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DOI: <https://doi.org/10.1016/j.clnu.2017.08.016>

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ZORA URL: <https://doi.org/10.5167/uzh-145801>

Journal Article

Published Version



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Originally published at:

Robinson, S M; et al; Bischoff-Ferrari, H A (2018). Does nutrition play a role in the prevention and management of sarcopenia? *Clinical Nutrition*, 37(4):1121-1132.

DOI: <https://doi.org/10.1016/j.clnu.2017.08.016>



Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>

Review

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

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ARTICLE INFO

Article history:

Received 13 February 2017

Accepted 15 August 2017

Keywords:

Sarcopenia

Muscle mass

Muscle strength

Physical performance

Nutrition

Supplementation

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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<http://dx.doi.org/10.1016/j.clnu.2017.08.016>

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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

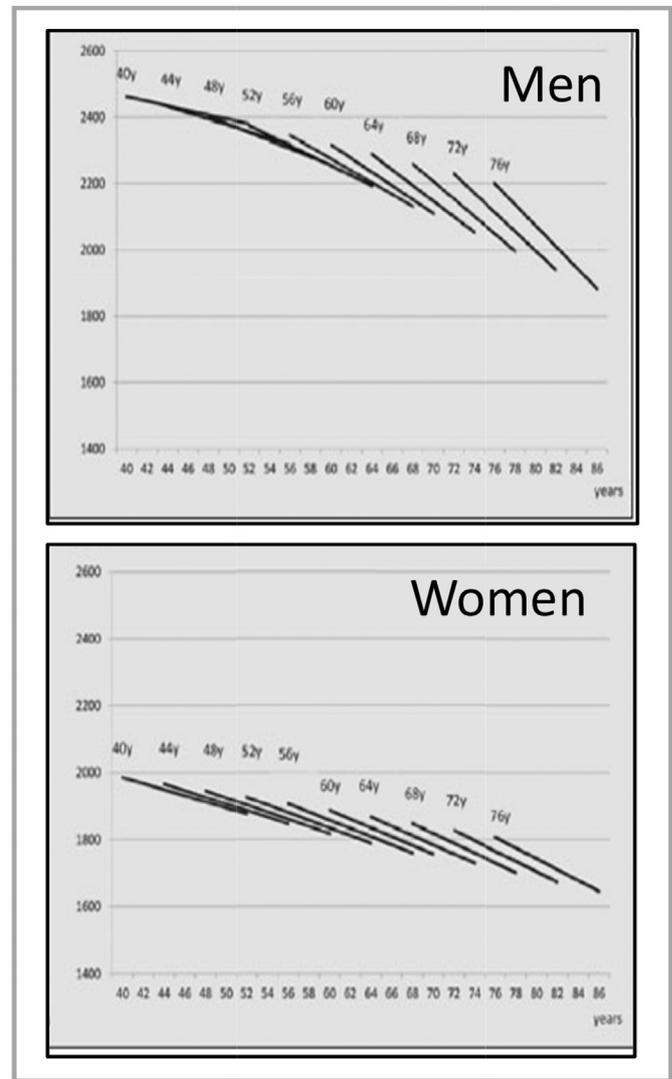


Fig. 1. Estimated linear changes in energy intake (kcal/day) in 922 men and 879 women over a 12-year follow-up period, according to (4-year) age group at baseline [9].

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 \pm 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

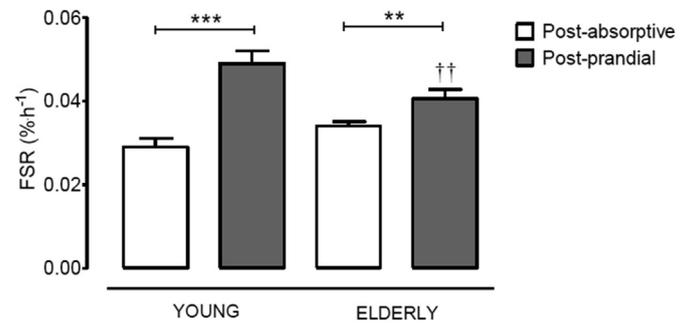


Fig. 2. Fractional mixed muscle protein synthesis rates (FSR) in healthy young and older men in the post-absorptive state (n = 34 young, n = 72 older) and post-prandial (n = 35 young, n = 40 older) state, following ingestion of 20 g protein. Significantly different comparing post-absorptive and post-prandial 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].

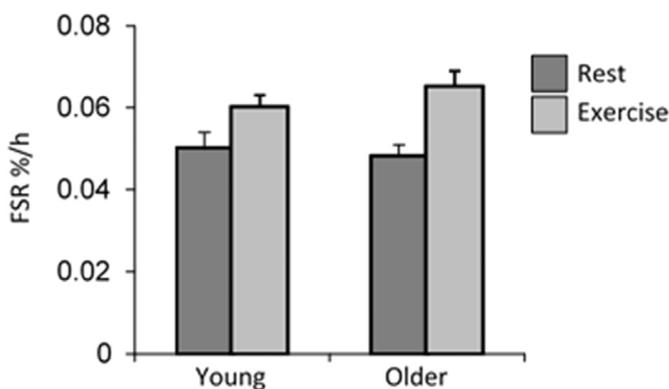


Fig. 3. Mean mixed-muscle protein fractional synthetic rates (FSR) after protein ingestion in young ($n = 24$) and older ($n = 24$) men at rest and after exercise based on L-[1-13C]phenylalanine (ingested tracer) enrichment. Data were analysed by ANOVA (age \cdot exercise): age effect, $P = 0.62$; exercise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

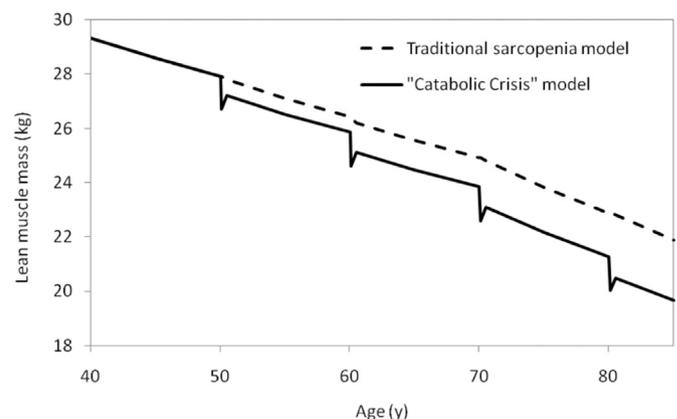


Fig. 4. Proposed model of age-related muscle loss punctuated by episodes of acute illness or injury [57].

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

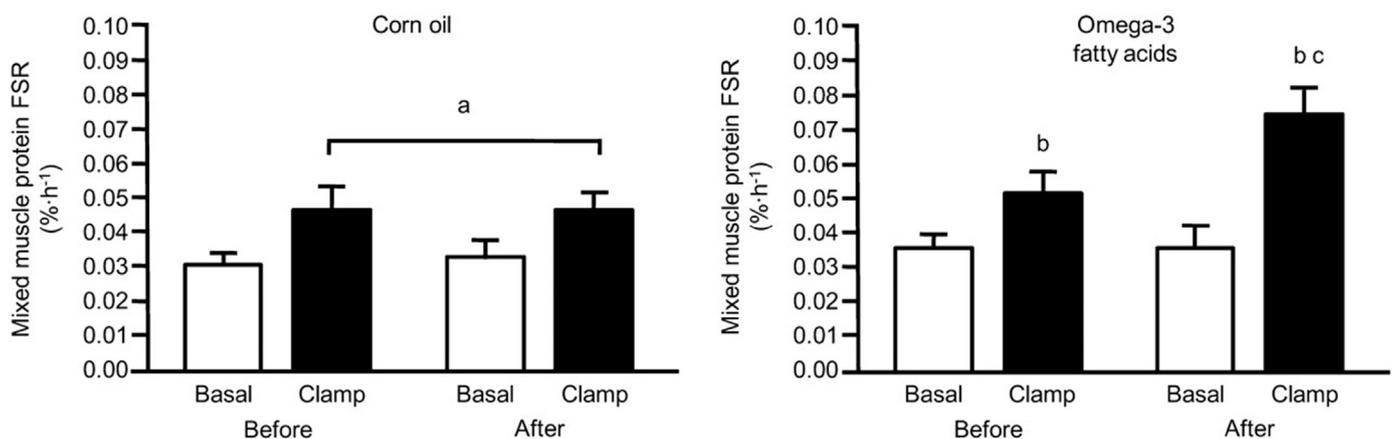


Fig. 5. Mean (\pm SEM) mixed skeletal muscle protein fractional synthesis rate (FSR) during postabsorptive conditions and hyperaminoacidemic-hyperinsulinemic clamp, before and after 8 weeks of supplementation with corn oil or n-3 fatty acids (a: significant effect of clamp, $P < 0.01$; b: significant 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.

Funding

The Working Group was fully funded by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), a Belgian not-for-profit

organization. ESCEO was responsible for the selection of participants to the preliminary meeting and for the choice of the authors of the manuscript, covering all expenses related to the organisation of the preliminary meeting and the presentation of outcomes of the working group at the 2017 World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (in Florence). ESCEO also covered all expenses pertaining to the preparation, writing and submission of the manuscript.

RF was partially supported by the U.S. Department of Agriculture – Agricultural Research Service (ARS), under Agreement No. #58-1950-4-003. The views expressed do not reflect those of the United States Department of Agriculture.

Conflicts of interest

SMR, JYR, SCS, JAK, IB, HBF, OB, MC, BDH, JMK, FL, VM, YR, BV, MV, NAD, SA, AC, ACJ, AL, SM, JP, and R Roubenoff declare no competing interests in relation to this paper.

R Rizzoli has received consultancy, lecture fees and honoraria from Radius Health, Labatec, Danone and Nestlé. R Fielding has received grants from Nestlé Inc. during the conduct of the study; personal fees from Amazentis Inc, grants and personal fees from Nestlé Inc, grants, personal fees and other from Axcella Health Inc, grants and personal fees from Astellas Inc., personal fees from Cytokinetics, personal fees from Biophytis, personal fees from Glaxo Smith Kline, outside the submitted work. LJ van Loon has received consultancy fees from Nutricia Research BV. C Cooper has received consultancy, lecture fees and honoraria from AMGEN, GSK, Alliance for Better Bone Health, MSD, Eli Lilly, Pfizer, Novartis, Servier, Medtronic and Roche. J Bauer has received scientific grants from Nestlé and Nutricia DANONE, acted as a consultant for Nestlé and Nutricia DANONE and has received speaker honoraria from Nestlé, Nutricia DANONE, Fresenius, Novartis and Bayer. T Cederholm has received research grants from Nutricia and Nestlé in the last five years. ML Brandi has acted as a consultant and has received grants from Alexion, Abiogen, Amgen, Eli Lilly and Shire. EV McCloskey is or has acted as a consultant, advisor, speaker and/or received research support from ActiveSignal, Amgen, Arthritis Research UK, AstraZeneca, Consilient Healthcare, EPSRC, GSK, Hologic, i3 Innovus, Internis, International Osteoporosis Foundation, Lilly, Medical Research Council, Medtronic, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Synexus, Tethys, UCB, Unilever and Warner Chilcott. R Rueda is an employee of Abbott Nutrition.

Acknowledgements

The Working Group was organized under the auspices of the World Health Organisation (WHO), the European Union Geriatric Medicine Society (EUGMS), the International Association of Gerontology and Geriatrics – Global Aging Research Network (IAGG–GARN) and the International Osteoporosis Foundation (IOF).

References

- [1] World Health Organisation. World report on ageing and health. 2015. Geneva, Switzerland.
- [2] Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc* 2004;52:80–5. <http://dx.doi.org/10.1111/j.1532-5415.2004.52014.x>.
- [3] Sousa AS, Guerra RS, Fonseca I, Pichel F, Ferreira S, Amaral TF. Financial impact of sarcopenia on hospitalization costs. *Eur J Clin Nutr* 2016;70:1046–51. <http://dx.doi.org/10.1038/ejcn.2016.73>.
- [4] Cao L, Morley JE. Sarcopenia is recognized as an independent condition by an international classification of disease, tenth revision, clinical modification (ICD-10-CM) code. *J Am Med Dir Assoc* 2016;17:675–7. <http://dx.doi.org/10.1016/j.jamda.2016.06.001>.
- [5] Argiles JM, Campos N, Lopez-Pedrosa JM, Rueda R, Rodriguez-Manas L. Skeletal muscle regulates metabolism via interorgan crosstalk: roles in health and disease. *J Am Med Dir Assoc* 2016;17:789–96. <http://dx.doi.org/10.1016/j.jamda.2016.04.019>.
- [6] Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip strength across the life course: normative data from twelve British studies. *PLoS One* 2014;9:e113637. <http://dx.doi.org/10.1371/journal.pone.0113637>.
- [7] Wakimoto P, Block G. Dietary intake, dietary patterns, and changes with age: an epidemiological perspective. *J Gerontol Ser A* 2001;56A:65–80. http://dx.doi.org/10.1093/gerona/56.suppl_2.65.
- [8] Nieuwenhuizen WF, Weenen H, Rigby P, Hetherington MM. Older adults and patients in need of nutritional support: review of current treatment options and factors influencing nutritional intake. *Clin Nutr* 2010;29:160–9. <http://dx.doi.org/10.1016/j.clnu.2009.09.003>.
- [9] Otsuka R, Kato Y, Nishita Y, Tange C, Tomida M, Nakamoto M, et al. Age-related changes in energy intake and weight in community-dwelling middle-aged and elderly Japanese. *J Nutr Health Aging* 2016;20:383–90. <http://dx.doi.org/10.1007/s12603-016-0715-0>.
- [10] Malafarina V, Uriz-Otano F, Gil-Guerrero L, Iñiesta R. The anorexia of ageing: physiopathology, prevalence, associated comorbidity and mortality. A systematic review. *Maturitas* 2013;74:293–302. <http://dx.doi.org/10.1016/j.maturitas.2013.01.016>.
- [11] Hedman S, Nydahl M, Faxen-Irving G. Individually prescribed diet is fundamental to optimize nutritional treatment in geriatric patients. *Clin Nutr* 2016;35:692–8. <http://dx.doi.org/10.1016/j.clnu.2015.04.018>.
- [12] Robinson S, Cooper C, Aihie Sayer A. Nutrition and sarcopenia: a review of the evidence and implications for preventive strategies. *J Aging Res* 2012;2012:510801. <http://dx.doi.org/10.1155/2012/510801>.
- [13] Bartali B, Salvini S, Turrini A, Lauretani F, Russo CR, Corsi AM, et al. Nutritional epidemiology age and disability affect dietary intake. *J Nutr* 2003;133:2868–73.
- [14] Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Frequency of malnutrition in older adults: a multinational perspective using the mini nutritional assessment. *J Am Geriatr Soc* 2010;58:1734–8. <http://dx.doi.org/10.1111/j.1532-5415.2010.03016.x>.
- [15] Freijer K, Tan SS, Koopmanschap MA, Meijers JMM, Halfens RJG, Nuijten MJC. The economic costs of disease related malnutrition. *Clin Nutr* 2013;32:136–41. <http://dx.doi.org/10.1016/j.clnu.2012.06.009>.
- [16] BAPEN. The cost of malnutrition in England and potential cost savings from nutritional interventions. 2015.
- [17] Cerri AP, Bellelli G, Mazzone A, Pittella F, Landi F, Zamboni A, et al. Sarcopenia and malnutrition in acutely ill hospitalized elderly: prevalence and outcomes. *Clin Nutr* 2015;34:745–51. <http://dx.doi.org/10.1016/j.clnu.2014.08.015>.
- [18] Artaza-Artabe I, Saez-Lopez P, Sanchez-Hernandez N, Fernandez-Gutierrez N, Malafarina V. The relationship between nutrition and frailty: effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. *Maturitas* 2016;93:89–99. <http://dx.doi.org/10.1016/j.maturitas.2016.04.009>.
- [19] Börsch-Supan A, Brüggemann A, Jürges H, Mackenbach J, Siegrist J, Weber G. Health, ageing and retirement in Europe – first results from the survey of health, ageing and retirement in Europe. Mannheim Mannheim Res Inst Econ Aging (MEA); 2005.
- [20] Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol* 2006;61:1059–64. <http://dx.doi.org/10.1093/gerona/61.10.1059>.
- [21] Kaiser M, Bandinelli S, Lunenfeld B. Frailty and the role of nutrition in older people. A review of the current literature. *Acta Biomed* 2010;81(Suppl. 1):37–45. <http://dx.doi.org/10.1136/bmj.2.5506.162-b>.
- [22] Groen BBL, Horstman AM, Hamer HM, de Haan M, van Kranenburg J, Bierau J, et al. Post-prandial protein handling: you are what you just ate. *PLoS One* 2015;10:e0141582. <http://dx.doi.org/10.1371/journal.pone.0141582>.
- [23] Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. *Clin Nutr* 2008;27:675–84. <http://dx.doi.org/10.1016/j.clnu.2008.06.008>.
- [24] Wall BT, Gorissen SH, Pennings B, Koopman R, Groen BBL, Verdijk LB, et al. Aging is accompanied by a blunted muscle protein synthetic response to protein ingestion. *PLoS One* 2015;10:e0140903. <http://dx.doi.org/10.1371/journal.pone.0140903>.
- [25] Millward DJ. Protein requirements and aging. *Am J Clin Nutr* 2014;100:1210–2. <http://dx.doi.org/10.3945/ajcn.114.089540>.
- [26] Houston DK, Nicklas BJ, Ding J, Harris TB, Tylavsky FA, Newman AB, et al. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) study. *Am J Clin Nutr* 2008;87:150–5. <http://dx.doi.org/10.1159/000115011> [pii].
- [27] Beasley JM, Wertheim BC, LaCroix AZ, Prentice RL, Neuhouser ML, Tinker LF, et al. Biomarker-calibrated protein intake and physical function in the Women's Health Initiative. *J Am Geriatr Soc* 2013;61:1863–71. <http://dx.doi.org/10.1111/jgs.12503>.
- [28] McLean RR, Mangano KM, Hannan MT, Kiel DP, Sahni S. Dietary protein intake is protective against loss of grip strength among older adults in the Framingham offspring cohort. *J Gerontol A Biol Sci Med Sci* 2016;71:356–61. <http://dx.doi.org/10.1093/gerona/glv184>.

- [29] Scott D, Blizzard L, Fell J, Giles G, Jones G. Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian older adult cohort study. *J Am Geriatr Soc* 2010;58:2129–34. <http://dx.doi.org/10.1111/j.1532-5415.2010.03147.x>.
- [30] Hickson M. Nutritional interventions in sarcopenia: a critical review. *Proc Nutr Soc* 2015;74:378–86. <http://dx.doi.org/10.1017/S0029665115002049>.
- [31] Borack MS, Volpi E. Efficacy and safety of leucine supplementation in the elderly. *J Nutr* 2016;146:2625S–9S. <http://dx.doi.org/10.3945/jn.116.230771>.
- [32] Verhoeven S, Vanschoonbeek K, Verdijk LB, Koopman R, Wodzig WKWH, Dendale P, et al. Long-term leucine supplementation does not increase muscle mass or strength in healthy elderly men. *Am J Clin Nutr* 2009;89:1468–75. <http://dx.doi.org/10.3945/ajcn.2008.26668>.
- [33] Xu Z, Tan Z, Zhang Q, Gui Q, Yang Y. The effectiveness of leucine on muscle protein synthesis, lean body mass and leg lean mass accretion in older people: a systematic review and meta-analysis. *Br J Nutr* 2014;113:1–10. <http://dx.doi.org/10.1017/S0007114514002475>.
- [34] McDonald CK, Ankarfeldt MZ, Capra S, Bauer J, Raymond K, Heitmann BL. Lean body mass change over 6 years is associated with dietary leucine intake in an older Danish population. *Br J Nutr* 2016;115:1556–62. <http://dx.doi.org/10.1017/S0007114516000611>.
- [35] Wilkinson DJ, Hossain T, Hill DS, Phillips BE, Crossland H, Williams J, et al. Effects of leucine and its metabolite β -hydroxy- β -methylbutyrate on human skeletal muscle protein metabolism. *J Physiol* 2013;591:2911–23. <http://dx.doi.org/10.1113/jphysiol.2013.253203>.
- [36] Girón M, Vilchez J, Salto R, Manzano M, Sevillano N, Campos N, et al. Conversion of leucine to β -hydroxy- β -methylbutyrate by α -keto isocaproate dioxygenase is required for a potent stimulation of protein synthesis in L6 rat myotubes. *J Cachexia Sarcopenia Muscle* 2016;7:68–78. <http://dx.doi.org/10.1002/jcsm.12032>.
- [37] Kuriyan R, Lokesh DP, Selvam S, Jayakumar J, Philip MG, Shreeram S, et al. The relationship of endogenous plasma concentrations of β -Hydroxy β -Methyl Butyrate (HMB) to age and total appendicular lean mass in humans. *Exp Gerontol* 2016;81:13–8. <http://dx.doi.org/10.1016/j.exger.2016.04.013>.
- [38] Deutz NEP, Pereira SL, Hays NP, Oliver JS, Edens NK, Evans CM, et al. Effect of beta-hydroxy-beta-methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. *Clin Nutr* 2013;32:704–12. <http://dx.doi.org/10.1016/j.clnu.2013.02.011>.
- [39] Wu H, Xia Y, Jiang J, Du H, Guo X, Liu X, et al. Effect of beta-hydroxy-beta-methylbutyrate supplementation on muscle loss in older adults: a systematic review and meta-analysis. *Arch Gerontol Geriatr* 2015;61:168–75. <http://dx.doi.org/10.1016/j.archger.2015.06.020>.
- [40] Chesley A, MacDougall JD, Tarnopolsky MA, Atkinson SA, Smith K. Changes in human muscle protein synthesis after resistance exercise. *J Appl Physiol* 1992;73:1383–8. <http://dx.doi.org/10.1151/JSC.0b013e3181def4a6>.
- [41] Moore DR, Tang JE, Burd NA, Rerich T, Tarnopolsky MA, Phillips SM. Differential stimulation of myofibrillar and sarcoplasmic protein synthesis with protein ingestion at rest and after resistance exercise. *J Physiol* 2009;587:897–904. <http://dx.doi.org/10.1113/jphysiol.2008.164087>.
- [42] Pennings B, Koopman R, Beelen M, Senden JMG, Saris WHM, van Loon LJC. Exercising before protein intake allows for greater use of dietary protein-derived amino acids for de novo muscle protein synthesis in both young and elderly men. *Am J Clin Nutr* 2011;93:322–31. <http://dx.doi.org/10.3945/ajcn.2010.29649>.
- [43] Cermak NM, Res PT, De Groot LCPGM, Saris WHM, Van Loon LJC. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. *Am J Clin Nutr* 2012;96:1454–64. <http://dx.doi.org/10.3945/ajcn.112.037556>.
- [44] Denison HJ, Cooper C, Sayer AA, Robinson SM. Prevention and optimal management of sarcopenia: a review of combined exercise and nutrition interventions to improve muscle outcomes in older people. *Clin Interv Aging* 2015;10:859–69. <http://dx.doi.org/10.2147/CI.A.S55842>.
- [45] Tieland M, van de Rest O, Dirks ML, van der Zwaluw N, Mensink M, van Loon LJC, et al. Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2012;13:720–6. <http://dx.doi.org/10.1016/j.jamda.2012.07.005>.
- [46] Daly RM, O'Connell SL, Mundell NL, Grimes CA, Dunstan DW, Nowson CA. Protein-enriched diet, with the use of lean red meat, combined with progressive resistance training enhances lean tissue mass and muscle strength and reduces circulating IL-6 concentrations in elderly women: a cluster randomized controlled trial. *Am J Clin Nutr* 2014;99:899–910. <http://dx.doi.org/10.3945/ajcn.113.064154>.
- [47] Chale A, Cloutier GJ, Hau C, Phillips EM, Dallal GE, Fielding RA. Efficacy of whey protein supplementation on resistance exercise-induced changes in lean mass, muscle strength, and physical function in mobility-limited older adults. *J Gerontol A Biol Sci Med Sci* 2013;68:682–90. <http://dx.doi.org/10.1093/gerona/gls221>.
- [48] Churchward-Venne TA, Holwerda AM, Phillips SM, van Loon LJC. What is the optimal amount of protein to support post-exercise skeletal muscle reconditioning in the older adult? *Sports Med* 2016;46:1205–12. <http://dx.doi.org/10.1007/s40279-016-0504-2>.
- [49] Witard OC, Wardle SL, Macnaughton LS, Hodgson AB, Tipton KD. Protein considerations for optimising skeletal muscle mass in healthy young and older adults. *Nutrients* 2016;8:181. <http://dx.doi.org/10.3390/nu8040181>.
- [50] van Vliet S, Burd NA, van Loon LJC. The skeletal muscle anabolic response to plant- versus animal-based protein consumption. *J Nutr* 2015;145:1981–91. <http://dx.doi.org/10.3945/jn.114.204305>.
- [51] Calvani R, Miccheli A, Landi F, Bossola M, Cesari M, Leeuwenburgh C, et al. Current nutritional recommendations and novel dietary strategies to manage sarcopenia. *J Frailty Aging* 2013;2:38–53. <http://dx.doi.org/10.1530/ERC-14-0411.Persistent>.
- [52] Farsijani S, Morais JA, Payette H, Gaudreau P, Shatenstein B, Gray-Donald K, et al. Relation between mealtime distribution of protein intake and lean mass loss in free-living older adults of the NuAge study. *Am J Clin Nutr* 2016;104:694–703. <http://dx.doi.org/10.3945/ajcn.116.130716>.
- [53] Loenneke JP, Loprinzi PD, Murphy CH, Phillips SM. Per meal dose and frequency of protein consumption is associated with lean mass and muscle performance. *Clin Nutr* 2016;35:1506–11. <http://dx.doi.org/10.1016/j.clnu.2016.04.002>.
- [54] Churchward-Venne TA, Tieland M, Verdijk LB, Leenders M, Dirks ML, de Groot LCPGM, et al. There are no nonresponders to resistance-type exercise training in older men and women. *J Am Med Dir Assoc* 2015;16:400–11. <http://dx.doi.org/10.1016/j.jamda.2015.01.071>.
- [55] Fei S, Norman IJ, While AE. Physical activity in older people: a systematic review. *BMC Public Health* 2013;13:1–17. <http://dx.doi.org/10.1186/1471-2458-13-449>.
- [56] Shad BJ, Wallis G, van Loon LJC, Thompson JL. Exercise prescription for the older population: the interactions between physical activity, sedentary time, and adequate nutrition in maintaining musculoskeletal health. *Maturitas* 2016;93:78–82. <http://dx.doi.org/10.1016/j.maturitas.2016.05.016>.
- [57] English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care* 2010;13:34–9. <http://dx.doi.org/10.1097/MCO.0b013e318333aa66>.
- [58] Wall BT, Dirks ML, Snijders T, van Dijk J-W, Fritsch M, Verdijk LB, et al. Short-term muscle disuse lowers myofibrillar protein synthesis rates and induces anabolic resistance to protein ingestion. *Am J Physiol Endocrinol Metab* 2016;310:E137–47. <http://dx.doi.org/10.1152/ajpendo.00227.2015>.
- [59] Wall BT, Dirks ML, van Loon LJC. Skeletal muscle atrophy during short-term disuse: implications for age-related sarcopenia. *Ageing Res Rev* 2013;12:898–906. <http://dx.doi.org/10.1016/j.arr.2013.07.003>.
- [60] Bauer J, Biolo G, Cederholm T, Cesari M, Cruz-Jentoft AJ, Morley JE, et al. Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the prot-age study group. *J Am Med Dir Assoc* 2013;14:542–59. <http://dx.doi.org/10.1016/j.jamda.2013.05.021>.
- [61] Deutz NEP, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. *Clin Nutr* 2014;33:929–36. <http://dx.doi.org/10.1016/j.clnu.2014.04.007>.
- [62] Paddon-Jones D, Campbell WW, Jacques PF, Kritchevsky SB, Moore LL, Rodriguez NR, et al. Protein and healthy aging. *Am J Clin Nutr* 2015;101:1339S–45S. <http://dx.doi.org/10.3945/ajcn.114.084061>.
- [63] Bischoff-Ferrari HA. Relevance of vitamin D in muscle health. *Rev Endocr Metab Disord* 2012;13:71–7. <http://dx.doi.org/10.1007/s11154-011-9200-6>.
- [64] Halfon M, Phan O, Theta D. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. *Biomed Res Int* 2015;2015:953241. <http://dx.doi.org/10.1155/2015/953241>.
- [65] Srikuera R, Zhang X, Park-Sarge O-K, Esser KA. VDR and CYP27B1 are expressed in C2C12 cells and regenerating skeletal muscle: potential role in suppression of myoblast proliferation. *Am J Physiol Cell Physiol* 2012;303:C396–405. <http://dx.doi.org/10.1152/ajpcell.00014.2012>.
- [66] Wang Y, DeLuca HF. Is the vitamin D receptor found in muscle? *Endocrinology* 2011;152:354–63. <http://dx.doi.org/10.1210/en.2010-1109>.
- [67] Bischoff-Ferrari HA, Borchers M, Gudat F, Durmuller U, Stahelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. *J Bone Min Res* 2004;19:265–9. <http://dx.doi.org/10.1359/jbmr.2004.19.2.265>.
- [68] Ceglia L, da Silva Morais M, Park LK, Morris E, Harris SS, Bischoff-Ferrari HA, et al. Multi-step immunofluorescent analysis of vitamin D receptor loci and myosin heavy chain isoforms in human skeletal muscle. *J Mol Histol* 2010;41:137–42. <http://dx.doi.org/10.1007/s10735-010-9270-x>.
- [69] Pojednic RM, Ceglia L, Olsson K, Gustafsson T, Lichtenstein AH, Dawson-Hughes B, et al. Effects of 1,25-dihydroxyvitamin D3 and vitamin D3 on the expression of the vitamin D receptor in human skeletal muscle cells. *Calcif Tissue Int* 2015;96:256–63. <http://dx.doi.org/10.1007/s00223-014-9932-x>.
- [70] Ceglia L, Niramitmahapanya S, da Silva Morais M, Rivas DA, Harris SS, Bischoff-Ferrari H, et al. A randomized study on the effect of vitamin D(3) supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. *J Clin Endocrinol Metab* 2013;98:E1927–35. <http://dx.doi.org/10.1210/jc.2013-2820>.
- [71] De Vita F, Lauretani F, Bauer J, Bautmans I, Shardell M, Cherubini A, et al. Relationship between vitamin D and inflammatory markers in older individuals. *Age (Dordr)* 2014;36:9694. <http://dx.doi.org/10.1007/s11357-014-9694-4>.
- [72] Pojednic RM, Ceglia L, Lichtenstein AH, Dawson-Hughes B, Fielding RA. Vitamin D receptor protein is associated with interleukin-6 in human skeletal muscle. *Endocrine* 2015;49:512–20. <http://dx.doi.org/10.1007/s12020-014-0505-6>.
- [73] Visser M, Deeg DJH, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass

- (sarcopenia): the longitudinal aging study Amsterdam. *J Clin Endocrinol Metab* 2003;88:5766–72. <http://dx.doi.org/10.1210/jc.2003-030604>.
- [74] Visser M, Deeg DJH, Puts MTE, Seidell JC, Lips P. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. *Am J Clin Nutr* 2006;84:616–22. [84/3/616 \[pii\]](http://dx.doi.org/10.1093/ajcn/84.3.616).
- [75] Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr* 2004;80:752–8. [80/3/752 \[pii\]](http://dx.doi.org/10.1093/ajcn/80.3.752).
- [76] Wicherts IS, Van Schoor NM, Boeke AJP, Visser M, Deeg DJH, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007;92:2058–65. <http://dx.doi.org/10.1210/jc.2006-1525>.
- [77] Wong YY, Flicker L. Hypovitaminosis D and frailty: epiphenomenon or causal? *Maturitas* 2015;82:328–35. <http://dx.doi.org/10.1016/j.maturitas.2015.07.027>.
- [78] Gilsanz V, Kremer A, Mo AO, Wren TAL, Kremer R. Vitamin D status and its relation to muscle mass and muscle fat in young women. *J Clin Endocrinol Metab* 2010;95:1595–601. <http://dx.doi.org/10.1210/jc.2009-2309>.
- [79] Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *J Gerontol A Biol Sci Med Sci* 2005;60:324–33. <http://dx.doi.org/10.1093/gerona/60.3.324>.
- [80] Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. *J Bone Min Res* 2010;25:513–9. <http://dx.doi.org/10.1359/jbmr.090807>.
- [81] ter Borg S, Verlaan S, Hemsworth J, Mijnders DM, Schols JMGA, Luiking YC, et al. Micronutrient intakes and potential inadequacies of community-dwelling older adults: a systematic review. *Br J Nutr* 2015;113:1195–206. <http://dx.doi.org/10.1017/S0007114515000203>.
- [82] Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2011;59:2291–300. <http://dx.doi.org/10.1111/j.1532-5415.2011.03733.x>.
- [83] Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slieman J, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014;99:4336–45. <http://dx.doi.org/10.1210/jc.2014-1742>.
- [84] Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. *Osteoporos Int* 2011;22:859–71. <http://dx.doi.org/10.1007/s00198-010-1407-y>.
- [85] Uusi-Rasi K, Patil R, Karinkanta S, Kannus P, Tokola K, Lamberg-Allardt C, et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. *JAMA Intern Med* 2015;175:703–11. <http://dx.doi.org/10.1001/jamainternmed.2015.0225>.
- [86] Ometto F, Stubbs B, Annweiler C, Duval GT, Jang W, Kim H-T, et al. Hypovitaminosis D and orthostatic hypotension: a systematic review and meta-analysis. *J Hypertens* 2016;34:1036–43. <http://dx.doi.org/10.1097/HJH.0000000000000907>.
- [87] Gangavati A, Hajjar I, Quach L, Jones RN, Kiely DK, Gagnon P, et al. Hypertension, orthostatic hypotension, and the risk of falls in a community-dwelling elderly population: the maintenance of balance, independent living, intellect, and zest in the elderly of Boston study. *J Am Geriatr Soc* 2011;59:383–9. <http://dx.doi.org/10.1111/j.1532-5415.2011.03317.x>.
- [88] Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: a meta-analysis. *JAMA* 2004;291:1999–2006. <http://dx.doi.org/10.1001/jama.291.16.1999>.
- [89] Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. *QJM* 2007;100:185–92. <http://dx.doi.org/10.1093/qjmed/hcm005>.
- [90] O'Donnell S, Moher D, Thomas K, Hanley DA, Cranney A. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. *J Bone Min Metab* 2008;26:531–42. <http://dx.doi.org/10.1007/s00774-008-0868-y>.
- [91] Richey F, Dukas L, Schacht E. Differential effects of D-hormone analogs and native vitamin D on the risk of falls: a comparative meta-analysis. *Calcif Tissue Int* 2008;82:102–7. <http://dx.doi.org/10.1007/s00223-008-9102-0>.
- [92] Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 2009;339:b3692. <http://dx.doi.org/10.1136/bmj.b3692>.
- [93] Kalyani RR, Stein B, Valiyyil R, Manno R, Maynard JW, Crews DC. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. *J Am Geriatr Soc* 2010;58:1299–310. <http://dx.doi.org/10.1111/j.1532-5415.2010.02949.x>.
- [94] Michael YL, Lin JS, Whitlock EP, Gold R, Fu R, O'Connor EA, et al. Interventions to prevent falls in older adults. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010.
- [95] Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourechi MM, et al. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:2997–3006. <http://dx.doi.org/10.1210/jc.2011-1193>.
- [96] Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev* 2012;12, CD005465. <http://dx.doi.org/10.1002/14651858.CD005465.pub3>.
- [97] Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol* 2014;2:307–20. [http://dx.doi.org/10.1016/S2213-8587\(13\)70212-2](http://dx.doi.org/10.1016/S2213-8587(13)70212-2).
- [98] Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, et al. Monthly high-dose vitamin D treatment for the prevention of functional decline: a randomized clinical trial. *JAMA Intern Med* 2016;176:175–83. <http://dx.doi.org/10.1001/jamainternmed.2015.7148>.
- [99] Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010;303:1815–22. <http://dx.doi.org/10.1001/jama.2010.594>.
- [100] Bauer JM, Verlaan S, Bautmans I, Brandt K, Donini LM, Maggio M, et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2015;16:740–7. <http://dx.doi.org/10.1016/j.jamda.2015.05.021>.
- [101] Semba RD, Ferrucci L, Sun K, Walston J, Varadhan R, Guralnik JM, et al. Oxidative stress and severe walking disability among older women. *Am J Med* 2007;120:1084–9. <http://dx.doi.org/10.1016/j.amjmed.2007.07.028>.
- [102] Kim J-S, Wilson JM, Lee S-R. Dietary implications on mechanisms of sarcopenia: roles of protein, amino acids and antioxidants. *J Nutr Biochem* 2010;21:1–13. <http://dx.doi.org/10.1016/j.jnutbio.2009.06.014>.
- [103] Chen Y-L, Yang K-C, Chang H-H, Lee L-T, Lu C-W, Huang K-C. Low serum selenium level is associated with low muscle mass in the community-dwelling elderly. *J Am Med Dir Assoc* 2014;15:807–11. <http://dx.doi.org/10.1016/j.jamda.2014.06.014>.
- [104] Semba RD, Blaum C, Guralnik JM, Moncrief DT, Ricks MO, Fried LP. Carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. *Aging Clin Exp Res* 2003;15:482–7.
- [105] Lauretani F, Semba RD, Bandinelli S, Dayhoff-Brannigan M, Lauretani F, Corsi AM, et al. Carotenoids as protection against disability in older persons. *Rejuvenation Res* 2008;11:557–63. <http://dx.doi.org/10.1089/rej.2007.0581>.
- [106] Myung S-K, Yang HJ. Efficacy of vitamin and antioxidant supplements in prevention of esophageal cancer: meta-analysis of randomized controlled trials. *J Cancer Prev* 2013;18:135–43. <http://dx.doi.org/10.15430/JCP.2013.18.2.135>.
- [107] Myung S-K, Ju W, Cho B, Oh S-W, Park SM, Koo B-K, et al. Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013;346:f10. <http://dx.doi.org/10.1136/bmj.f10>.
- [108] Fusco D, Colloca G, Lo Monaco MR, Cesari M. Effects of antioxidant supplementation on the aging process. *Clin Interv Aging* 2007;2:377–87.
- [109] Jackson MJ. Strategies for reducing oxidative damage in ageing skeletal muscle. *Adv Drug Deliv Rev* 2009;61:1363–8. <http://dx.doi.org/10.1016/j.addr.2009.07.018>.
- [110] Bjornsen T, Salvesen S, Berntsen S, Hetlelid KJ, Stea TH, Lohne-Seiler H, et al. Vitamin C and E supplementation blunts increases in total lean body mass in elderly men after strength training. *Scand J Med Sci Sports* 2016;26:755–63. <http://dx.doi.org/10.1111/sms.12506>.
- [111] Li K, Huang T, Zheng J, Wu K, Li D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor alpha: a meta-analysis. *PLoS One* 2014;9:e88103. <http://dx.doi.org/10.1371/journal.pone.0088103>.
- [112] Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 1999;47:639–46. <http://dx.doi.org/10.1111/j.1532-5415.1999.tb01583.x>.
- [113] Jeffery CA, Shum DWC, Hubbard RE. Emerging drug therapies for frailty. *Maturitas* 2013;74:21–5. <http://dx.doi.org/10.1016/j.maturitas.2012.10.010>.
- [114] Penninx BWJH, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, et al. Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc* 2004;52:1105–13. <http://dx.doi.org/10.1111/j.1532-5415.2004.52308.x>.
- [115] Baylis D, Ntani G, Edwards MH, Syddall HE, Bartlett DB, Dennison EM, et al. Inflammation, telomere length, and grip strength: a 10-year longitudinal study. *Calcif Tissue Int* 2014;95:54–63. <http://dx.doi.org/10.1007/s00223-014-9862-7>.
- [116] Raphael W, Sordillo LM. Dietary polyunsaturated fatty acids and inflammation: the role of phospholipid biosynthesis. *Int J Mol Sci* 2013;14:21167–88. <http://dx.doi.org/10.3390/ijms141021167>.
- [117] Casas-Agustench P, Cherubini A, Andres-Lacueva C. Lipids and physical function in older adults. *Curr Opin Clin Nutr Metab Care* 2017;20:16–25. <http://dx.doi.org/10.1097/MCO.0000000000000333>.
- [118] Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr* 2006;83:1505S–19S. 16841861.
- [119] Smith GI. The effects of dietary Omega-3s on muscle composition and quality in older adults. *Curr Nutr Rep* 2016;5:99–105. <http://dx.doi.org/10.1007/s13668-016-0161-y>.

- [120] Smith GI, Atherton P, Reeds DN, Mohammed BS, Rankin D, Rennie MJ, et al. Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. *Am J Clin Nutr* 2011;93:402–12. <http://dx.doi.org/10.3945/ajcn.110.005611>.
- [121] Robinson SM, Jameson KA, Batelaan SF, Martin HJ, Syddall HE, Dennison EM, et al. Diet and its relationship with grip strength in community-dwelling older men and women: the Hertfordshire cohort study. *J Am Geriatr Soc* 2008;56:84–90. <http://dx.doi.org/10.1111/j.1532-5415.2007.01478.x>.
- [122] Reinders I, Murphy RA, Song X, Visser M, Cotch MF, Lang TF, et al. Polyunsaturated fatty acids in relation to incident mobility disability and decline in gait speed; the Age, Gene/Environment Susceptibility-Reykjavik Study. *Eur J Clin Nutr* 2015;69:489–93. <http://dx.doi.org/10.1038/ejcn.2014.277>.
- [123] Welch AA, MacGregor AJ, Minihane A-M, Skinner J, Valdes AA, Spector TD, et al. Dietary fat and fatty acid profile are associated with indices of skeletal muscle mass in women aged 18–79 years. *J Nutr* 2014;144:327–34. <http://dx.doi.org/10.3945/jn.113.185256>.
- [124] Hutchins-Wiese HL, Kleppinger A, Annis K, Liva E, Lammi-Keefe CJ, Durham HA, et al. The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women. *J Nutr Health Aging* 2013;17:76–80. <http://dx.doi.org/10.1007/s12603-012-0415-3>.
- [125] Rodacki CLN, Rodacki ALF, Pereira G, Naliwaiko K, Coelho I, Pequito D, et al. Fish-oil supplementation enhances the effects of strength training in elderly women. *Am J Clin Nutr* 2012;95:428–36. <http://dx.doi.org/10.3945/ajcn.111.021915>.
- [126] Smith GI, Julliard S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. *Am J Clin Nutr* 2015;102:115–22. <http://dx.doi.org/10.3945/ajcn.114.105833>.
- [127] Krzymińska-Siemaszko R, Czepulis N, Lewandowicz M, Zasadzka E, Suwalska A, Witowski J, et al. The effect of a 12-week Omega-3 supplementation on body composition, muscle strength and physical performance in elderly individuals with decreased muscle mass. *Int J Environ Res Public Health* 2015;12:10558–74. <http://dx.doi.org/10.3390/ijerph120910558>.
- [128] Bos C, Gaudichon C, Tomé D. Nutritional and physiological criteria in the assessment of milk protein quality for humans. *J Am Coll Nutr* 2000;19:191S–205S. <http://dx.doi.org/10.1080/07315724.2000.10718068>.
- [129] Draganidis D, Karagounis LG, Athanailidis I, Chatzinikolaou A, Jamurtas AZ, Fatouros IG. Inflammaging and skeletal muscle: can protein intake make a difference? *J Nutr* 2016;146:1–13. <http://dx.doi.org/10.3945/jn.116.230912>.
- [130] Radavelli-Bagatini S, Zhu K, Lewis JR, Dhaliwal SS, Prince RL. Association of dairy intake with body composition and physical function in older community-dwelling women. *J Acad Nutr Diet* 2013;113:1669–74. <http://dx.doi.org/10.1016/j.jand.2013.05.019>.
- [131] Alemán-Mateo H, Carreón VR, Macías L, Astiazaran-García H, Gallegos-Aguilar AC, Ramos Enriquez JR. Nutrient-rich dairy proteins improve appendicular skeletal muscle mass and physical performance, and attenuate the loss of muscle strength in older men and women subjects: a single-blind randomized clinical trial. *Clin Interv Aging* 2014;9:1517–25. <http://dx.doi.org/10.2147/CLIA.S67449>.
- [132] Elliot TA, Cree MG, Sanford AP, Wolfe RR, Tipton KD. Milk ingestion stimulates net muscle protein synthesis following resistance exercise. *Med Sci Sports Exerc* 2006;38:667–74. <http://dx.doi.org/10.1249/01.mss.000021-0190.64458.25>.
- [133] Josse AR, Tang JE, Tarnopolsky MA, Phillips SM. Body composition and strength changes in women with milk and resistance exercise. *Med Sci Sports Exerc* 2010;42:1122–30. <http://dx.doi.org/10.1249/MSS.0b013e-3181c854f6>.
- [134] Josse AR, Atkinson SA, Tarnopolsky MA, Phillips SM. Increased consumption of dairy foods and protein during diet- and exercise-induced weight loss promotes fat mass loss and lean mass gain in overweight and obese premenopausal women. *J Nutr* 2011;141:1626–34. <http://dx.doi.org/10.3945/jn.111.141028>.
- [135] Kukuljan S, Nowson CA, Sanders K, Daly RM. Effects of resistance exercise and fortified milk on skeletal muscle mass, muscle size, and functional performance in middle-aged and older men: an 18-mo randomized controlled trial. *J Appl Physiol* 2009;107:1864–73. <http://dx.doi.org/10.1152/jappphysiol.00392.2009>.
- [136] Schoenfeld BJ, Aragon AA, Krieger JW. The effect of protein timing on muscle strength and hypertrophy: a meta-analysis. *J Int Soc Sports Nutr* 2013;10:53. <http://dx.doi.org/10.1186/1550-2783-10-53>.
- [137] Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, et al. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. *Am J Clin Nutr* 2007;86:373–81. [http://dx.doi.org/10.1016/S0162-0908\(08\)79232-8](http://dx.doi.org/10.1016/S0162-0908(08)79232-8).
- [138] Thomson RL, Brinkworth GD, Noakes M, Buckley JD. Muscle strength gains during resistance exercise training are attenuated with soy compared with dairy or usual protein intake in older adults: a randomized controlled trial. *Clin Nutr* 2016;35:27–33. <http://dx.doi.org/10.1016/j.clnu.2015.01.018>.
- [139] Siero M, Oggioni C, Jakovljevic DG, Trenell M, Mathers JC, Houghton D, et al. Dietary nitrate does not affect physical activity or outcomes in healthy older adults in a randomized, cross-over trial. *Nutr Res* 2016;36:1361–9. <http://dx.doi.org/10.1016/j.nutres.2016.11.004>.
- [140] Jones AM. Dietary nitrate supplementation and exercise performance. *Sports Med* 2014;44(Suppl. 1):S35–45. <http://dx.doi.org/10.1007/s40279-014-0149-y>.
- [141] Coggan AR, Peterson LR. Dietary nitrate and skeletal muscle contractile function in heart failure. *Curr Heart Fail Rep* 2016;13:158–65. <http://dx.doi.org/10.1007/s11897-016-0293-9>.
- [142] Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* 2002;13:3–9.
- [143] Rabassa M, Zamora-Ros R, Andres-Lacueva C, Urpi-Sarda M, Bandinelli S, Ferrucci L, et al. Association between both total baseline urinary and dietary polyphenols and substantial physical performance decline risk in older adults: a 9-year follow-up of the InCHIANTI study. *J Nutr Health Aging* 2016;20:478–84. <http://dx.doi.org/10.1007/s12603-015-0600-2>.
- [144] Millward DJ. Nutrition and sarcopenia: evidence for an interaction. *Proc Nutr Soc* 2012;71:566–75. <http://dx.doi.org/10.1017/S0029665112000201>.
- [145] Welch AA, MacGregor AJ, Skinner J, Spector TD, Moayyeri A, Cassidy A. A higher alkaline dietary load is associated with greater indexes of skeletal muscle mass in women. *Osteoporos Int* 2013;24:1899–908. <http://dx.doi.org/10.1007/s00198-012-2203-7>.
- [146] Dawson-Hughes B, Harris SS, Ceglia L. Alkaline diets favor lean tissue mass in older adults. *Am J Clin Nutr* 2008;87:662–5. <http://dx.doi.org/10.1016/j.biotechadv.2011.08.021.Secreted>.
- [147] Hagan KA, Chiuev SE, Stampfer MJ, Katz JN, Grodstein F. Greater adherence to the alternative healthy eating index is associated with lower incidence of physical function impairment in the nurses' health study. *J Nutr* 2016;146:1341–7. <http://dx.doi.org/10.3945/jn.115.227900>.
- [148] Robinson SM, Jameson KA, Syddall HE, Dennison EM, Cooper C, Aihie Sayer A. Clustering of lifestyle risk factors and poor physical function in older adults: the Hertfordshire cohort study. *J Am Geriatr Soc* 2013;61:1684–91. <http://dx.doi.org/10.1111/jgs.12457>.
- [149] Xu B, Houston DK, Locher JL, Ellison KJ, Gropper S, Buys DR, et al. Higher healthy eating index-2005 scores are associated with better physical performance. *J Gerontol – Ser A Biol Sci Med Sci* 2012;67A:93–9. <http://dx.doi.org/10.1093/gerona/glr159>.
- [150] Bollwein J, Diekmann R, Kaiser MJ, Bauer JM, Uter W, Sieber CC, et al. Dietary quality is related to frailty in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2013;68:483–9. <http://dx.doi.org/10.1093/gerona/gls204>.
- [151] Henriquez Sanchez P, Ruano C, de Irala J, Ruiz-Canela M, Martinez-Gonzalez MA, Sanchez-Villegas A. Adherence to the Mediterranean diet and quality of life in the SUN project. *Eur J Clin Nutr* 2012;66:360–8. <http://dx.doi.org/10.1038/ejcn.2011.146>.
- [152] Feart C, Peres K, Samieri C, Letenneur L, Dartigues J-F, Barberger-Gateau P. Adherence to a Mediterranean diet and onset of disability in older persons. *Eur J Epidemiol* 2011;26:747–56. <http://dx.doi.org/10.1007/s10654-011-9611-4>.
- [153] Milaneschi Y, Bandinelli S, Corsi AM, Lauretani F, Paolisso G, Dominguez LJ, et al. Mediterranean diet and mobility decline in older persons. *Exp Gerontol* 2011;46:303–8. <http://dx.doi.org/10.1016/j.exger.2010.11.030>.
- [154] Talegawkar SA, Bandinelli S, Bandeen-Roche K, Chen P, Milaneschi Y, Tanaka T, et al. A higher adherence to a mediterranean-style diet is inversely associated with the development of frailty in community-dwelling elderly men and women. *J Nutr* 2012;142:2161–6. <http://dx.doi.org/10.3945/jn.112.165498>.
- [155] Shahar DR, Houston DK, Hue TF, Lee JS, Sahyoun NR, Tylavsky FA, et al. Adherence to mediterranean diet and decline in walking speed over 8 years in community-dwelling older adults. *J Am Geriatr Soc* 2012;60:1881–8. <http://dx.doi.org/10.1111/j.1532-5415.2012.04167.x>.
- [156] Studenski S. Target population for clinical trials. *J Nutr Health Aging* 2009;13:729–32.