Nutritional supplementation to enhance the efficacy of exercise training in older adults: what is the evidence from the latest randomized controlled trials?

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Purpose of review
This review summarizes recent studies that assessed whether nutritional supplementation enhances the efficacy of exercise training in older adults, focusing on the benefits for physical/functional performance of protein, vitamin D, or multi-ingredient supplementation.

Recent findings
Studies applying long-term exercise training strongly support the benefits of different exercise regimens for muscle strength and function but most studies do not provide direct evidence for protein, vitamin D, or multi-ingredient supplementation to further augment such improvements in older adults. Several methodological limitations are addressed that likely limited the reliability to convincingly establish or refute any additive effects of supplementation. Only when specifically tailored to the population under study, ensuring proper intensity, duration, and adherence to exercise, and aiming for a daily intake of \( \sim 1.5 \) g protein per kg body mass, and \( \sim 800 \) IU of vitamin D supplementation, there appears to be some potential to augment the efficacy of long-term exercise training in older adults, with potentially greater benefits in compromised older subpopulations.

Summary
There is some support for the efficacy of nutritional supplementation to further augment the beneficial effects of prolonged exercise training in older adults but any intervention needs tailoring of both the exercise and the nutritional intervention towards the intended (sub)population.

Keywords
ageing, exercise, multi-ingredient, protein, vitamin D

INTRODUCTION
The world’s population is ageing rapidly, with an expected doubling of the number of people aged over 65 years by 2050. Though increased life expectancy is the successful result of improved healthcare, nutrition, and hygiene over the past 100 years, ageing in itself is associated with several detrimental consequences. Too often, increased lifespan is accompanied by a disproportionate increase in the number of years spent in ill health. Indeed, ageing is associated with a reduction in muscle mass, functionality, and physical performance capacity, along with compromised metabolic and/or cardiovascular health, impaired immune function, lower cognitive abilities, and an increased risk to develop various diseases, such as cancer, obesity, type 2 diabetes, and chronic obstructive pulmonary disease (COPD). In light of the importance of (physical) functioning, the WHO has defined ‘healthy ageing’ as the process of developing and maintaining functional ability that enables well being in older age [1]. As such, any intervention aiming to support healthy ageing...
should preferably take some form of physical functioning into account.

In general, ageing represents a diverse process, and several hallmarks of ageing have been identified that dictate the way in which each individual ages successfully or not [2]. Although some of these hallmarks may not be modified easily, it is commonly accepted that in general, lifestyle can have a major positive impact on the biological processes that drive human ageing. As such, it is not surprising that two of the key lifestyle factors, that is, physical activity and nutrition, have received much attention as antiageing strategies. An overall physically active lifestyle as well as specific exercise training programs have clearly been shown to counteract age-related declines in, for example, cardiovascular and metabolic health, and to effectively improve muscle mass and functional performance in both healthy and more compromised older populations [3]. As elegantly stated by Garatachea et al. [4], exercise cannot reverse the ageing process, but it does attenuate many of its deleterious systemic and cellular effects, effectively counteracting many of the hallmarks of ageing. Likewise, good nutrition is imperative for overall health and both epidemiologic and intervention studies provide ample evidence for the potential of various nutritional strategies to elicit specific health benefits and support healthy ageing. Moreover, good nutrition is essential to facilitate the adaptive response to exercise training programs. In fact, it is suggested that any improvements in response to exercise training alone may be attenuated in (subgroups of) the older population. Therefore, numerous efforts have been made to further augment the benefits of exercise in older people through nutritional supplementation, although with varying success [5,6].

The current review serves to summarize recent findings of those studies that aimed to assess whether nutritional supplementation can enhance the efficacy of exercise training in older adults. A literature search was performed on studies published between October 2019 and April 2021 that used a randomized approach and with the requirement of at least a comparison between a combined exercise and nutritional intervention versus an ‘exercise-only’ intervention. The latter could include either a placebo/control nutritional intervention or no nutritional intervention, and the total intervention period was set at minimally 4 weeks. On the basis of the studies found, a further selection was made for the inclusion of ‘protein-like’ nutritional interventions, ‘vitamin D’ interventions, or ‘multi-ingredient’ interventions. As outcome measures, at least one measure of physical functioning should be assessed.

### Key Points

- Exercise remains the cornerstone of interventions to counteract age-associated impairments in physical functioning and (metabolic) health. Selecting the appropriate type, duration, and intensity, and ensuring adherence through supervision are essential.
- Optimizing the nutritional supplementation strategy is key to the ability to accurately attain or refute any added benefits: minimally 12 weeks, providing ~40 to 50 g additional protein (or a total of 1.5 g/kg body mass per day), and ~800 IU vitamin D.
- Recent work indicates that specific (compromised) subpopulations may respond better to specific interventions, such as those with greater fat mass or those with evident sarcopenia.
- Future work should confirm the effectiveness of combined exercise plus multi-ingredient supplementation per se, and establish whether multi-ingredient is superior to single-nutrient supplementation on top of exercise in older adults.

### Exercise Training and Supplementation of Protein, Amino Acids, or β-Hydroxy-β-Methylbutyrate

Dietary protein provides the amino acids needed to build new muscle. Apart from serving as building blocks to sustain the essential transient increases in muscle protein synthesis following muscle contractions, specific amino acids also act as signalling molecules to further stimulate anabolic pathways that drive the muscle growth response to (resistance) exercise. As such, there continues to be a vast interest into the potential of supplemental protein, specific amino acids, or amino acid derivatives as a means to augment the response to exercise training. Interestingly, recent work has investigated this matter not only in healthy community-dwelling older adults but also in more compromised older individuals. Gade et al. [7*] included 141 geriatric medical patients above 70 years who performed progressive low-intensity resistance exercise throughout hospitalization (supervised, ~5 days on average) as well as at home up to 12 weeks after hospital discharge (unsupervised, four sessions per week). Participants ingested either a daily dose of 27.5 g whey-based protein supplement, or an isocaloric placebo. Overall, muscle mass and strength, as well as physical performance and quality of life improved but with no differences between placebo and protein-supplemented groups. Unfortunately, compliance to the...
intervention was quite low, at about 50% ‘good compliance’ for both the exercise and the nutritional intervention. Furthermore, total protein intake remained well below the recommended intake for compromised patient populations, even in the protein-supplemented group [7]. In a similar fashion, Amasene et al. [9] showed that 12 weeks of posthospitalization resistance exercise (supervised, two sessions per week) elicits improvements in physical functioning in 41 sarcopenic patients (≥70 years), with no added benefit of a leucine-enriched whey protein supplement. Although compliance was good for the nutritional intervention, supplements were only provided twice per week, that is, postexercise, which may have limited its anabolic potential. Furthermore, the study was limited by the relatively low sample size and fairly large dropout of ~30% [9].

In contrast to this work, a more prolonged intervention period may be necessary to induce benefits with a postexercise supplementation strategy. Indeed, postexercise branched-chain amino acid (BCAA) supplementation resulted in the most profound improvements in sit-to-stand performance following a 16-week training, 8-week detraining, and subsequent 16-week retraining program in older (≥75 years) care home residents when compared with exercise alone, BCAA alone, or no intervention [10]. Whereas these findings indicate the potential of BCAA to further optimize prolonged exercise intervention effects, the nonprobabilistic sampling approach as well as the small sample size (n = 7/8 in the intervention groups) that mostly lead to non-significant interactions, are major limitations to this work [10], and larger studies are needed to verify the outcomes. Such a larger study in older sarcopenic men and women (75–96 years) was undertaken in Finland [11*]. Instructions for a low-intensity home-based exercise program were combined with daily supplementation of 40 g milk protein, an isocaloric placebo, or no nutritional co-intervention. Contrary to the expectation, physical performance tended to decline over the 1-year study period, with no differences between groups and thus, no benefit of protein supplementation. Including the large number of 218 sarcopenic elderly in this ‘real-life’ study, with only 18% dropout, clearly adds to the novelty and relevance of the observations. Unfortunately, compliance in this study was again problematic with only ~50% adhering to both the exercise and nutritional intervention. Yet, the results did not change when only the ‘compliant’ participants were included in the analyses [11*].

In line with some of the studies in more compromised older populations, recent work in community-dwelling, healthy older adults also employed home-based exercise strategies. Nakayama et al. [12*] recruited 122 healthy older men and women (60–84 years) who performed 6 months of home-based low-to-moderate intensity weight training on a daily basis, with or without additional milk protein supplementation (10 g/day). Importantly, monthly supervised sessions were organized, likely contributing to the good compliance, which was well above 90% for both the exercise and nutritional intervention. All measures of physical performance improved similarly in both groups. In contrast, only in the protein-supplemented group, lean mass increased and fat mass decreased. Thus, it could be argued that, although high-intensity exercise usually increases muscle mass by itself, a modest but feasible amount of supplemental protein may be needed to elicit a similar effect with low-to-moderate intensity exercise in older individuals [12*]. Somewhat similar to this work, Kim et al. [13*] included 130 community-dwelling older Japanese women (≥65 years) who performed a moderate intensity, home-based functional strength training program, with one supervised class per week for a total of 12 weeks. Although leg strength, walking speed and timed-up-and-go function improved, measures of lean mass actually slightly declined throughout intervention. Moreover, these results were not affected by daily supplementation of 3 g EAA. This likely highlights the importance of providing an ample amount of protein/amino acids to enable any potential effect to be elicited. In accordance, supplementation of a small amount of soy peptide (4 g/day) was also reported to be ineffective in further increasing muscle mass and functional improvements in response to a 3-month supervised aerobic exercise training program including 67 older (≥60 years) Japanese men and women [14]. In another study, only 3 g/day of β-hydroxy-β-methyl-butyrure (HMB) supplementation for 6 weeks was not enough to enhance the improvements in muscle mass and strength in response to a 3×/week supervised, high-intensity resistance exercise program in healthy older men (~69 years) [15]. The authors argued that there may still be a (marginal) effect of HMB on muscle mass but the study may not have been of long enough duration and/or sufficient sample size to statistically establish this [15]. However, the actual data on lean mass as well as vastus lateralis muscle thickness do not seem to provide any indication of a differential response in the exercise only versus exercise+HMB group.

Finally, a recent study that did show an added benefit of protein supplementation on top of a moderate-intensity to high-intensity exercise program was performed by Timmons et al. [16**]. In their study, 56 healthy older men and women
performed 12 weeks of supervised, high-intensity concurrent exercise known to improve muscle strength, physical function, and body composition. Of interest, a ‘whole-food protein approach’ was used to increase protein intake in the protein+exercise and the protein-only group from ~1.0 to ~1.5 g/kg body mass per day. The combined protein+exercise intervention resulted in a statistically larger improvement in lower extremity strength when compared with the exercise-only group, as well as a larger improvement in appendicular lean mass, although the latter finding did not reach statistical significance [16**]. As noted by the authors, the benefits may be explained by the large increase in protein intake reached through their whole-food approach, adding an extra 40–55 g protein on a daily basis. Taken together, the above findings may very well imply that the daily protein dose needed to further facilitate the beneficial effects of exercise training in older adults is simply not reached in many intervention studies.

In summary, the majority of recent work does not provide much direct evidence for protein supplementation to further augment any functional improvements on top of the benefits induced by long-term exercise training, both in compromised frail/sarcopenic populations and in healthy elderly men and women. That said, specific methodological issues, including the utilization of suboptimal (home-based) exercise intensities, low subject numbers, low subject compliance, and suboptimal protein supplementation strategies in terms of timing, dosing and/or study duration, may have seriously hampered the ability to reliably establish or refute any potential benefits in many of the recent studies. As such, future work aiming to optimize the adaptive response to prolonged exercise programs in the older population should strive to maximize sample size; aim for at least 12–16 weeks of intervention, with properly supervised exercise sessions tailored to the target population in terms of workload intensity; and daily provision of ample amounts of (supplemental) protein, targeting the previously proposed 1.2–1.5 g/kg body mass per day [16**].

**EXERCISE TRAINING AND VITAMIN D SUPPLEMENTATION**

Vitamin D represents one of the compounds that is already high on the list of many older people taking supplements. Vitamin D plays a role in many physiological processes in the human body and has, with regard to ageing, been associated with changes in bone health, muscle health, immune function, and neural health. Most research in this area has focused on musculoskeletal health, and benefits for muscle strength have been proposed for vitamin D supplementation per se, especially in those with low vitamin D status [17]. Yet, it remains questionable whether vitamin D supplementation can further augment the benefits of exercise training in older individuals. Indeed, a recent meta-analyses provided only ‘tentative support’ for an additive effect on muscle strength gains but not any other functional performance measures, and highlighted the scarcity of available literature [18]. To further build the evidence base on this matter, two recent studies have evaluated the potential effect of vitamin D supplementation on top of resistance exercise training. Brech et al. [19] used a 12-week supervised, combined resistance and postural balance training program with or without vitamin D supplementation in 46 older women with low bone mineral density and vitamin D insufficiency (i.e. <30 ng/ml). Although some minor benefits were observed for certain balance control measures, the vast majority of strength, functional, and balance outcomes was improved by the exercise program, with no additive effect of vitamin D supplementation. This lead the authors to conclude that vitamin D did not further improve muscle strength and postural balance in response to the combined exercise program [19]. Using a slightly different approach, Molmen et al. [20*] attempted to prime the myocellular milieu for adaptations by first deploying a 12-week placebo-controlled vitamin D supplementation protocol, which was then followed by 13 weeks of continued supplementation combined with 2×/week, supervised whole-body resistance exercise training. Using a very extensive set of outcome measures in both healthy and compromised (i.e. COPD) older men and women, this study confirmed the previously well established beneficial effects of supervised resistance exercise training on muscle mass, muscle strength, endurance performance, muscle function, myocellular characteristics (e.g. muscle fibre size and myonuclear content), and several (blood) markers of metabolic health. In contrast to the hypothesis, no additional improvements were observed in the vitamin D versus placebo-supplemented group for any of the primary or secondary outcome measures, which was also not affected by baseline vitamin D status [20*]. Overall, current evidence in humans does not yet convincingly indicate that vitamin D supplementation can further boost the effects of (resistance) exercise training on musculoskeletal health. It should be noted though that the body of work addressing this specific matter is still limited. There have so far not been any studies using endurance training, and it remains to be determined whether vitamin D may further enhance the

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exercise training response in specific older subpopulations, such as those with very low levels of circulating vitamin D (below 20 ng/ml) or those with (overt) obesity [20*].

**EXERCISE TRAINING AND MULTI-INGREDIENT SUPPLEMENTATION**

In terms of methodological approach, it is obvious that the potential additive effects of a specific nutritional compound are best tested in a randomized, controlled study with the requirement of at least one ‘exercise-only’ group, and one ‘exercise plus experimental product’ group. Any beneficial effects on top of the exercise-only effects can then be attributed to the specific nutritional compound under investigation, be it protein, vitamin D, or any other macronutrient or micronutrient. At the same time, we realize more and more that the consequences of ageing are explained by a multitude of factors. Even when only looking at nutritional factors, the underlying causes for ageing phenomena may range from generalized energy overnutrition to undernutrition, as well as deficiency of specific macronutrients or micronutrients, such as protein, vitamin D, calcium, vitamin K, poly-unsaturated fatty acids, and many others. Hence, a multi-ingredient supplementation approach would arguably have a larger potential to augment the adaptive response to an exercise training regimen. A glance at recent literature seems to corroborate this line of reasoning as based on the increasing number of studies performed. Yet, although multi-ingredient supplementation has the capacity to enable greater gains in muscle mass and strength in response to (resistance) exercise training in both young and older adults, it is still unclear whether the effect is larger than with, for example, protein supplements only [21].

By far, the largest trial that evaluated both the combined and separate effects of prolonged exercise and nutritional supplementation in older adults was recently published in JAMA [22**]. In this multicenter study, more than 2000 healthy, community-dwelling older men and women (≥70 years) were randomized to daily vitamin D supplementation, daily omega-3 supplementation, 3×/week 30 min home-based strength training, or any combination of these interventions, yielding a total of eight treatment groups. Total follow-up time was 3 years and clinical outcomes included blood pressure, physical performance (short physical performance battery; SPPB), cognitive status, and incidence rate of fractures and infections. In terms of the multi-ingredient approach, no differences were observed between the exercise-only group and the exercise group also receiving vitamin D and omega-3 supplementation. More surprisingly, no differences in any of the outcome measures were observed between any of the treatment groups, including the control group. As such, the authors concluded that their findings did not support the effectiveness of vitamin D supplementation, omega-3 supplementation or a strength training program, either alone or combined, for physical performance or any of the other clinical outcomes in healthy older adults [22**]. Importantly though, despite the complex, long-term, and rigorous study design and the high adherence rates reported [22**], a number of key methodological issues may very well explain the lack of improvements observed, especially in response to the exercise program. These include the recruitment of very active and healthy participants, the application of a relatively low-intensity exercise program, in combination with the selection of a functional outcome measure (SPPB) that was already high at baseline (11 out of 12 points), altogether hardly leaving any room for improvements to be accomplished.

As mentioned earlier, both the exercise and nutritional intervention should be designed in such a way as to maximize the effects for the specific population at stake. Recent work from de Carvalho Bastone et al. [23*] provides interesting insights in this respect. By providing proper supervision, they were able to apply a 3-month home-based resistance exercise program at high intensity, resulting in large improvements in all measures of physical functioning (strength, gait speed, sit-to-stand) in older adults with low muscle strength and low protein intake at baseline. Nonetheless, daily supplementation of a protein-based multi-ingredient mixture did not affect any of the outcomes [23*]. In accordance, Miller et al. [24**] showed that 6 months of progressive, supervised resistance training in metabolically compromised, overweight/obese type 2 diabetes patients effectively improved body composition, lean mass, muscle strength, and glucose homeostasis. Of note, the daily protein with vitamin D supplementation strategy only further increased sit-to-stand performance and tended to further increase muscle mass. Yet, these added benefits became significant in the preplanned per-protocol analyses [24**]. Combined, these findings underline the importance of proper supervision or any other measures needed to maximize compliance and adherence to the interventional strategies. Furthermore, as certain benefits may be easier to attain in more compromised populations, it is of key importance to tailor both the exercise and nutritional intervention to the specific population under study.

As an example of such a tailored strategy, Rathmacher et al. [25*] worked on the premise that
vitamin D status plays a role in the efficacy of HMB supplementation, and included vitamin D-insufficient older adults in their study. Although the 12-month combined vitamin D and HMB supplementation period effectively abolished the vitamin D insufficiency, no added benefit on top of moderate-intensity supervised resistance exercise was shown, rendering the HMB supplementation ineffective. Interestingly, without the exercise component, vitamin D plus HMB supplementation did result in improved functional performance, with similar benefits as compared with the exercise-only and the exercise-supplemented groups [25]. Finally, Nilsson et al. [26] specifically recruited overweight/mildly obese, inactive older men and developed a tailored, home-based, moderate-intensity resistance exercise program with elastic bands, either with or without daily multi-ingredient supplementation (i.e. 40 g protein, 3 g creatine, vitamin D, and omega-3). Whereas no time × treatment interactions were observed for body composition, muscle strength, and function after the 12-week program, the authors concluded that the multi-ingredient supplementation was an effective complement to the resistance training program [26]. This was based on within-group analyses that only showed improvements in the supplemented group and not in the exercise-only group. Clearly, the statistical approach taken here is inappropriate, and any ‘lack of interaction effects’ is likely explained by the combination of low participants numbers and large interindividual variation in the exercise response. Yet, the observations from this study do indirectly support the potential for multi-ingredient supplementation to augment the benefits of exercise training in older individuals. Furthermore, in line with the potentially larger window of opportunity in compromised older adults, preplanned secondary analyses in this study indicated a greater potential for improvements in sarcopenic versus nonsarcopenic participants [26].

Summarizing, recent findings from combined exercise and multi-ingredient supplementation studies (often combining protein and vitamin D, with or without additional nutrients) tentatively provide a larger potential for additional benefits to be induced on top of the exercise effects, when compared with ‘single nutrient’ interventions. In line with the protein supplementation studies though, direct evidence from multi-ingredient studies is marginal, mostly owing to limitations in the design and/or execution phase of these studies. Of note, more compromised subpopulations within the older community (e.g. sarcopenic, vitamin D-deficient, dynapenic, etc.) may possess a greater potential for any benefits to be attained by combined exercise and nutritional interventions; further work is needed to provide convincing evidence in this regard.

**CONCLUSION**

On the basis of recent work, there appears to be some potential for the efficacy of nutritional supplementation to further augment the beneficial effects of prolonged exercise training in older adults, with likely greater potential for multi-ingredient supplementation. The suggestion that specific compromised subpopulations may benefit even more calls for future research into the various factors that drive the responsiveness to combined exercise and nutritional interventions, with the final aim to develop better tailored interventions for all older individuals.

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- of special interest
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