

Nutrition and physical activity countermeasures for sarcopenia: Time to get personal?

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Abstract

Population ageing is a global phenomenon. It is regarded as a major cause of upward pressure on healthcare costs. One of the greatest threats to healthy, independent ageing is sarcopenia, the progressive loss of skeletal muscle mass and function with age. Physical inactivity and poor nutrition represent crucial and imminently modifiable risk factors for sarcopenia. Resistance exercise training is the most effective method for improving muscle mass and function in older adults. Evidence indicates that resistance training-induced improvements in muscle mass, strength and function may be further augmented by certain nutrients and nutritional strategies. Ageing is associated with a reduction in the anabolic sensitivity of skeletal muscle to dietary protein ingestion and accumulating evidence indicates that older adults require protein intakes 50%–100% higher than the recommended daily allowance (0.8 g/kg/day) to preserve muscle mass and function. Protein quality, the pattern of protein intake over the day (*i.e.* per-meal protein), specific amino acids (*i.e.* leucine) and other nutrients (*i.e.* vitamin D, long-chain *n*-3 polyunsaturated fatty acids) are also key considerations. From the personalised nutrition perspective, it is now acknowledged that individual responses to nutrition/exercise interventions are highly variable, despite equivalent compliance, thus highlighting the inadequacy of a ‘one-size-fits-all’ approach. The application of personalised medicine to sarcopenia represents an exciting emerging field of research with the potential to dramatically improve patient outcomes. This approach makes use of recent developments in ‘omics’ technologies and aims to identify the factors (*i.e.* genes, key biomarkers, medical history, environment, lifestyle) that determine whether an individual is a higher or a lower responder to a particular intervention. This narrative review discusses current evidence regarding nutrition and exercise countermeasures for sarcopenia, with a specific emphasis on recent developments in personalised approaches.

Keywords: dietary protein, healthy ageing, nutrition, personalised medicine, resistance exercise, sarcopenia

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Introduction

Population ageing is a global phenomenon, with virtually every country in the world experiencing growth in

the number and proportion of older persons in their population (United Nations 2017). The number of people worldwide aged 60 years and over is projected to more than double to 2.1 billion by 2050 and more than triple to 3.1 billion by 2100 (United Nations 2017). The fastest growing segment of society is the 'oldest old'. Remarkably, the number of persons aged 80 years or over is projected to triple by 2050 and reach nearly seven times its current value by 2100 (United Nations 2017). Population ageing in many ways represents a major achievement of humankind, driven by economic, social and medical developments. Notwithstanding, the unprecedented rise in the older population also poses a major societal challenge due to the concomitant increase in age-related disability, disease and healthcare expenditure. As such, 'ensuring adults live not only longer but *healthier* lives' has become a major public health priority (WHO 2017).

The World Health Organization (WHO) defines healthy ageing 'as the process of developing and maintaining the functional ability that enables wellbeing in older age', with functional ability influenced by a person's intrinsic capacity (including all physical and mental capacities), their environment and the interactions between these (WHO 2015). Central to this definition of healthy ageing is skeletal muscle health and functionality. Skeletal muscle is fundamental to locomotion and the ability to perform the activities necessary to maintain independent living, in addition to having a number of important metabolic roles (*i.e.* glucose disposal, fat oxidation, endocrine function). It follows that one of the greatest threats to healthy, independent ageing is the progressive loss of skeletal muscle mass and function with advancing age, termed sarcopenia.

Sarcopenia

The term sarcopenia, which is derived from the Greek words *sarx*, meaning flesh, and *penia*, meaning loss, was first introduced by Irwin Rosenberg ~30 years ago (Rosenberg 1989). Although reports of the age-related loss of muscle mass date back as far as 1931 (Critchley 1931), Rosenberg recognised that this important condition was not receiving the attention it deserved and coined the term to stimulate scientific and clinical interest in the area (Rosenberg 1989). This was followed by an exponential rise in research into, and funding for, the condition and in 2016, sarcopenia was formally recognised as a disease when the WHO released an International Classification of Diseases for sarcopenia [10th revision, Clinical

Modification (ICD-10-CM) code (M62.84)]. Although there is still no global consensus on the operational definition for sarcopenia, it encompasses both quantitative (muscle mass) and qualitative (strength and function) declines in skeletal muscle (Cruz-Jentoft *et al.* 2010; Fielding *et al.* 2011). Sarcopenia constitutes a large component of physical frailty (Fried *et al.* 2001) and is an independent risk factor for physical disability (Baumgartner *et al.* 1998), falls (Baumgartner *et al.* 1998), hospitalisation (Bianchi *et al.* 2016), reduced quality of life (Trombetti *et al.* 2016) and death (Landi *et al.* 2013). The reported prevalence of sarcopenia varies widely, due to the variations between the populations studied and the various approaches used to define sarcopenia. Using the definition proposed by the European Working Group on Sarcopenia (Cruz-Jentoft *et al.* 2010), a 2014 systematic review determined that among adults aged ≥ 50 years, the prevalence of sarcopenia was 1%–29% in community-dwelling populations, with substantially higher rates (14%–33%) reported in long-term care settings (Cruz-Jentoft *et al.* 2014).

The mechanisms that contribute to sarcopenia are complex, overlapping and interdependent and may include (but are not limited to) neuromuscular deterioration (Luff 1998), alterations in endocrine function (Morley 2003), low-grade systemic inflammation (Wahlin-Larsson *et al.* 2017), changes in muscle protein turnover (Cuthbertson *et al.* 2005; Kumar *et al.* 2009), physical inactivity (Hughes *et al.* 2002; Kortebein *et al.* 2007) and poor nutrition (Visser *et al.* 2003; Houston *et al.* 2008; Fig. 1). Moreover, the contribution of each of the putative mechanisms likely varies between individuals. While pharmaceutical interventions for this condition have generally been unsuccessful to date (Onder *et al.* 2009; De Spiegeleer *et al.* 2018), physical inactivity and poor nutrition represent imminently modifiable risk factors and form the basis for lifestyle-based countermeasures for sarcopenia.

Regulation of muscle mass – role of muscle protein turnover

The size of human skeletal muscle mass is determined, at least in part, by the balance between rates of muscle protein synthesis (MPS) and muscle protein breakdown (MPB), processes collectively referred to as muscle protein turnover. The balance between these two processes fluctuates over the day in response to anabolic stimuli (*i.e.* feeding, muscle contraction) (Rennie *et al.* 2004). In healthy younger persons, the

periods of time spent in positive ($MPS > MPB$) and negative ($MPS < MPB$) net muscle protein balance are approximately equivalent, thereby serving to maintain a stable muscle mass (Rennie *et al.* 2004). Ageing, however, is characterised by a disturbance in skeletal muscle protein turnover, whereby rates of MPB chronically exceed rates of MPS (Rennie *et al.* 2004). The available data in humans suggest that in normal (non-pathological) ageing, this imbalance is primarily driven by an attenuated response of MPS to normally robust anabolic stimuli such as protein/amino acid intake (Cuthbertson *et al.* 2005; Moore *et al.* 2015; Wall *et al.* 2015) and resistance exercise (Kumar *et al.* 2009). This phenomenon, termed ‘anabolic resistance’, is now established as a key contributor to sarcopenic muscle loss. As such, strategies targeted at alleviating age-related declines in muscle mass often aim to do so by enhancing MPS rates.

Physical activity

Physical activity is widely considered to be the most influential modifiable lifestyle factor affecting the change of muscle mass and function with age. Indeed, reductions in physical activity levels (Sun *et al.* 2013) and increases in sedentary behaviour (Jefferis *et al.* 2015; Shad *et al.* 2016) that accompany ageing are central drivers of the decline in muscle mass and function across the lifespan (Breen *et al.* 2013; Gianoudis *et al.* 2015; McKendry *et al.* 2018). On top of this, older adults are susceptible to periods of muscle disuse (*e.g.* due to bed-rest in illness or following injury) that are associated with accelerated declines in muscle mass and strength (Kortebein *et al.* 2007). Importantly, disuse events tend to be followed by incomplete recovery in older adults (Suetta *et al.* 2009) meaning that the cumulative effect of these events over the lifespan, particularly in combination with chronic sedentary behaviour, may be an important contributor to the onset of impaired mobility in ageing (English & Paddon-Jones 2010).

Resistance exercise, defined as exercising muscles against an external force (Liu & Latham 2009), is the most effective strategy to counteract sarcopenia. Resistance exercise results in a robust increase in MPS rates following the exercise bout (Rennie *et al.* 2004). Resistance exercise also sensitises the muscle protein synthetic machinery to protein feeding, meaning that when a protein-containing meal is consumed after resistance exercise more of the ingested amino acids are incorporated into newly synthesised skeletal muscle protein (Pennings *et al.* 2011). Of note, the

enhanced sensitivity of MPS to protein ingestion following intense resistance exercise persists for 24–48 hours following the exercise bout (Burd *et al.* 2011; Murphy *et al.* 2015a), indicating that prior exercise can augment the MPS response not only to the post-exercise meal but to every meal consumed over a 1- to 2-day period. It is now well established through meta-analyses and systematic reviews that resistance training is an effective means of improving muscle mass (Peterson *et al.* 2011), strength (Liu & Latham 2009; Peterson *et al.* 2010) and physical performance (Liu & Latham 2009), and reducing disability risk (Liu & Latham 2011) and functional limitation (Liu & Latham 2009) in older adults. Moreover, resistance training is successful in people in their nineties (Serra-Rexach *et al.* 2011) and in those living in residential care (Fiatarone *et al.* 1990). Further illustrating the potency of resistance training, it has been shown that the incorporation of a relatively low dose of resistance exercise during disuse events (such as reduced daily step count, limb immobilisation, bed-rest) can attenuate or even abolish the decline in MPS (Devries *et al.* 2015), muscle mass (Oates *et al.* 2010; Devries *et al.* 2015) and strength (Bamman *et al.* 1998; Oates *et al.* 2010), and can attenuate inactivity-induced alterations in muscle fibre morphology (Moore *et al.* 2018).

Aerobic exercise may also improve the MPS response to dietary protein intake (Timmerman *et al.* 2012) and muscle mass and function (Harber *et al.* 2009) among older adults. On the other hand, a recent meta-analysis showed that masters (veteran)

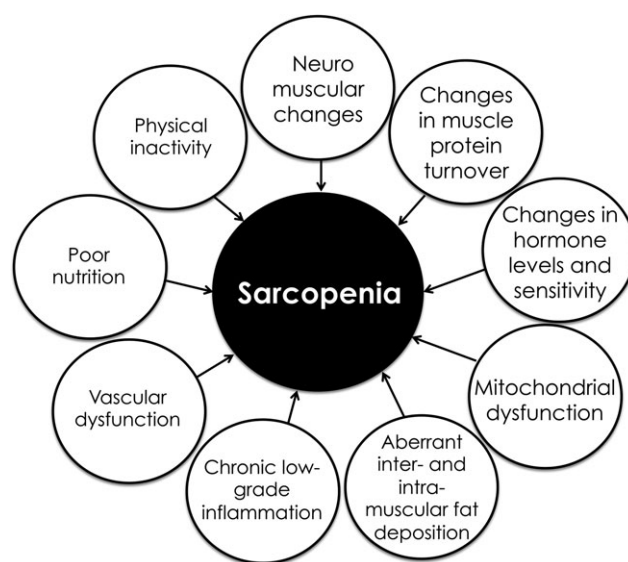


Figure 1 Aetiological factors associated with sarcopenia.

strength/power athletes, but not masters endurance athletes, exhibited attenuated strength loss compared to untrained, age-matched controls (McKendry *et al.* 2018). This suggests that chronic endurance exercise does not confer the same protection against age-related declines in muscular strength as resistance training (McKendry *et al.* 2018). Furthermore, randomised clinical trials demonstrate superior gains in strength in older adults following resistance training compared to aerobic training (Liu & Latham 2009). As such, multi-modal exercise strategies combining resistance training to conserve muscular strength and aerobic training to maintain cardiorespiratory fitness may be optimal for preserving physical function and health in ageing. This approach may be further enhanced if combined with a reduction in sedentary time. Indeed, the potential for breaking up or reducing sedentary time as a strategy to preserve skeletal muscle anabolic sensitivity, muscle mass and physical function represents an emerging area of investigation (Shad *et al.* 2016).

Nutrition

A growing body of evidence links nutritional intake to muscle mass, strength and physical performance in older adults indicating that it has an important role to play in the prevention and treatment of sarcopenia (Robinson *et al.* 2017). Evidence also shows that certain nutrients may augment resistance training induced improvements in muscle mass and function, suggesting that combined nutrition and physical activity strategies may be particularly effective for combatting age-related declines.

Daily protein intake

Dietary protein is a nutrient of particular interest as a regulator of skeletal muscle mass and the most appropriate intake for older adults is an issue of intense scientific debate (Volpi *et al.* 2013; Paddon-Jones & Leidy 2014; Traylor *et al.* 2018). The recommended intake for dietary protein is 0.83 g/kg bodyweight/day (WHO 2007). This value is derived from a meta-analysis of nitrogen balance studies (Rand *et al.* 2003) and reflects the estimated intake necessary to cover daily protein losses and prevent deficiency in 97.5% of the population. Numerous other national and international authorities [*i.e.* European Food Safety Authority (EFSA), UK Department of Health, US Institute of Medicine (IOM)] have recommended similar values ranging from 0.75

to 0.83 g protein/kg/day (EFSA 2012; Department of Health 1991; IOM 2005). Importantly, these values are recommended for all healthy adults regardless of age. However, it is noteworthy that only one study included in the meta-analysis used to determine protein requirements was conducted in older adults (Uauy *et al.* 1978; Rand *et al.* 2003). These recommendations have been widely criticised on the basis that (1) the nitrogen balance method is inherently flawed and (2) there is no association between being in nitrogen balance and any important physiologic or health outcome (Traylor *et al.* 2018). Moreover, given the importance of dietary protein as a regulator of MPS and muscle mass, it has been argued that for older adults, the minimum amount of protein required to prevent deficiency (and maintain nitrogen balance) is unlikely to represent the protein requirement to optimise the preservation of muscle mass and function (Bauer *et al.* 2013; Deutz *et al.* 2014). Indeed, a growing body of evidence supports that older adults require more protein than the current recommendations and a number of expert groups have advocated for protein intakes of 1.0–1.2 g/kg/day in healthy older adults, specifically to support the preservation of muscle mass and potentially strength (Bauer *et al.* 2013; Deutz *et al.* 2014).

A strong theoretical basis for why older adults might require higher protein intakes to attenuate the age-related decline in muscle mass comes from evidence of anabolic resistance to dietary protein consumption in older adults, whereby the transient MPS response to ingested protein is suppressed relative to younger individuals, particularly at lower protein doses (Moore *et al.* 2015; Wall *et al.* 2015). For example, while a protein dose of approximately 0.24 g/kg is sufficient to maximise postprandial MPS rates in younger adults, this protein dose is associated with a blunted MPS response in older individuals (Moore *et al.* 2015). Nonetheless, it appears that healthy older adults can overcome the anabolic resistance to protein feeding and achieve MPS rates similar to those of younger adults if a larger dose of protein is ingested (~0.4 g protein/kg; Moore *et al.* 2015). Further supporting a beneficial impact of protein intake above the current recommendations (~0.8 g/kg/day) on MPS, Kim *et al.* (2015) demonstrated higher rates of MPS in older adults over a 24-hour period when they consumed 1.5 g/kg/day compared to 0.8 g/kg/day. A recent randomised controlled trial (RCT) compared the impact of a diet providing the Recommended Daily Allowance (RDA; 0.8 g/kg/day) or twice the RDA for dietary protein on muscle mass and

function in men aged >70 years (Mitchell *et al.* 2017). Following the 10-week controlled diet, which imposed a slight energy deficit of ~200 kcal/day, appendicular lean mass [assessed by dual-energy X-ray absorptiometry (DXA)] decreased in the group that consumed the RDA (~600 g) but not in the group that consumed twice the RDA. In addition, whole-body lean mass and knee-extensor peak power output was increased in the group that consumed twice the RDA (Mitchell *et al.* 2017). Consistent with these data, in a 14-week intervention in which healthy, older men and women were fed the RDA for protein, participants experienced a decrease in mid-thigh muscle area despite no change in body mass (Campbell *et al.* 2001). Taken together, these data imply that the current dietary recommendation for protein may be insufficient to maintain muscle mass and physical function in ageing.

Protein supplementation

As protein needs are higher in older adults, it follows that increasing protein intake via supplementation may represent an effective strategy to improve muscle mass and function. A recent meta-analysis of double-blind RCTs assessed the effects of isolated protein and/or amino acid supplementation in older adults and reported no effects of supplementation on muscle mass and strength (Tieland *et al.* 2017). However, it is important to note that habitual protein intake (in the five trials that recorded it) was higher at the outset (1.0 g/kg/day) (Tieland *et al.* 2017). This level of protein intake might be too high to observe any additional effects of dietary protein or amino acid supplementation on muscle mass or strength, as opposed to supplementing individuals below or at the RDA. Moreover, an imperative consideration when attempting to determine the ability of protein supplementation (or indeed any nutritional intervention) to attenuate sarcopenia is the length of time over which we can expect to detect an effect. The majority of studies included in the above analysis (seven out of the eight studies) lasted ≤24 weeks. At best, in the absence of resistance exercise training, protein supplementation may be able to offset the loss of muscle mass, which occurs at a rate of ~0.5%–1.0% per year in older adults (Mitchell *et al.* 2012). As such, for a ~70 kg man with ~28 kg of muscle mass this would translate to a loss of ~0.07–0.14 kg of muscle in a 6-month period. Considering the measurement error associated with the methods used to assess changes in lean mass (DXA, bioelectrical impedance), such small

differences in changes between the protein supplemented and the placebo groups may not be detected. As such, more sensitive methodologies and/or more prolonged interventions (years) may be required to detect subtle, but potentially important, nutrition induced effects.

In addition, this meta-analysis did not include nutritional interventions with concomitant exercise intervention. As mentioned previously, resistance exercise sensitises skeletal muscle tissue allowing a greater uptake of ingested amino acids for muscle protein synthesis (Pennings *et al.* 2011). Therefore, the impact of protein supplementation may be more effective if combined with exercise. Indeed, several studies have demonstrated greater gains in muscle mass and strength in healthy and frail older adults supplemented with protein during resistance training (Tieland *et al.* 2012b; Daly *et al.* 2015). Nevertheless, a recently published meta-regression and subgroup analysis showed that protein supplementation during resistance training becomes less effective with increasing age and does not influence changes in fat-free mass in older individuals (Morton *et al.* 2018). Importantly, however, only two of the 13 studies included in the analysis provided post-exercise protein at a dose that could be considered close to optimal (35–40 g protein) to stimulate MPS and muscle mass accretion in older adults (Morton *et al.* 2018).

Protein quality

Protein quality represents another important factor that can influence skeletal muscle preservation in older adults. The 'quality' of a protein source is determined by the indispensable amino acid (IAA) composition and ileal digestibility (FAO 2011), factors that are also important determinants of a protein's ability to stimulate MPS (Tang & Phillips 2009). In general, animal-based proteins provide a better quality of protein compared to plant-based sources (IOM 2005). Protein from animal sources provides all nine of the IAA, whereas plant-based sources (with the exception of quinoa and potato) are deficient in one or more of the IAA (IOM 2005). Importantly, animal proteins generally have a higher content of leucine (van Vliet *et al.* 2015), an IAA that acts as a signal to stimulate the muscle protein synthetic machinery and appears to be a major determinant of the magnitude of the MPS response (Atherton *et al.* 2010; Devries *et al.* 2018). In addition to the differences in IAA content, lower digestibility (FAO 2011) and greater splanchnic extraction of amino acids (Fouillet *et al.* 2002; Bos

et al. 2005) may result in a smaller proportion of the amino acids ingested from plant proteins becoming available in plasma where they can serve as substrate for the synthesis of muscle.

Indeed, plant-based proteins such as soya and wheat were shown to stimulate postprandial MPS in older adults to a lesser extent than some higher quality, animal-based sources (Phillips 2012; Yang *et al.* 2012; Gorissen *et al.* 2016). However, beyond their protein content, consumption of plant-based foods is associated with numerous health benefits (Mudryj *et al.* 2014) and, in comparison with animal-derived protein sources, may be considered more environmentally sustainable (Gorissen & Witard 2017). Studies examining the influence of plant-based proteins on MPS in humans have been limited to soya and wheat, and further work is needed to determine the ability, as well as the dose dependency, of individual plant-based protein sources and foods to stimulate postprandial MPS rates in older adults. Potential ways to overcome the lower anabolic capacity of plant-based proteins include the following: ingesting a greater protein dose (Gorissen *et al.* 2016), fortifying plant-based foods with leucine (Murphy *et al.* 2016), combining plant-based proteins with higher quality (and higher leucine) animal-based sources (Reidy *et al.* 2013) and selectively combining multiple plant-based protein sources to allow for the ingestion of a 'complete' IAA profile within a single meal (van Vliet *et al.* 2015). Nonetheless, the efficacy of these purported strategies remains to be determined, and well-designed, long-term studies are required to compare the impact of different protein sources on muscle mass and function.

Per-meal protein pattern

An additional consideration is the pattern of protein intake across the day. A rationale for the importance of the 'per-meal' dose of protein comes from findings that older adults require ~0.4 g protein/kg/meal (equivalent to ~25–35 g protein/meal) to maximally stimulate MPS (Moore *et al.* 2015). This has led to speculation that an even distribution of total protein intake, with the consumption of at least 0.4 g/kg of protein at each of the daily meals, would more effectively stimulate rates of MPS throughout the day and, if practised over months and years, may slow muscle mass loss (Paddon-Jones & Rasmussen 2009; Murphy *et al.* 2015b). This contrasts with the 'skewed' pattern in which older adults typically consume their daily protein, whereby the majority of

daily protein (50%–60%) is consumed in the dinner (usually evening) meal with smaller, suboptimal amounts (~0.1–0.3 g/kg) typically consumed at the other meals (Tieland *et al.* 2012a; USDA 2018). However, despite a strong theoretical basis and cross-sectional data showing a positive association between an even pattern of protein intake and muscle mass and strength (Farsijani *et al.* 2016, 2017), these findings were not supported by a short-term (8-week) RCT comparing the impact of an even and skewed protein intake pattern on measures of muscle mass and function in men and women aged between 51 and 69 years (Kim *et al.* 2018). However, as mentioned previously, subtle, diet-induced effects on the gradual trajectory of the age-related decline in muscle mass and function would be difficult to detect after such time periods using the currently available methods. Interestingly, acute (12- to 24-hour) rates of MPS were higher with an even compared to a skewed pattern of protein intake in older adults undergoing weight loss (Murphy *et al.* 2015a), but not in those in energy balance (Kim *et al.* 2015, 2018), suggesting that the pattern of protein intake becomes increasingly important in older adults undergoing intentional (*i.e.* in obesity) or unintentional caloric restriction (*i.e.* illness, anorexia of ageing, malnutrition).

Long-chain *n*-3 polyunsaturated fatty acids

Increasing evidence suggests that long-chain *n*-3 polyunsaturated fatty acids (LC *n*-3 PUFA) [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] may have a role as a countermeasure for sarcopenia. An RCT in older men and women demonstrated a ~three-fold increase in MPS during a hyperaminoacidaemic-hyperinsulinaemic clamp in response to LC *n*-3 PUFA supplementation (1.9 g/day EPA and 1.5 g/day DHA for 12 weeks) (Smith *et al.* 2011). Corroborating these data, a follow-up double-blind RCT reported that thigh muscle volume and strength improved after 6 months of the same LC *n*-3 PUFA supplementation in healthy older adults (Smith *et al.* 2015). Importantly, the treatment effects [increases in muscle volume: 3.6% (95% CI: 0.2%–7.0%); hand-grip strength: 2.3 kg (95% CI: 0.8–3.7 kg)] were clinically relevant, equivalent to average age-related losses over a 2- to 3-year period (Smith 2016). Similarly, another double-blind RCT reported increased walking speed in post-menopausal women supplemented with 1.2 g/day LC *n*-3 PUFA, but not oleic acid, for 6 months (Hutchins-Wiese *et al.* 2013). However, it is

important to note that not all supplementation studies support a beneficial effect of LC *n*-3 PUFA on skeletal muscle outcomes in older adults. For example, in an unblinded trial of 53 older men and women, 12 weeks of supplementation with LC *n*-3 PUFA at a similar dose to the previous trial (0.66 g/day EPA + 0.44 g/day DHA) did not impact muscle mass (assessed by bioelectrical impedance analysis), handgrip strength or physical performance (Krzyżmińska-Siemaszkó *et al.* 2015).

Long-chain *n*-3 polyunsaturated fatty acids and resistance exercise

The potential for LC *n*-3 PUFA supplementation to further augment gains in muscle mass and strength with resistance training has also been investigated. Rodacki *et al.* (2012) reported greater resistance training induced improvements in strength and functional capacity among older women supplemented with fish oil (0.4 g/day EPA + 0.3 g/day DHA) compared with women who participated in the same training without supplementation. Interestingly, recent evidence suggests that the beneficial effects of fish oil supplementation during resistance training may be exclusive to females. Da Boit *et al.* (2018) reported that LC *n*-3 PUFA supplementation (2.1 g/day EPA + 0.6 g/day DHA) during 18 weeks of supervised resistance training further improved the gains in knee-extensor peak torque and muscle quality (defined in this case as peak torque relative to muscle mass) in older women, but not in older men, compared to a placebo (safflower oil). These differences were apparent despite similar increases in erythrocyte EPA and DHA content in men and women, although the inter-individual variability was large (Da Boit *et al.* 2018). Further research is needed to confirm the existence of sex-based differences in responsiveness to fish oil-derived *n*-3 PUFA, to identify the optimal dose and to determine whether skeletal muscle benefits can also be achieved via a diet rich in oily fish.

Vitamin D

Lower vitamin D status is common in older adults (ter Borg *et al.* 2015) and often co-occurs with weakness, falls and frailty in this population (Halfon *et al.* 2015). Observational studies have reported worse physical function (Bischoff-Ferrari *et al.* 2004; Wicherts *et al.* 2007) and a greater risk of decline in physical performance (Wicherts *et al.* 2007), muscle mass and grip strength (Visser *et al.* 2003) among

older adults who have lower vitamin D status. The mechanisms underpinning the effects of vitamin D on skeletal muscle are not fully understood; however, there is growing *in vitro* evidence supporting an anabolic role for vitamin D. For example, vitamin D treatment sensitises muscle cells to the stimulatory effects of leucine and insulin on MPS in culture (Salles *et al.* 2013). Recently, 30 RCTs, including 5615 individuals across a range of ages, were pooled in the largest meta-analysis on the effect of vitamin D supplementation on muscle-related outcomes to date (Beaudart *et al.* 2014). Vitamin D supplementation had a small but significant positive effect on global muscle strength, but no effect on muscle mass and muscle power (Beaudart *et al.* 2014). The effects on muscle strength were substantially more robust for participants aged 65 years and over and for those with a lower baseline serum 25-hydroxyvitamin D (25OHD) concentration (<30 nmol/l). This suggests that the benefits of vitamin D supplementation on skeletal muscle outcomes may be confined to those with lower vitamin D status (Beaudart *et al.* 2014). Consistent with these results, another meta-analysis of 17 RCTs reported that vitamin D supplementation did not impact muscle strength in adults with serum 25OHD concentration >25 nmol/l, but using pooled data from two studies of vitamin D-deficient participants [defined in this case as 25OHD <25 nmol/l], a large effect of supplementation on hip muscle strength was detected (Stockton *et al.* 2011).

Vitamin D and resistance exercise

A small number of studies have investigated whether vitamin D supplementation has the capacity to augment adaptations in resistance training in older adults. A recent meta-analysis on this topic found that vitamin D supplementation enhanced the resistance training induced increase in lower limb strength (Antoniak & Greig 2017). Interestingly, although the three studies included in this meta-analysis did not specify participant serum 25OHD concentrations as inclusion/exclusion criteria, mean baseline and post-intervention concentrations were within the 'sufficient' range (>30 nmol/l), indicating that when combined with exercise, the benefits of vitamin D supplementation may not be confined to those in the deficient range. As such, it appears that vitamin D status may be an important nutritional consideration for sarcopenia, and research is needed to identify the optimal supplementation protocol (*i.e.* dose, mode of administration, duration of supplementation).

Energy

Energy deficit negatively impacts MPS rates both in the fasted state and in response to a protein-rich meal in young and older adults (Areta *et al.* 2014; Hector *et al.* 2015; Murphy *et al.* 2015a). As a matter of concern, this blunting of MPS has been shown to occur after just 5 days of negative energy balance (Areta *et al.* 2014) and in response to even mild energy deficits (300 kcal/day) (Murphy *et al.* 2015a). Indeed, ~25% of weight lost in response to energy restriction is lean mass (Weinheimer *et al.* 2010). Moreover, this loss of lean mass is often accompanied by a decline in muscle strength (Weiss *et al.* 2007; Backx *et al.* 2015). As such, energy deficits associated with undernutrition or with weight loss interventions in obese older adults may accelerate sarcopenia and further exacerbate disability risk. Achieving energy requirements in undernourished older adults is clearly a goal of dietetic intervention. However, in obese older adults who are not acutely unwell, an energy deficit is necessary to induce fat mass loss associated with a reduction in co-morbidities, mortality and improved quality of life (Vilareal *et al.* 2005). This highlights the need for weight loss interventions in older persons that are tailored towards achieving 'high-quality' weight loss, which can be defined as the loss of bodyweight with the greatest fat-to-lean ratio (Josse *et al.* 2011). The available evidence suggests that a number of dietary strategies may help to improve MPS and promote higher quality weight loss in older adults during energy restriction. These include higher protein intakes (≥ 1.0 g protein/kg/day) (Kim *et al.* 2016), greater consumption of dairy proteins (Abargouei *et al.* 2012) and, potentially, an even distribution of protein intake across the day with the consumption of an optimal quantity of protein (~0.4 g protein/kg) at each meal (McDonald *et al.* 2015). Milder energy deficits (<500 kcal/day) and slower rates of weight loss have been shown to attenuate muscle loss compared to larger energy deficits (Garthe *et al.* 2011). However, the current literature indicates that preservation of lean mass is not possible with a dietary intervention alone (Wycherley *et al.* 2012; Backx *et al.* 2015) and studies that have included exercise (particularly resistance exercise training) as a co-intervention generally show a greater effect of higher protein intake on lean mass and strength preservation (Layman *et al.* 2005). This highlights the importance of examining combined nutrition and exercise strategies.

Sarcopenia – a need for a more personalised perspective?

In January 2015, US President Barack Obama announced a US \$215 million national Precision Medicine Initiative to 'Bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalised information we need to keep ourselves and our families healthier'. 'Precision' or 'personalised medicine' is an approach in which the individual characteristics of a patient guide treatment planning, including his or her genes, key biomarkers, medical history, environment and lifestyle. This approach has the potential to revolutionise health care by providing clinicians with new tools to more accurately customise care for individuals and to dramatically improve patient outcomes (Schork 2015). Sarcopenia represents a condition that could benefit substantially from the application of a more personalised perspective. Indeed, inter-individual variation in the rate of decline in muscle mass and strength with advancing age is well documented, pointing towards the relevance of individualised factors (*i.e.* heritability, environment, lifestyle) (Xue *et al.* 2010; Dodds *et al.* 2014). In addition, a growing body of evidence indicates that individual responses to interventions commonly employed to prevent and treat sarcopenia (*i.e.* diet and exercise) are highly variable and poorly predictable (de Roos & Brennan 2017). In the case of sarcopenia, a positive outcome for a dietary intervention is represented by either the preservation or a very slight increase in muscle mass and function. These changes occur very gradually meaning that prolonged periods of exposure are necessary to establish therapeutic efficacy and to allow a decision to continue or switch to an alternative, potentially better, treatment. Clearly, this represents a suboptimal approach to patient care. As such, the identification of biomarkers that have the capacity to predict whether an individual is likely to be a higher or lower responder to a particular nutrition strategy could have profound implications for clinical management.

Personalised nutrition

Variations in the response of individuals to different dietary components have been documented for almost a century (Ordovas *et al.* 2018). Data from RCTs investigating the impact of dietary strategies on various health outcomes generally report that ~40% of participants respond favourably (Tierney *et al.* 2011). To date, the variability in and determinants of the

individualised response to dietary interventions for sarcopenia have been under-researched and the vast majority of studies only report mean outcomes (Bischoff *et al.* 2003; Rodacki *et al.* 2012; Tieland *et al.* 2012b; Bauer *et al.* 2015; Murphy *et al.* 2015a; Smith *et al.* 2015; Zhu *et al.* 2015; Kim *et al.* 2018). As discussed previously, while there are undoubtedly important links between nutrition and sarcopenia, intervention studies often yield inconsistent results with respect to the impact of various nutritional strategies, both alone and in combination with exercise, on muscle outcomes in older adults. One of the reasons for this could be that the use of mean outcomes may mask or conflate ‘higher responder’ and ‘lower responder’ populations, thus underestimating benefit in a responsive population. Indeed, a growing body of evidence hints at the importance of a number of personal factors in determining the responsiveness of an individual to a given nutritional approach. For example, studies indicate that vitamin D supplementation, in the absence of concomitant exercise, may only be effective in older adults who exhibit low vitamin D status at baseline (Stockton *et al.* 2011; Beaudart *et al.* 2014). Obesity status may be another important determinant of the response to nutrition intervention. For example, a recent study reported that the MPS response to protein ingestion was lower in obese older men compared to age-matched lean men (Smeuninx *et al.* 2017). This suggests that high body fat levels exacerbate anabolic resistance to protein intake and could potentially influence the responsiveness of an individual to longer term protein supplementation. LC *n*-3 PUFA supplementation with an identical dose and for an identical duration is associated with marked

inter-individual variability with respect to erythrocyte EPA and DHA enrichment (Da Boit *et al.* 2018). Moreover, the effect of LC *n*-3 PUFA supplementation on muscular outcomes in older adults appears to be dependent on sex, at least when combined with resistance training (Da Boit *et al.* 2018). Taken together, these data suggest that we cannot expect a particular nutrition intervention for sarcopenia to elicit the same response in all older adults.

Personalisation and exercise

The individual response to exercise interventions may also vary. Previous work has shown substantial heterogeneity in changes in muscle mass and strength after a period of standardised resistance training, wherein some individuals seem to demonstrate exceptionally large responses and others show only a minimal response in a given training outcome (Hubal *et al.* 2005; Bamman *et al.* 2007; Davidsen *et al.* 2011). Interestingly, however, a recent study in older men and women showed that when multiple training outcomes were taken into account (*i.e.* lean mass, muscle fibre size, strength and physical function), every participant demonstrated increases in at least one outcome after 12–24 weeks of resistance training (Churchward-Venne *et al.* 2015). Recently, efforts have been made to identify a molecular signature associated with magnitude of gain in muscle mass following prolonged resistance training (Phillips *et al.* 2013). These data provide an exciting step towards establishing molecular predictors of trainability and individualising exercise prescriptions. Nonetheless, it has recently been argued that the true inter-individuality in response to

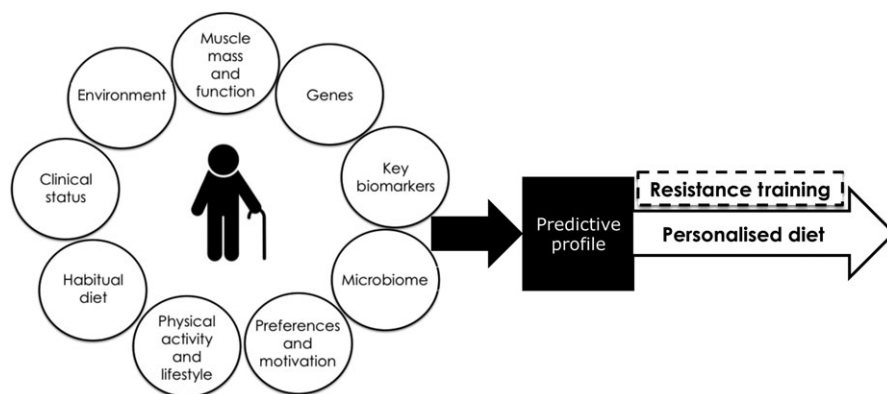


Figure 2 Conceptual illustration of personalised approaches to sarcopenia prevention and treatment. The person's genes, phenotypic profile, environment, life-style and preferences are considered to determine the nutritional approaches the individual is most likely to respond to. The dashed box indicates that resistance exercise is effective in all older adults for improving at least one outcome measure pertinent to sarcopenia (*i.e.* muscle mass, strength and/or physical performance). However, some level of personalisation within the exercise prescription (*i.e.* frequency, intensity, volume, introduction of additional modes) may further enhance the individual response.

exercise interventions may have been previously overstated, as the statistical approaches used by some studies did not adequately account for within participant random variation in the outcome measures (Atkinson *et al.* 2018). As such, further work using appropriate study designs and statistical approaches (Atkinson *et al.* 2018) is required to characterise the individual responses to exercise (and nutrition) interventions for the prevention and treatment of sarcopenia.

Personalisation and sarcopenia in the future

‘Omics’ technologies such as metabolomics, transcriptomics, proteomics and microbiomics offer an exciting opportunity for an unbiased systematic discovery route for novel response biomarkers. We propose that future studies combining omics, clinical (*i.e.* stage of sarcopenia, co-morbidities) and lifestyle (*i.e.* diet, physical activity levels, smoking status) data may have the potential to tease out the key determinants of the individual responses to various interventions for sarcopenia. Such an approach, if successful, could allow clinicians to better predict which intervention(s) will work for their patients and, ultimately, help to optimise health outcomes among the growing older population (Fig. 2).

Conclusion

Physical activity/exercise and good nutrition represent cornerstones in healthy ageing. Although the effects of nutritional interventions adults on muscular outcomes in older adults are more subtle than those of exercise, nutrition has the capacity to positively influence muscle mass and function, both alone and in combination with exercise training. Evidence, to date, points towards important roles for protein, vitamin D and LC *n*-3 PUFA, as well as energy intake. Numerous genetic, clinical, environmental and lifestyle factors may affect the response of an individual to diet and exercise interventions aimed at attenuating the age-related deterioration in muscle mass and function. The application of ‘personalised’ approaches to sarcopenia research may have the potential to optimise outcomes for older adults and support healthy ageing. However, further research is required to establish the extent to which this approach is effective.

Conflict of Interest

The authors have no conflict of interest to disclose.

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