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Review

Does nutrition play a role in the prevention and management of sarcopenia?

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SUMMARY

There is a growing body of evidence that links nutrition to muscle mass, strength and function in older adults, suggesting that it has an important role to play both in the prevention and management of sarcopenia. This review summarises the discussions of a working group [ESCEO working group meeting 8th September 2016] that met to review current evidence and to consider its implications for preventive and treatment strategies. The review points to the importance of 'healthier' dietary patterns that are adequate in quality in older age, to ensure sufficient intakes of protein, vitamin D, antioxidant nutrients and long-chain polyunsaturated fatty acids. In particular, there is substantial evidence to support the roles of dietary protein and physical activity as key anabolic stimuli for muscle protein synthesis. However, much of the evidence is observational and from high-income countries. Further high-quality trials, particularly from more diverse populations, are needed to enable an understanding of dose and duration effects of individual nutrients on function, to elucidate mechanistic links, and to define optimal profiles and patterns of nutrient intake for older adults.

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1. Background

Healthy ageing is defined by the World Health Organisation as '*the process of developing and maintaining the functional ability that enables wellbeing in older age*' [1], with functional ability made up of an individual's intrinsic capacity (a composite of all physical and mental capacities), their relevant environmental characteristics and the interactions between these. The WHO report on Ageing and Health, published in 2015, recognises the growing evidence of the importance of health-related behaviours, such as engaging in physical activity and maintaining adequate nutrition, as influences on intrinsic capacity in older age, and separate from effects on risk of non-communicable diseases. Their broader impact on intrinsic capacity is less extensively researched, but may be central to strategies to reverse or delay declines in functional ability, including conditions such as frailty [1].

Sarcopenia, the loss of muscle mass and physical function that occurs with advancing age, is a common condition that is associated with huge personal and financial costs [2,3]. Present in an estimated 50%–70% of frail individuals, it is widely recognised, now with an ICD code (ICD-10-CM) [4]. Loss of muscle mass, that results from the shrinking (atrophy) and elimination of muscle fibres, may be an expected component of the ageing process [5]. However, variation in the rates of decline in muscle mass and strength across the population [6] point to the influence of modifiable behavioural factors such as diet and lifestyle in the aetiology of sarcopenia, suggesting that these factors may be effective both for its prevention and treatment. This review documents the discussions of a working group [ESCEO working group meeting 8th September 2016] that reviewed current evidence that links diet to muscle mass, strength and physical function in older age, and considered the implications of this evidence for preventive and treatment strategies.

2. Ageing and nutrition

There is a significant decline in food and energy intake with increasing age, as energy needs decrease [7], amounting to an average fall of around 25% between the ages of 40 and 70 years [8]. Older adults may eat more slowly, consume smaller meals, and eat fewer snacks between meals than younger adults [8]. In a recent analysis of longitudinal intake data, Otsuka and colleagues showed that energy intakes fell in both men and women from their 40s–70s (Fig. 1), but notably, among men, the reduction was greater in the older age groups [9].

Declining food and energy intakes occur alongside changes in appetite and a lack of hunger, and have been described as the 'anorexia of ageing' [10]. The mechanisms are not fully understood but include a range of physiological, psychological and social factors that influence appetite and food consumption. Specific age-related changes include loss of acuity in taste, smell and sight, changes in the secretion and peripheral action of appetite hormones, effects on gastrointestinal motility, chewing and swallowing difficulties, as well as other effects of chronic disease that can affect food intake [8,10,11]. The negative consequences of these changes may be compounded by the effects of functional impairments that impact on ability to access and prepare food, psychological problems such as depression and dementia, as well as the social effects of living and eating alone [12].

Low food intakes and monotonous diets put older people at risk [13] because, as total food intake falls, for most nutrients there is a corresponding decline in intake [7]. Exact estimates of the prevalence of poor nutrition in older populations differ according to definitions used and the groups studied. However, a consistent

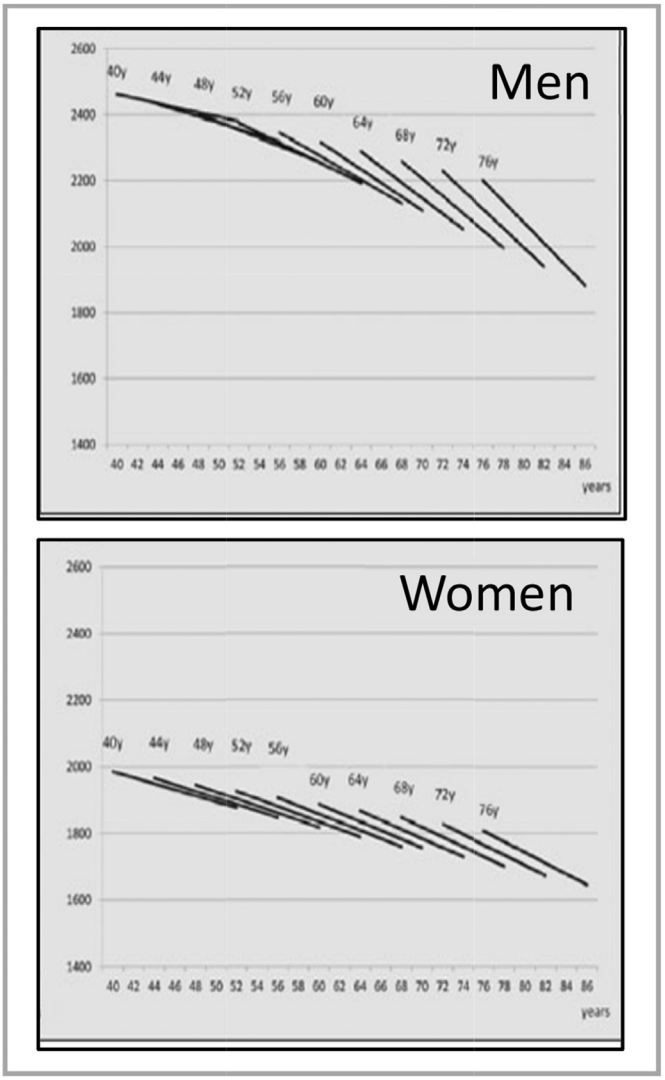

Fig. 1. Estimated linear changes in energy intake (kcal/day) in 922 men and 879 women over a 12-year follow-up period, according to (4-year) age group at baseline [9].

message from studies of community-dwelling adults is that poor nutrition is common in older age, with substantial numbers of older adults who are malnourished or at risk of malnutrition. For example, in a pooled analysis of data from 12 countries, approximately two-thirds of older study participants were identified as being at nutritional risk or malnourished [14]. The estimated economic costs of disease-related malnutrition are high [15,16]. Sarcopenia frequently co-exists with malnutrition in older patients [17], and poor nutritional status is associated with the onset of frailty [18]. Routine screening of nutritional status and early diagnosis of malnutrition in older adults is therefore essential, both in the community as well as in hospital settings. However, this may not be prioritised; for example, in the Survey of Health, Ageing and Retirement in Europe, a third of adults over the age of 80 years reported that they had not been weighed by their general practitioner [19]; and older adults commonly report that they do not receive advice on diet from their physician or other health professionals. The situation is worse in low and middle-income countries.

Declining food intakes in older age contribute to weight loss, with implications for muscle mass, strength and physical function

[20]. The importance of adequate nutrition in older age has been recognised for a long time. However, much of the research exploring the effects of diet on muscle mass and physical function is relatively recent [21]. A number of interventions has been studied, ranging from provision of nutritional support, to supplementation with specific nutrients. The nutrients that have been most consistently linked to the components of sarcopenia and frailty in observational studies include protein, vitamin D, antioxidant nutrients (that include carotenoids, selenium and vitamins E and C) and long-chain polyunsaturated fatty acids. This review considers current evidence of their effects on muscle mass and strength and physical function in older people. Comment is also included on the roles of other dietary components (dairy and nitrate-rich foods) and the importance of overall dietary patterns.

3. Nutrition, muscle mass, strength and physical function

3.1. Protein

Dietary protein provides amino acids that are needed for the synthesis of muscle protein, as well as acting as an anabolic stimulus, with direct effects on protein synthesis. For example, in a feeding study that provided 20 g of labelled casein to examine the effects of dietary protein ingestion on muscle protein synthesis in younger adults, Groen and colleagues demonstrated that more than half (~55%) of the protein-derived amino acids became available in the circulation over a 5-hour period following the meal, with ~11% of these amino acids (2.2 ± 0.3 g) incorporated in *de novo* muscle protein over that period [22]. A key concern for older adults is that the anabolic response to protein ingestion may be blunted, suggesting that protein requirements need to be higher in order to maintain nitrogen balance and prevent loss of muscle mass and strength [23]. There has been some inconsistency across studies in the extent to which the anabolic response to protein is reduced in older age [24], and there is debate regarding the importance of low protein intakes, and whether they are causally related to losses of muscle mass and strength in older adults [25]. Whilst some of the inconsistency in study findings may be due to differences in methodological approaches and based on small studies with limited statistical power, a clear understanding of changes in synthetic responses to protein feeding in older age is essential to ensure the protein needs of older adults are met. An important contribution to this evidence is a recent publication by Wall and colleagues, in which they bring together data from a series of stable isotope tracer studies to enable comparison of post-absorptive and postprandial protein synthesis rates in larger groups of young and older men (Fig. 2) [24]. Muscle protein synthesis in the post-absorptive state did not differ between groups. However, synthesis rates after ingestion of 20 g protein were 16% lower in the older men, with a substantial difference between young and older men in the change in rates from the post-absorptive to the postprandial state [24].

There is some observational evidence that links low protein intakes to losses of muscle mass and strength in older age. For example, in the Health, Aging and Body Composition Study, a greater loss of lean mass, assessed using dual-energy X-ray absorptiometry, was found over a 3-year follow-up period among older community-dwelling men and women who had low energy-adjusted protein intakes at baseline. The differences were substantial, such that the participants with protein intakes in the top fifth of the distribution (mean intake ± SD; 1.2 ± 0.4 g/kg body weight) lost 40% less lean mass and appendicular lean mass over the follow-up period when compared with those in the bottom fifth (0.8 ± 0.3 g/kg) [26]. Consistent with this finding, in more recent follow-up studies of the Women's Health Initiative [27] and the

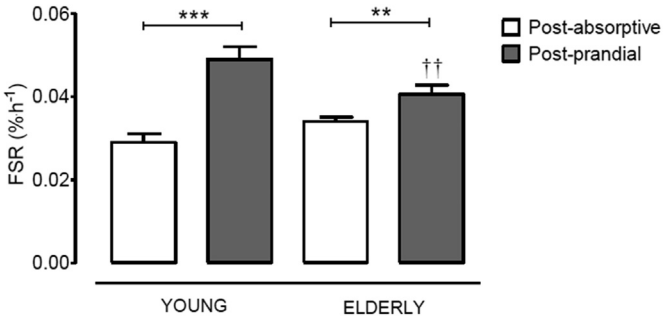

Fig. 2. Fractional mixed muscle protein synthesis rates (FSR) in healthy young and older men in the post-absorptive state (n = 34 young, n = 72 older) and post-prandial (n = 35 young, n = 40 older) state, following ingestion of 20 g protein. Significantly different comparing post-absorptive and post-prandial values for each group: ** (P < 0.01), *** (P < 0.001); significantly different comparison of older and young men: †† (P < 0.01) [24].

Framingham Offspring cohort [28], higher intakes of protein at baseline were associated with reduced loss of grip strength over the period of study. But, in a prospective cohort study of community-dwelling older adults in Tasmania, whilst energy-adjusted protein intake was a positive predictor of change in appendicular lean mass, differences in grip strength were not observed [29]. Overall, the evidence suggests that protein supplementation should have the potential to slow sarcopenic muscle loss, particularly among older adults with low habitual intakes. However, whilst there are studies that show positive effects, evidence of functional benefits of supplementation is mixed [30].

Branched-chain amino acids have been shown to increase skeletal muscle protein synthesis and net balance, and supplementation with leucine, isoleucine, and valine has been used to improve athletic performance and to attenuate muscle loss [31]. Although there are some differences between individual studies [32], a systematic review and meta-analysis concluded that leucine ingestion increases muscle protein fractional synthetic rate in older individuals, and may be of benefit to address age-related declines in muscle mass [33]. Consistent with this finding, greater leucine intake was found to be associated with long-term lean body mass retention in a healthy older Danish population [34]. There is also interest in β-hydroxy-β-methylbutyrate (HMB), a key metabolite of leucine, with demonstrated effects on protein synthesis and protein breakdown [35,36]. Findings from a recent study suggested an age-related decline in endogenous HMB; plasma concentrations were positively correlated with appendicular lean mass and muscle strength in young and older adults [37]. HMB supplementation has been tested in older adults, and there is a growing body of evidence that suggests HMB may help slow muscle loss and improve measures of muscle strength [5]. For example, in healthy older adults, HMB supplementation preserved muscle mass during a 10-day period of bed rest [38]. A meta-analysis of seven randomized controlled trials of HMB supplementation in older adults showed greater muscle mass gain in the intervention groups, compared with the control groups [39]. The authors concluded that HMB supplementation may be useful in the prevention of muscle atrophy but further studies are needed to determine the precise effects of HMB on muscle strength and physical function in older adults [39].

There is greater interest in the combined effects of protein supplementation and exercise to increase postprandial protein synthesis to promote muscle protein accretion. Resistance exercise increases muscle protein synthesis [40], and synergistic effects of resistance exercise and protein ingestion have been described in some studies [41], suggesting that exercise may enable greater use

of ingested amino acids for protein synthesis. An important finding therefore is that dietary protein digestion and absorption kinetics after exercise appear to be comparable when measured following a single meal in young and older men [42](Fig. 3).

Until recently, the implications of these experimental findings for longer-term strategies to prevent loss of muscle mass and strength were unclear. However, pooled estimates from a meta-analysis of 22 RCTs of protein supplementation during prolonged (more than 6 weeks) resistance-type exercise training, have confirmed significantly greater gains in fat free mass, type I and II muscle fibre cross sectional area and 1-RM leg press strength in supplemented participants, when compared with participants receiving exercise training alone [43]. The augmented response to exercise training resulting from protein supplementation was seen both in older (50 years or older) and younger (49 years or less) participants. In order to reduce heterogeneity between studies, only healthy subject groups were included in this meta-analysis, and the authors suggest that there is potential for greater benefits among frail older adults whose habitual protein intakes are low [43]. Although trials of resistance exercise training combined with protein/amino acid supplementation of older adults (65 years and older) have not always found interactive effects on muscle mass, strength and physical performance [44], consistent with this suggestion, a trial of frail older men and women showed that lean body mass increased in the protein-supplemented group (in addition to resistance-type exercise training), whereas there was no change in the placebo (exercise only) group [45]. Although comparable effects have also been described in an intervention study that provided additional lean red meat, to increase dietary protein intake among older adults, combined with resistance exercise training [46], a recent trial of supplementation of mobility-limited older adults with whey protein concentrate (40 g/day), in combination with progressive high-intensity resistance training, did not result in statistically significant differences in lean mass, muscle cross sectional area or stair-climbing performance, when compared to the control group [47]. An additional consideration is that the muscle protein synthetic response to protein ingestion in older age is affected by the amount and pattern of protein intake [48] as well as other dietary components, such as carbohydrate, consumed at the same time [49]. There is also evidence that effects on muscle protein synthetic response differ according to the protein source, with lesser anabolic effects of plant proteins observed in comparison with animal protein [50]. This may be due to differences in content and balance of amino acids, particularly to the relatively lower leucine content of plant proteins. Although strategies have been proposed to improve the anabolic properties of plant proteins, evidence of their effectiveness is currently lacking [50]. An additional consideration is the distribution of protein intake across different meals [51,52]; this was highlighted in a recent analysis of NHANES data, showing that more frequent consumption of meals containing at least 30 g of protein was associated with greater leg lean mass and knee extensor muscle strength [53]. Further data are needed to define and test recommendations for optimal dietary profiles, amounts of patterns of protein intake and their interaction with exercise in older adults.

There are many clear benefits of exercise training for older adults that include effects on muscle mass and strength. Whilst heterogeneity in the adaptive response (lean body mass, muscle fibre size, strength, and physical function) to prolonged resistance-type exercise training was described in a recent retrospective analysis of data from older men and women, an important finding is that there were no non-responders [54]. Population approaches to increase resistance-type exercise among older people therefore have enormous potential to promote better physical function and to support healthier ageing. Declining levels of physical activity [55] and increased sedentary behaviour [56], both commonly observed, are therefore challenges to the health of older adults. The combination of physical inactivity and high levels of sedentary behaviour can result in a diminished muscle protein synthetic response to protein ingestion, making a significant contribution to loss of muscle mass and strength in older adults [56], further exacerbated when inactivity is enforced following injury or illness. Successive short periods of bed-rest may be particularly important in the development of sarcopenia as their effects accumulate across the lifecourse. This is represented in the model proposed by English & Paddon-Jones (Fig. 4), in which age-related muscle loss is punctuated by episodes of acute illness or injury; each 'catabolic crisis' is characterized by accelerated muscle loss and followed by incomplete recovery [57].

Although the mechanisms that underpin the effects of muscle disuse are not fully understood, a recent study of younger adults has shown that one-legged knee immobilization over 5 days was sufficient to lower post-absorptive myofibrillar protein synthesis rates and to induce anabolic resistance to protein ingestion [58]. Further research is needed to define nutritional and/or exercise interventions that will improve muscle sensitivity and prevent or attenuate muscle loss during periods of disuse [59], and to determine the preventive effects, for healthy older community-dwelling adults, of breaking up prolonged bouts of sedentary activity on skeletal muscle mass and physical function [56].

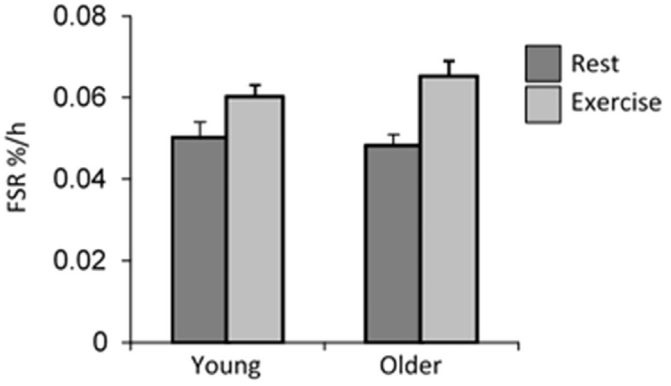

Fig. 3. Mean mixed-muscle protein fractional synthetic rates (FSR) after protein ingestion in young (n = 24) and older (n = 24) men at rest and after exercise based on L-[1-13C]phenylalanine (ingested tracer) enrichment. Data were analysed by ANOVA (age · exercise): age effect, P = 0.62; exercise effect, P = 0.05; age × exercise effect, P = 0.52 [42].

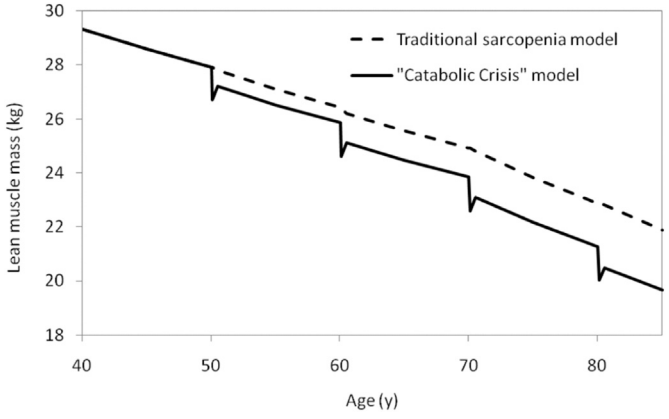

Fig. 4. Proposed model of age-related muscle loss punctuated by episodes of acute illness or injury [57].

In summary, there is significant evidence of the importance of protein intake and physical activity as principal anabolic stimuli for muscle protein synthesis. Physical activity sensitizes skeletal muscle tissue to the anabolic properties of amino acids. While the additional benefits of appropriate nutritional support may vary, depending on the exercise programme and the age and status of the participants, combining exercise with appropriate nutritional support is likely to be an important strategy to maintain muscle mass and strength in older age. A number of expert groups have proposed an increase in dietary protein recommendations for older age groups to 1.0–1.2 g/kg body weight per day [60,61]. However, these reviews also highlight the need for further trial data, particularly with respect to protein source and pattern of consumption, to understand the potential for beneficial effects of additional dietary protein on physical function [60,62].

3.2. Vitamin D

Loss of muscle mass and vitamin D deficiency often occur together and are interrelated; both are linked to common clinical outcomes that include weakness, falls and frailty in older age [63,64]. The mechanisms by which vitamin D affects muscle strength and function are not fully understood, but may be mediated by the vitamin D receptor (VDR). VDR and 1-alpha hydroxylase are expressed in muscle tissue, and notably, VDR knockout mice have small and variable muscle fibres [63,65,66]. The number of VDR present in human muscle tissue has been shown to decline with age [67,68]. However, an important recent finding is that VDR expression can be changed by vitamin D supplementation [69]. For example, in a 4-month RCT in which older mobility-limited women were given 4000 IU vitamin D3 or placebo, a greater change in intramyonuclear VDR concentration was found among supplemented women, with more pronounced differences observed in Type II muscle fibres [70]. Furthermore, there was a strong correlation between the change in serum 25(OH)D over the trial period and percent change in VDR concentration ($r = 0.87$, $P < 0.001$), providing supportive evidence of sustained clinical effects of vitamin D supplementation on muscle function [70]. In addition, findings from recent studies suggest a potential anti-inflammatory role for vitamin D. For example, among older adults in the InCHIANTI Study, there was an inverse association between serum 25(OH)D concentration and the proinflammatory cytokine IL-6 [71]. Further evidence has come from a study of older, mobility-limited adults, in which intramuscular VDR protein concentration was found to be positively associated with intramuscular IL-6 gene expression, but negatively associated with intramuscular IL-6 protein concentration, suggesting a relationship between VDR and IL-6 in human skeletal muscle [72].

There is substantial clinical and epidemiological evidence that links vitamin D status in older age to differences in muscle strength and function. For example, more than a decade ago, Visser and colleagues showed that older adults in the Longitudinal Aging Study Amsterdam who had serum 25(OH)D concentrations below 25 nmol/L were twice as likely to have sarcopenia (defined as loss of grip strength or loss of appendicular skeletal muscle mass) over a 3-year follow-up period, when compared with participants who had higher (>50 nmol/L) concentrations [73]. Furthermore, in continued follow-up of this cohort, lower vitamin D status at baseline was associated with a higher future risk of nursing home admission [74]. Proximal weakness is a feature of clinical vitamin D deficiency, with suggestion from biopsy studies that severe deficiency preferentially affects type II muscle fibres [63]. Consistent with this observation, a number of epidemiological studies have shown worse lower extremity function, such as longer walk and sit-to-stand times, among older adults who have low vitamin D status [75,76]. However, in comparison with such evidence of functional benefits of higher vitamin D status, the effects on muscle mass and composition are less clear [77]. In younger adults, serum 25(OH)D concentrations have been shown to be inversely related to measured muscle fat infiltration, an effect that was independent of differences in body mass index and activity levels [78]. Such changes in muscle lipid content have important implications for musculoskeletal function; for example, in the Health ABC study, older adults with high mid-thigh intramuscular fat content (in top quarter) had a 58% increased risk of hip fracture over a 7-year follow up period, when compared with those in the lowest quarter, and a higher incidence of mobility limitations [79]. Although attenuated, the difference in fracture risk remained after adjustment for differences in muscle strength and physical performance (SPPB) [80].

As low vitamin D status is common in many older populations [81], much attention has been focused on the potential therapeutic benefits of supplementation. A systematic review and meta-analysis of trials of vitamin D supplementation to improve strength and function of older adults was published in 2011; in 10 of the 12 studies included in the systematic review that reported baseline vitamin D status, participants' mean serum 25(OH)D concentrations were in the deficiency range (<50 nmol/L) [82]. Supplementation with vitamin D was shown to have beneficial effects on muscle function, with evidence of reduced postural sway, decreased time for the Timed Up and Go test, and gains in lower extremity strength [82]. More recently, a larger meta-analysis of 29 vitamin D supplementation trials has confirmed a small but positive effect on muscle strength [83]. However, benefits of supplementation may be confined to adults of lower vitamin D status. This was described by Stockton and colleagues in a meta-analysis of 17 RCTs; there was no significant effect of vitamin D supplementation on muscle strength (grip or proximal lower limb) in adults with serum 25(OH)D concentrations >25 nmol/L, but using pooled data from two studies of vitamin D deficient participants (25(OH)D < 25 nmol/L), a large effect of supplementation on hip muscle strength was observed [84]. Differences in strength in response to supplementation, according to status at baseline, were also observed in the larger meta-analysis [83], and may explain negative findings in some trials. For example, vitamin D supplementation (800 IU/d) did not improve physical function in a recent study of older Finnish women; but as fluid milk products are fortified in Finland, status may have been too high to show benefits [85].

There have been a number of trials of vitamin D supplementation to prevent falls in older adults. Apart from potential effects of vitamin D on muscle mass and strength, low status has also been linked to orthostatic hypotension [86], commonly considered to be a risk factor for falls [87]. To date, ten meta-analyses of fall prevention trials have been published (Table 1).

With the exception of one meta-analysis, that did not show benefits of supplementation [97], the remaining studies described a

Table 1
Meta-analyses, published between 2004 and 2014, of supplemental vitamin D trials to prevent falls (OR odds ratio; RR relative risk; RaR rate ratio).

		Effect of supplementation on falls
2004	Bischoff-Ferrari HA et al. [88]	−22% [OR 0.78 (95% CI 0.64, 0.92)]
2007	Jackson C et al. [89]	−12% [RR 0.88 (95% CI 0.78, 1.00)]
2008	O'Donnell S et al. [90]	−34% [OR 0.66 (95% CI 0.44, 0.98)]
2008	Richy F et al. [91]	−21% [RR 0.79 (95% CI 0.64, 0.96)]
2009	Bischoff-Ferrari HA et al. [92]	−19% [RR 0.81 (95% CI 0.71, 0.92)]
2010	Kalyani RR et al. [93]	−14% [RR 0.86 (95% CI 0.79, 0.93)]
2010	Michael YL et al. [94]	−17% [RR 0.83 (95% CI 0.75, 0.91)]
2011	Murad MH et al. [95]	−14% [OR 0.86 (95% CI 0.77, 0.96)]
2012	Cameron ID et al. [96]	−37% [RaR 0.63 (95% CI 0.46, 0.86)]
2014	Bolland M et al. [97]	−5% [RR 0.95 (95% CI 0.89, 1.02)]

reduction in rates of falls that range from 12% to 37% following vitamin D supplementation. However, an important addition to this evidence has recently come from the Zurich Disability Prevention Trial [98]. In this RCT, community-dwelling older men and women with a prior fall were allocated to have monthly treatments with 24,000 IU of vitamin D3 (equivalent to 800 IU/day; reference group), 60,000 IU, or 24,000 IU of vitamin D3 plus 300 μg of calcifediol over one year. The majority of participants (58.0%) were vitamin D deficient (<20 ng/mL) at baseline. Intention-to-treat analyses showed that, while the higher dose and combined dose groups were more likely to achieve 25-hydroxyvitamin D levels of at least 30 ng/mL at 12 months ($P = 0.001$), mean changes in function (SPPB) did not differ among the treatment groups ($P = 0.26$). More than half the participants (60.5%) fell during the 12-month follow-up period; a higher incidence of falls was found in the 60 000 IU group (67%; 95% CI, 54–78) and the 24 000 IU plus calcifediol group (66%; 95% CI, 54–77%) group when compared with the 24 000 IU reference group (48%; 95% CI, 36%–60%) ($P = 0.048$) [98]. Overall, fewest falls were observed among participants with vitamin D status in the lower replete range of 25(OH)D (21.3–30.3 ng/ml) with most falls observed in the range 44.7–98.9 ng/ml. This finding is consistent with an increased risk of falls observed in another trial of vitamin D supplementation; older community-dwelling women at risk of fracture, who received an annual oral dose of 500,000 IU cholecalciferol, had 15% more falls than other women [99]. It is possible that there is a therapeutic range of vitamin D status required to prevent falls in older age.

In summary, there is significant evidence of potential benefits of use of supplemental vitamin D to preserve muscle mass, strength and physical function in older age and to prevent and treat sarcopenia. Additionally, data from the PROVIDE Study suggest that supplementation with vitamin D in combination with other nutrients may be important; in this trial, provision of a supplement, containing vitamin D, leucine-enriched whey protein and a mixture of micronutrients, over a 13-week period, resulted in greater gains in appendicular muscle mass and improved chair rise time in sarcopenic older adults, when compared with a control group given an isocaloric supplement (without protein or micronutrients) [100]. However, further data from large clinical trials that test the benefits of supplementary vitamin D, and establish therapeutic ranges, are needed. An example is the ongoing DO-HEALTH study (http://do-health.eu/wordpress/), conducted across seven European cities ($2 \times 2 \times 2$ factorial design trial over a 3-year period: home exercise program and/or vitamin D, and/or omega-3 fatty acids) that will provide key information on the individual and combined effects of these treatments on the risk of functional decline in older age.

3.3. Antioxidant nutrients

Markers of oxidative damage have been shown to predict impairments in physical function in older adults [101]. Damage to biomolecules such as DNA, lipid and proteins may occur when reactive oxygen species (ROS) are present in cells in excess. The actions of ROS are normally counterbalanced by antioxidant defence mechanisms that include the enzymes superoxide dismutase and glutathione peroxidase, as well as exogenous antioxidants derived from the diet, such as selenium, carotenoids, tocopherols, flavonoids and other plant polyphenols [101]. As an accumulation of ROS may lead to oxidative damage, with the potential to contribute to losses of muscle mass and strength in older age [102], there is interest in the role of dietary antioxidants and their effects on age-related losses in muscle mass and function.

A number of observational studies have shown positive associations between higher antioxidant status and measures of physical function [21], and more recently, low selenium status has been linked to low muscle mass in an older population [103]. Importantly, associations with antioxidant nutrients have been found both in cross-sectional analyses [104] and in longitudinal studies [105]. Poorer status is predictive of decline in function, and the observed effect sizes are large. For example, among older men and women in the InCHIANTI study, higher plasma carotenoid concentrations were associated with a lower risk of developing a severe walking disability over a follow-up period of 6 years; after taking account of confounders that included level of physical activity and other morbidity, the odds ratio was 0.44 (95% CI 0.27–0.74) [105]. Inverse associations have also been described for vitamin E and selenium status in relation to risk of impaired physical function [21]. However, in general, trials of antioxidant supplementation to prevent disease have not had the effects predicted from epidemiological studies [106,107]; to date, there is little trial evidence in relation to muscle outcomes, and none to determine the effects of antioxidant supplementation in sarcopenic individuals. The benefits of antioxidant supplementation to prevent or treat sarcopenia are therefore uncertain [108].

Additionally, as ROS have both physiological and pathological roles, interventions based on simple suppression of their activities may be unlikely to improve age-related declines in muscle mass and function [109]. Important evidence, consistent with the proposed lack of benefit of antioxidant supplements, has come from a recent trial that investigated the effects of vitamin C (500 mg/day) and E (117.5 mg/day) supplementation on muscle mass and strength in a group of older (60–81 years) men who participated in a 12-week period of strength training [110]. DXA-assessed body composition at follow-up revealed a *smaller* increase in total lean mass in the supplemented group (1.4% (95% CI 0, 5.4) vs 3.9% (3.0, 5.2)), and *lower* gains in muscle thickness (rectus femoris). The authors' conclusion, that high-dose vitamin C and E supplementation blunted some of the muscular adaptations to strength training in older men [110], raises significant concerns about the use of antioxidant supplements to prevent age-related losses of muscle mass and strength, particularly in relation to strength training. But further evidence is needed.

3.4. Long-chain polyunsaturated fatty acids

Low-grade systemic inflammation, involving increases in the production of inflammatory factors, such as C-reactive protein (CRP), tumour necrosis factor-α (TNF-α) and interleukin 6 (IL-6), and recognised to have an important role in numerous chronic conditions [111], has also been implicated in age-related disease [112,113]. For example, inflammation has been shown to predict incident mobility limitation [114], and, in a 10-year follow-up of the older participants in the Hertfordshire Ageing Study, 'inflammaging' burden (defined by blood concentration of inflammatory biomarkers) at baseline was associated with lower grip strength at follow-up [115]. Since eicosanoids derived from 20-carbon polyunsaturated fatty acids are among the mediators and regulators of inflammation [116], this raises the possibility that variations in dietary intakes of n-3 and n-6 long chain polyunsaturated fatty acids (LCPUFAs), and their balance in the diet, could be of importance [117]; in particular, n-3 LCPUFAs have the potential to be potent anti-inflammatory agents [118]. In a recent meta-analysis that included 68 trials, supplementation with marine-derived n-3 LCPUFAs was shown to have a significant lowering effect on CRP, IL-6 and TNF-α levels, with longer duration of supplementation associated with greater change [111].

However, apart from effects on the inflammatory response, there is now also increasing evidence of direct effects of omega-3 fatty acids on muscle protein synthesis; acting via effects on mTOR signalling; with the suggestion that n-3 fatty acid

supplementation could enhance gains in muscle mass in older adults by over-coming age-related effects on anabolic resistance [119]. In a randomised controlled trial, supplementation of older adults with n-3 LCPUFA (eicosapentaenoic and docosahexaenoic acids) had no effect on the basal rates of muscle protein synthesis, when compared with adults given corn oil, but the increase in the rate of muscle protein synthesis during a hyperaminoacidemic-hyperinsulinemic clamp was ~3-fold greater. This effect appeared to be at least partially mediated via changes in the muscle mTOR signalling pathway (Fig. 5) [120].

These novel data, showing augmentation of the anabolic response, are consistent both with evidence from animal and in vitro models that support a stimulatory effect of omega-3 fatty acids on muscle protein synthesis after feeding [119], and with findings from younger adults [120].

There is some observational evidence that supports the positive benefits of diets higher in n-3 LPUFAs for muscle strength and measured physical function [121,122], and in a large study of women aged 18–79 years, a higher dietary polyunsaturated: saturated fatty acid ratio was associated with a greater fat-free mass, which may be suggestive of muscle conservation [123]. Supplementation studies of older women to increase intakes of n-3 LCPUFAs have achieved improvement in walking speed [124], and in a strength-training trial, the use of fish oil supplements (2 g/day) resulted in greater improvements in muscle strength and functional capacity when compared with women who participated in strength training alone [125]. In a trial of n-3 LCPUFA supplementation (1.86 g eicosapentaenoic acid (EPA), 1.50 g docosahexaenoic acid (DHA)) of older adults aged 60–85 years, thigh muscle volume increased over a 6-month follow-up period in supplemented group, whereas there was no change in the control group who were given corn oil. Muscle strength at follow-up was also greater in the supplemented group [126]. Importantly, the treatment effects (increases in muscle volume: 3.6% (95% CI 0.2, 7.0%; handgrip strength: 2.3 kg; 95% CI: 0.8, 3.7 kg)) are clinically relevant, approximating expected losses over a 2–3-year period [119].

These new data offer promise of a simple low-cost approach for the prevention and treatment of age-related losses of muscle mass and function in older age. However, considerable gaps in our knowledge remain [119]. One challenge is that not all supplementation trials are effective. For example, in a recent trial of n-3 LCPUFA supplementation of 53 older women with low muscle mass, there were no differences in muscle mass, hand grip or TUG in any group over a 12-week follow-up when comparing the supplemented and placebo groups [127]. Some of the inconsistency in findings across studies may be due to methodological differences, particularly in dose and duration of studies, status of participants studied and methods of assessment of outcome – and further trial data are needed. Particular questions relate to the dose-dependent nature of effects, the latency and duration of the beneficial responses, and the individual roles of EPA and DHA in the regulation of muscle function [119].

3.5. Foods and dietary patterns

A limitation of the observational evidence that links individual nutrients to differences in muscle mass and function in older age is that many dietary components are highly correlated with each other. Whilst this challenges any causal inferences that can be drawn, it also means that intakes of individual nutrients may act as markers for other components, including a range of bioactive compounds, such as plant phytochemicals. There is less evidence on the effects of whole foods, or that use whole-diet approaches to understand the role of diet in the aetiology of age-related losses of muscle mass and function, although this is a rapidly growing area of interest.

3.5.1. Dairy foods

One of the types of foods most studied in relation to muscle mass and function is dairy products. They may be important due to their whey protein content, which is relatively high in branched-chain amino acids [128] and that also has antioxidant properties [129]. In a cross-sectional study of a large Australian population of older women, high dairy consumption (milk, yogurt, and cheese) was associated with greater lean mass and appendicular skeletal muscle mass, and with greater grip strength and lower odds for a poor Timed-Up-and-Go test [130]. There is some experimental evidence to support these observational data; for example the addition of ricotta cheese (210 g/day) to the diets of older men and women over a 12-week period improved appendicular skeletal muscle mass and balance, when compared with a control group who were following habitual diets [131]. Amino acid balance studies suggest that ingestion of milk following resistance exercise increases amino acid uptake, indicative of net muscle protein synthesis [132], and a number of studies have investigated the combined effects of dairy protein supplements with exercise training. Among younger adults undergoing 12 weeks of resistance training, those given a milk drink after exercise achieved greater gains in lean mass and greater losses in fat mass when compared with participants given an isocaloric carbohydrate drink [133]; the

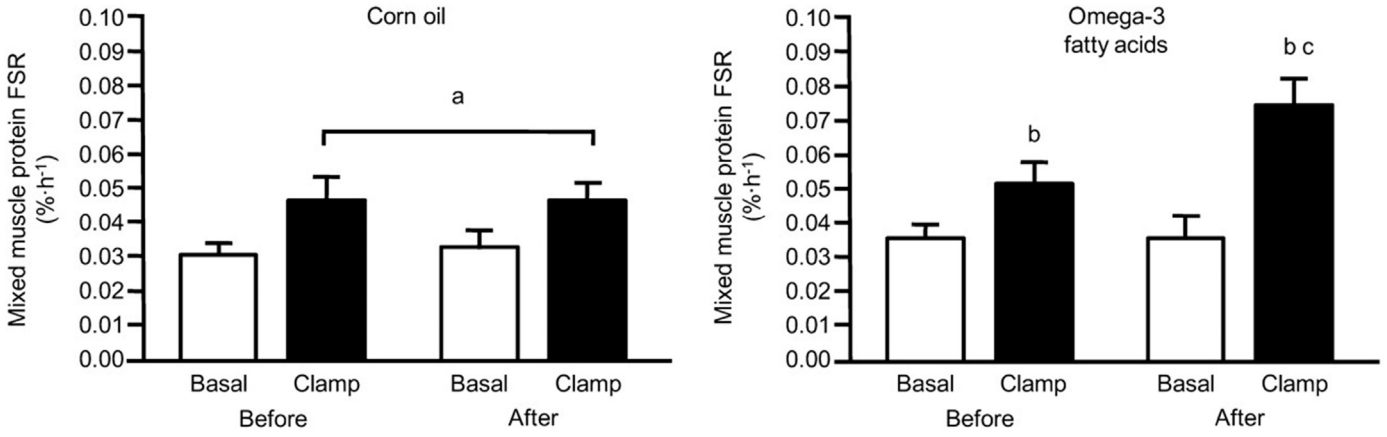

Fig. 5. Mean (±SEM) mixed skeletal muscle protein fractional synthesis rate (FSR) during postabsorptive conditions and hyperaminoacidemic-hyperinsulinemic clamp, before and after 8 weeks of supplementation with corn oil or n-3 fatty acids (a :significant effect of clamp, P < 0.01; b: significant effect of clamp P < 0.01; c: significantly different from the corresponding value before omega-3 fatty acid supplementation, P < 0.01) [120].

milk group also had greater gains in isotonic strength for some exercises. In a separate study of overweight and obese women, Josse and colleagues have also shown more favourable body composition changes (greater total and visceral fat loss, lean mass gain) in response to a diet and exercise regime among women randomized to a high-protein, high-dairy group, when compared with other women with adequate protein but medium/low dairy foods [134].

However, other studies have not found effects of combining exercise training with dairy food supplements. In an 18-month trial, designed to assess the use of fortified milk to enhance the effects of resistance training in men aged 50–79 years, there were no effects on skeletal muscle size, strength or function [135]. A possible explanation of these disparate findings is that the timing of milk consumption after exercise is key to its benefits, which was not closely controlled in this study; although a recent meta-analysis suggests that timing of protein intake may not be critical to muscular adaptations to exercise training [136]. Whilst one challenge in collating data across studies is the difference in the status and age of participants, another is the compositional differences across apparently similar dairy foods. The most notable difference may be the fortification of milk with vitamin D in some countries (eg US) but not others (eg UK). Benefits of soya milk consumption after exercise have not been shown [137]. Furthermore, in a recent study of older adults, those with increased soy protein intake had lower gains in muscle strength during resistance training when compared to participants with increased dairy protein intakes or usual intakes; there were no differences between the dairy protein and usual protein groups [138].

3.5.2. Nitrate-rich foods

Some anti-oxidant rich foods are also rich in inorganic nitrates, for example green leafy vegetables like lettuce, spinach and celery, and beetroot. Dietary nitrate ingestion appears to enhance exercise capacity and performance in young individuals [139], and beetroot juice has become popular among some endurance athletes. In the body nitrate is converted to nitrite and to nitric oxide that is pleiotropic and has effects on various muscle performance-related functions that are related to muscle contraction efficiency. However, no long-lasting effects on for example protein synthesis have been reported [140], and in a recent trial of consumption of beetroot juice by older participants (60–75 years), short-term supplementation did not modify measures of physical capability (walking speed, time-up-and-go, repeated chair rising test, hand-grip strength) [139]. Dietary nitrates have been discussed as a supportive remedy in congestive heart failure [141], but there are no studies in frail or sarcopenic older adults.

3.5.3. Dietary patterns

Since diets are patterned, and foods as well as nutrients are collinear, isolating effects of individual dietary components is not possible using observational data. It is therefore of value to consider effects of whole diets, commonly using a dietary patterns approach. An additional advantage of this approach is that it can also take account of complex interactions between food constituents, including potential synergistic or antagonistic effects on health outcomes [142]. In general, 'healthier' diets that are characterised by greater fruit and vegetable consumption indicate higher intakes of a range of nutrients that could be important for muscle function, such as greater consumption of oily fish and higher intakes of vitamin D and n-3 LCPUFAs, and higher antioxidant and protein intakes [121]. They are also higher in a range of plant phytochemicals, such as polyphenols, that may have important antioxidant and anti-inflammatory effects on muscle mass and function [143]. Additionally, fruit and vegetables, due to their content of potassium salts can buffer sulphuric and phosphoric acid derived from the catabolism of the sulphur-containing amino acids and phytates, and provide protection from known catabolic effects of acidosis on muscle tissue [144]. Although the role of the dietary acid-base load has not been extensively studied [145], there is evidence that links more alkaline diets, rich in fruit and vegetables, to greater lean tissue mass in middle-aged [145] and older adults [146], suggesting they may have protective effects.

Compared with the evidence that links variations in nutrient intake and status to physical function, less is known about the influence of dietary patterns and dietary quality in older age. 'Healthier' diets, characterised by greater fruit and vegetable consumption, wholemeal cereals and oily fish have been shown to be associated with greater muscle strength and with better measures of physical function in older adults [121,147–149] and lower risk of frailty [150]. However, the most significant body of evidence, based on longitudinal studies of older adults, considers compliance with a Mediterranean dietary pattern; high pattern scores at baseline are related to better self-reported physical function [151], lower risk of incident disability [152], lower decline in measured physical function and lower risk of developing mobility disability [153,154], and better walking performance [155] The consistency in this observational evidence suggests that intervention studies that take a food-based or 'whole diet' approach, resulting in changes in intakes of a range of nutrients and other food constituents, have potential to be very effective strategies for the prevention and/or treatment of age-related losses in muscle mass and strength.

4. Conclusions

The considerable evidence that links nutrition to muscle mass, strength and function of older adults, suggests that nutrition has an important role to play in both the prevention and management of sarcopenia. It points to the importance of dietary patterns that are adequate in quality for older adults, to ensure sufficient intakes of protein, vitamin D, antioxidant nutrients and long-chain polyunsaturated fatty acids. Since much of the evidence is observational and from high-income countries, further high quality trials, particularly from more diverse populations, are needed to enable an understanding of dose and duration effects of individual nutrients on function, to elucidate mechanistic links, and to define optimal profiles and patterns of nutrient intake for older adults. Future work should also consider the role of targeted interventions to reach more vulnerable sub-groups of the population who have specific phenotypic characteristics, or who differ according to stage of sarcopenia, or in their habitual diets and nutrient status [156]. This will contribute to evidence of the functional effects of variations in nutrient intake needed to inform dietary recommendations and to allow scale-up to population level. However, the high prevalence of poor nutrition currently observed among older populations, including in high-income countries, highlights the immediate need to ensure all older adults are supported effectively to have sufficient dietary intakes and adequate nutritional status. Whilst routine screening and early diagnosis of malnutrition are key components of such strategies, wider efforts to promote diet quality alongside a physically active lifestyle are also essential; they have significant potential to slow losses of muscle mass and strength and protect physical function, central to enabling mobility and independence in older age.

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Conflicts of interest

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