MORRIS DL, GUSTAFSSON T, KRAUS WE, ATHERTON PJ, VOLLAARD NBJ, ROOYACKERS O, TIMMONS JA. A Practical and Time-Efficient High-Intensity Interval Training Program Modifies Cardio-Metabolic Risk Factors in Adults with Risk Factors for Type II Diabetes. *Front Endocrinol* (Lausanne). 2017; Sep 8;8:229. |
| BOEREBOOM CL, PHILLIPS BE, WILLIAMS JP, LUND JN. A 31-day time to surgery compliant exercise training programme improves aerobic health in the elderly *Tech Coloproctol*. 2016; 20(6), 375-382. |
| NYASAVAJJALA SM, PHILLIPS BE, LUND JN, WILLIAMS JP. Creatinine and myoglobin are poor predictors of anaerobic threshold in colorectal cancer and health. *J Cachexia Sarcopenia Muscle*. 2015; Jun;6(2):125-31. |
| GJESSING PF, CONSTANTIN-TEODOSIU D, HAGVE M, LOBO DN, REVHAUG A, IRTUN O. Preoperative carbohydrate supplementation attenuates post-surgery insulin resistance via reduced inflammatory inhibition of the insulin-mediated |

| Knowledge Translation Articles |
|---|
| restraint on muscle pyruvate dehydrogenase kinase 4 expression. *Clin Nutr.* 2015; Dec;34(6):1177-83. |
| WILLIAMS JP, NYASAVAJJALA SM, PHILLIPS BE, CHAKRABARTY M, LUND JN. Surgical resection of primary tumour improves aerobic performance in colorectal cancer. *J Eur Soc Surg Oncol and Br Assoc Surg Oncol*. 2014; 40(2), 220-6. |
| PHILLIPS BE, SMITH K, LIPTROT S, ATHERTON PJ, VARADHAN K, RENNIE MJ, LARVIN M, LUND JN, WILLIAMS JP. Effect of colon cancer and surgical resection on skeletal muscle mitochondrial enzyme activity in colon cancer patients: a pilot study. *J Cachexia Sarcopenia Muscle*. 2013; 4(1), 71-7. |
| WILLIAMS JP, PHILLIPS BE, SMITH K, ATHERTON, PJ, RANKIN D, SELBY AL, LIPTROT S, LUND J, LARVIN M, RENNIE MJ. Effect of tumor burden and subsequent surgical resection on skeletal muscle mass and protein turnover in colorectal cancer patients. *Am Journal Clin Nutr*. 2012; 96(5), 1064-1070. |

## 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

1 Economic and Social Research Council. *What is impact?* https://esrc.ukri.org/research/impact-toolkit/what-is-impact/ [Last accessed 23rd September 2020]

2 Sir David Cooksey. A review of UK health research funding. HMSO. December 2006. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/228984/0118404881.pdf [Last accessed 23rd September 2020]

3 Office for National Statistics (ONS) People, population and community report. *https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/changesintheolderresidentcarehomepopulationbetween2001and2011/2014-08-01* (accessed 21.09.20).

4 Department for Work and Pensions and the Department for Communities and Local Government- Supported accommodation review. *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/572454/rr927-supported-accommodation-review.pdf* (accessed 21.09.20).

5 Clegg A, Young J, Iliffe S, Rikkert M, Rockwood K. Frailty in elderly people. *The Lancet.* 2013; Mar 02:752-762.

6 Poh A and Teo S. Utility of frailty screening tools in older surgical patients. Ann *Geriatr Med Res*. 2020; Jun 24(2):75-82.

7 Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O et al., Sarcopenia: revised European consensus on definition and diagnosis. Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. *Age Ageing*. 2019 Jan; 1;48(1):16-31.

8 Jackson AS, Sui X, Hebert JR, Church TS, Blair SN. Role of lifestyle and aging on the longitudinal change in cardiorespiratory fitness. *Arch Intern Med*. 2009; Oct 26;169(19): 1781-1787.

9 Marzetti E et al. on behalf of the SPRINTT Consortium. Sarcopenia: an overview. *Aging Clin Exp Res*. 2017;29:11-17.

10 Gander J, Lee C, Sui X, Hebert JR, Hooker SP, Blair SN. Self-rated health status and cardiorespiratory fitness as predictors of mortality in men. *Br J Sports Med.* 2011;45:1095–1100.

11 Yarasheski KE. Managing sarcopenia with progressive resistance exercise training. *J Nutr Health Aging.* 2001;6:1-8.

12 Steinhaus A, Dustman RE, Ruhlings RO, Emmerson RY, Johnson SC et al. Cardiorespiratory fitness of young and older active and sedentary men. *Br J Sports Med.* 1988;22(4):163-166.

13 Yang R, Wolfson M, Lewis MC. Unique aspects of the elderly surgical population: an anaesthesiologist's perspective. *Geriatr Orthop Surg Rehabil*. 2011; Mar 2(2):56-64.

14 National cancer intelligence network – Major surgical resections England 2004-2006 report. *https://ncin.org.uk (NCIN_Major_surgical_resections_report_web_v2%20.pdf)* (accessed 21.09.20).

15 Access all ages: Assessing the impact of age on access to surgical treatment. *https://rcseng.ac.uk (access_all_ages%20.pdf)* (accessed 21.09.20).

16 Prentis JM, Trenell MI, Vasdev N, French R, Dines G et al. Impaired cardiopulmonary reserve in an elderly population is related to postoperative morbidity and length of hospital stay after radical cystectomy. *BJU Int*. 2013; Jul;112(2):E13-19.

17 Snowden CP, Prentis J, Jacques B, Anderson H, Manas D et al. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. *Ann Surg*. 2013; Jun;257(6):999-1004.

18 West MA, Parry MG, Lythgoe D, Barben CP, Kemp GJ et al. Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. *Br J Surg*. 2014; Aug;101(9):1166-1172.

19 Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest*. 1993; 104: 701-704.

20 Hennis PJ, Meale PM, Hurst RA, O'Doherty AF, Otto J et al. Cardiopulmonary exercise testing predicts postoperative outcome in patients undergoing gastric bypass surgery. *Br J Anaesth.* 2012; Oct;109(4):566-571.

21 Tolchard S, Angell J, Pyke M, Lewis S, Dodds N et al. Cardiopulmonary reserve as determined by cardiopulmonary exercise testing correlates with length of stay and predicts complications after radical cystectomy. *BJU Int* 2015;115:554–561.

22 Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT et al. Randomized clinical trial of prehabilitation before planned liver resection. *Br J Surg*. 2016; Apr;103(5):504-512.

23 Delivering cancer waiting times: A good practice guide. https://www.england.nhs.uk/wp-content/uploads/2015/03/delivering-cancer-wait-times.pdf

24 Bhalla A, Williams JP, Hurst NG, Speake WJ, Tierney GM et al. One-third of patients fail to return to work 1 year after surgery for colorectal cancer. *Tech Coloproctol*. 2014; Dec;18(12):1153-1159.

25 Nyasavajjala SM, Phillips BE, Lund JN, Williams JP. Creatinine and myoglobin are poor predictors of anaerobic threshold in colorectal cancer and health. *J Cachexia Sarcopenia Muscle*. 2015; Jun;6(2):125-131.