

Dietary protein, exercise, and frailty domains

Author(s)

Schoufour, Josje D.; Overdevest, Elvera; Weijs, Peter J.M.; Tieland, Michael

DOI

[10.3390/nu11102399](https://doi.org/10.3390/nu11102399)

Publication date

2019

Document Version

Final published version

Published in

Nutrients

[Link to publication](#)**Citation for published version (APA):**

Schoufour, J. D., Overdevest, E., Weijs, P. J. M., & Tieland, M. (2019). Dietary protein, exercise, and frailty domains. *Nutrients*, 11(10). <https://doi.org/10.3390/nu11102399>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please contact the library: <https://www.amsterdamuas.com/library/contact>, or send a letter to: University Library (Library of the University of Amsterdam and Amsterdam University of Applied Sciences), Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Dietary Protein, Exercise, and Frailty Domains

Josje D. Schoufour ^{1,2}, Elvera Overdevest ¹, Peter J. M. Weijs ^{1,3} and Michael Tieland ^{1,*}

¹ Faculty of Sports and Nutrition, Center of Expertise Urban Vitality, Amsterdam University of Applied Sciences, 1097 DZ Amsterdam, The Netherlands; j.d.schoufour@hva.nl (J.D.S.); e.overdevest@hva.nl (E.O.); p.j.m.weijs@hva.nl (P.J.M.W.)

² Faculty Health, Center of Expertise Urban Vitality, Amsterdam University of Applied Sciences, 1097 DZ Amsterdam, The Netherlands

³ Amsterdam University Medical Centers, University of Amsterdam, 1012 WX Amsterdam, The Netherlands

* Correspondence: m.tieland@hva.nl

Received: 28 July 2019; Accepted: 6 September 2019; Published: 8 October 2019



Abstract: Increasing awareness of the impact of frailty on elderly people resulted in research focusing on factors that contribute to the development and persistence of frailty including nutrition and physical activity. Most effort so far has been spent on understanding the association between protein intake and the physical domain of frailty. Far less is known for other domains of frailty: cognition, mood, social health and comorbidity. Therefore, in the present narrative review, we elaborate on the evidence currently known on the association between protein and exercise as well as the broader concept of frailty. Most, but not all, identified studies concluded that low protein intake is associated with a higher prevalence and incidence of physical frailty. Far less is known on the broader concept of frailty. The few studies that do look into this association find a clear beneficial effect of physical activity but no conclusions regarding protein intake can be made yet. Similar, for other important aspects of frailty including mood, cognition, and comorbidity, the number of studies are limited and results are inconclusive. Future studies need to focus on the relation between dietary protein and the broader concept of frailty and should also consider the protein source, amount and timing.

Keywords: frailty; protein; physical activity

1. Introduction

Frailty is a complex cascade that involves several age-related physiological alterations eventually leading to loss of function and failure to respond to stress [1]. Frail people are in a state of increased vulnerability to adverse health outcomes including diseases, hospitalization and early death [1].

Although experts generally agree upon the concept of frailty, there is an ongoing debate on how to operationalize and measure frailty in elderly people. There are two major frailty operationalizations, the physical frailty phenotype, and the multidimensional frailty phenotype. The first phenotype, originally operated by Fried and colleagues, is based on five core clinical features that together form the frailty phenotype: unintentional weight loss, low muscle strength, feeling of exhaustion, reduced physical activity capacity and slow walking speed [2]. The second phenotype, often operationalized as the frailty index [3,4], includes physical impairments, mood, cognition, social environment, comorbidity and disabilities [5]. Where the physical frailty phenotype is based on pre-defined physical variables, the multidimensional frailty focuses on the total number of deficits in an individual and pays less attention to the exact nature of the problems. Both measures have been applied in several populations and have shown predictive validity in terms of survival and health indicators [5–8].

As our society is ageing, frailty will become a major threat. As a result, research has focused into factors that contribute to the development and persistence of frailty. Nutrition and physical activity are two factors closely related to frailty. Inadequate energy, macronutrient and/or micronutrient intake are

associated with both the physical frailty phenotype and the multidimensional frailty phenotype [9,10]. Most efforts so far have been spent on understanding the association and relation between protein intake and the physical frailty phenotype [11]. Dietary protein plays an essential role in maintaining skeletal muscle mass in elderly people. Low dietary protein intake, especially when accompanied with low physical activity, has been linked to progressive loss of muscle mass leading to loss of muscle function and low muscle strength, low walking speed, and feeling of exhaustion, all associated with the physical frailty phenotype [12–15]. Indeed, several randomized controlled trials observed that the combination of physical activity and protein intake have a beneficial effect on muscle mass and muscle function and can help to prevent frailty [16,17]. Far less is known on the association between protein intake with or without physical activity and the broader concept of frailty (including the frailty index). On one hand, dietary protein deficiency may impact several physiological systems, including the immune system [18] and bone health [19,20]. On the other hand, excessive protein use may negatively influence health outcomes [21,22]. Therefore, in the present narrative review, we elaborate on the evidence currently known on the association between protein and physical activity and the broader concept of frailty.

2. Dietary Protein Intake and Recommendations in Frail Older Adults

Dietary protein intakes have been recorded among multiple studies and show similar observations for frail older people. Among others, Tieland et al. showed a dietary protein intake of 1.0 g/kg/d in community-dwelling frail older people [23], but lower intakes have been found for institutionalized frail older adults (0.8 g/kg/d). Although these intakes are above the recommended dietary allowance of 0.8 g/kg/d, 10% of the community-dwelling elderly people and frail elderly people, and 35% of the institutionalized frail elderly people fail to meet the minimum protein intake required to sustain overall health [23]. Moreover, to maintain muscle mass and physical performance even higher protein intakes up to 1.0–1.2 g/kg/d or even 1.2–1.5 g/kg/d have been suggested [23–26]. Considering these recommendations, more than 90% of the frail population might not meet these recommendations and higher protein intake in frail elderly people are suggested to attenuate the onset of frailty.

3. Dietary Protein Intake and Frailty Domains

The broader multidimensional frailty phenotype considers several domains, including physical health, disability, mood, cognition, social wellbeing, and comorbidity, that together determine the frailty status. The most well-known and applied operationalization of this approach is the frailty index, based on the accumulation of deficits from a broad range of health domains [4]. Although the frailty index has been applied extensively to study aging and trajectories of aging, the association with protein intake and/or physical activity is less well considered. In general, the few studies that do look into the association between physical activity and the frailty index observe less frailty with increasing levels of physical activity [27–30]. Similar, approaches that looked into multidimensional constructs other than the frailty index also observed a positive effect of physical activity [31]. To our knowledge only one study looked into the association between a combination of frailty domains and protein intake, using the frailty index. They observed that a high protein intake was associated with a higher frailty index (worse frailty status) over time [32] when adjusting for total energy intake. This association was completely driven by animal protein. It could be that this association reflects the association between poor dietary quality (high in animal products) and higher levels of frailty. This hypothesis is in line with previous findings that show that adherence to a diet high in animal products or low adherence to dietary guidelines that stimulate a plant-based diet are associated with higher frailty levels [7,10,30,33]. Additionally, a recent cohort study shows that adhering to a higher quality diet, high in plant protein, lead to an attenuation of frailty in older adults [34]. Although very few studies investigate the association between the multidimensional frailty phenotype and protein intake, several efforts were made to understand the association between protein intake and several important aspects

of frailty. Below we elaborate on the effects of dietary protein intake on different frailty domains: physical frailty (including physical disability), mood, cognition, and comorbidity.

3.1. Protein Intake and Physical Frailty

The physical frailty phenotype is operationalized as a biological syndrome, based on a cluster of symptoms that are commonly observed in frail older people: unintended weight loss, low physical activity, weakness, slowness and fatigue [2]. It is hypothesized that inadequate dietary protein may be associated with physical frailty and that increasing dietary protein intake may attenuate the onset of physical frailty or even improve the cluster of physical frailty. Indeed, a recent meta-analysis showed that inadequate protein intake is associated with higher frailty prevalence's in older adults [15]. In this analysis of observational studies, the heterogeneity was high, indicating large inconsistencies among studies. Whereas the majority showed that adequate dietary protein intake is associated with lower risk for or a lower prevalence of physical frailty [12–14,35], some did not observe an association between protein intake and physical frailty [36,37]. The apparent contradictory findings may be due to the adaptations made to the Fried criteria and cut-off points in most of these studies and differences in analytical techniques (e.g., important confounders and effect modifiers including total energy intake, physical activity and BMI). For example, associations between dietary protein intake and frailty can be confounded by energy intake in which a positive energy balance, rather than protein intake was associated with frailty prevalence [37]. Despite these differences in results, pooled analysis showed that inadequate protein intake is associated with a higher frailty prevalence in older adults [15].

Multiple human intervention studies have been performed to study the impact of increased dietary protein intake on muscle mass, physical performance, and frailty. In line with the observational studies, there are some discrepancies between studies. Whereas some studies show a beneficial effect of dietary protein on muscle mass [16] or physical performance [17] in frail elderly people, other studies did not find an effect of increased dietary protein intake on muscle mass, strength or performance in elderly people that consume adequate daily protein [38,39]. An explanation for these apparent differences between studies include differences in design, outcomes measures, dietary protein strategy, and the inclusion of exercise.

3.2. Protein Intake and Mood

The observed association between dietary protein intake and mood is mainly found as an indirect effect of dietary protein on maintaining weight or weight loss. A high protein intake in a low energy diet can help to maintain or lose weight. In obese or overweight participants, it has been observed that weight loss is frequently, but not always, associated with a higher quality of life [40–42]. Nevertheless, in a recent RCT among adults with obesity and type 2 diabetes, weight loss itself was associated with an increase in quality of life, but it did not matter whether this was achieved with a high or low protein diet [41]. There are a few observational studies that evaluated the association between protein intake and components of mood including mental wellbeing, depression, and anxiety. Generally, these studies do not find an association between protein intake and mood [43,44]. In conclusion, at this moment there is very little evidence supporting a direct link between protein intake and mood.

3.3. Protein Intake and Cognition

The role of protein intake on cognitive performance is not well understood and only a few studies report on the association between protein intake and cognition. Observational studies found that high protein intake was associated with better cognitive performance [45–47]. Nevertheless, such associations are prone to confounding and reversed causation. Trials investigating the short time effect of protein intake on cognitive performance generally observed small improvement [48–50], but not all trials observe this effect [51]. An RCT investigating the effect of protein supplementation on long term effects (24 weeks) in prefrail and frail elderly found that the protein group (1.4 g protein/kg/d) significantly improved reaction time (executive functioning), but not in other cognitive functions

compared to the placebo group (1.0 g protein/kg/d) [52]. In another RCT among pilot's there was no effect of protein intake on memory [53]. At this moment there is limited evidence that cognitive performance is influenced by dietary protein intake [54,55]. Trials with longer follow-up among elderly people are needed in order to determine whether protein, in general or specific amino acids, may reduce the occurrence of cognitive limitations.

3.4. Protein Intake and Comorbidity

It is beyond the scope of this paper to discuss all diseases and conditions and how protein intake may beneficially or harmfully influence incidence and severeness of the condition. We will briefly touch upon a few common diseases and conditions that have been frequently associated with dietary protein intake.

3.4.1. Metabolic Disease

Dietary protein has been shown effective for body-weight management and related risk factors including adiposity, blood pressure, and triglyceride levels [56,57]. On the short-term, protein enhances satiety and increases energy expenditure caused by a combination of factors including anorexigenic hormone concentrations and increased thermogenesis [58]. In the long-term, when losing weight sufficient protein intake results in better fat free mass preservation [59]. A high body weight, or more specifically a high fat mass, is associated with several non-communicable diseases including type 2 diabetes, cardiovascular diseases and non-alcoholic fatty liver disease (NAFLD). Following the generally positive effect of high-protein diets it is, therefore, hypothesized that it would also beneficially influence the prevention of several non-communicable diseases. Indeed, risk factors for cardiovascular and metabolic diseases generally change in a favorable direction during weight loss. Even so, if a high protein diet also beneficially influences risk factors beyond the effect of weight loss remains inconclusive [60–62]. For example, high protein diets applied during weight loss and weight maintenance show favorable effects on insulin sensitivity but it is unlikely that protein itself promotes insulin sensitivity beyond the effect of weight loss [60].

3.4.2. Cardiovascular Disease

It is difficult to make clear conclusions regarding the direct relation between dietary protein intake and cardiometabolic health because overweight and obesity are established risk factors for negative cardiometabolic outcomes. In general, current evidence, mainly from cohort studies and short-term clinical trials, does not show a clear association between dietary protein intake and risk for coronary heart disease, stroke or blood pressure [61,63–65]. Long-term adherence to low carbohydrate-high protein diets have been associated with an increased risk of developing type 2 diabetes, but total protein and fasting blood glucose do not seem to be associated [61]. The association between dietary protein intake and cardiometabolic health is further complicated as the source of dietary protein seems to be important as well. For example, from a systematic review, it was concluded that there is a reversed association between plant protein and soy protein on blood pressure and LDL cholesterol, respectively [61]. Whereas, diets high in proteins from red meat appear to increase the risk of coronary heart diseases and diets high in plant proteins appear to prevent cardiovascular diseases [66].

3.4.3. Bone Health

The relation between protein intake and bone health has been studied in detail and several meta-analyses have been performed. Pedersen et al. concluded in their systematic review that insufficient evidence is currently available to state an association between protein intake and fractures, bone loss, and osteoporosis [61]. In a more recent systematic review and meta-analysis Wallace et al. concluded that optimal protein intake is key for the development and maintenance of bone throughout the life span and that even protein intake above the recommended daily allowance (RDA) can be beneficial to prevent hip fracture and the loss of bone mineral density [20]. A similar conclusion was

formulated after a systematic review and meta-analysis by Shams-White et al. [19]. They observed a positive association between bone mineral density and protein intake, especially in lumbar spine bone mineral density (BMD).

3.4.4. Cancer

The association between protein intake and cancer risk remains inconclusive. Low protein diets have been associated with lower levels of IGF-1 which could delay aging and cancer [21,67,68]. To interpret these studies, it is of paramount importance to consider the protein source. Indeed, when reported, animal-based protein in diets often worsen the negative association between protein intake and health outcomes, whereas plant-based protein nullified or even reversed these trends [21,61]. For example, Pedersen et al., concluded that there is no effect between overall dietary protein intake and breast cancer, whereas Wu et al., concluded that diets high in dietary proteins from red meat increase the risk for breast cancer and proteins from soy and skim milk reduce the risk of breast cancer [61,69]. Even so, it has to be taken into consideration that a plant-based diet is also associated with other beneficial lifestyle habits including high physical activity and non-smoking, which could potentially confound this association.

Overall, high protein diets can have beneficial effects on cardiometabolic outcomes and bone health, mainly via the positive effect on adiposity. Nevertheless, there also have been concerns about the adverse effects of high dietary protein intake on organ functioning. High protein intake for a long period of time (>2 g/kg/bw) could potentially harm the liver, kidney and gastrointestinal tract [70]. Indeed, high dietary protein intake can lead to glomerular hyperfiltration which can contribute to the progression of kidney disease [71] and protein intake was associated with higher prevalence of non-alcoholic liver disease [72]. Importantly, different protein sources appear to have different health effects and should be taken into consideration.

4. Dietary Protein Intake, Physical Activity, and Frailty

4.1. Physical Activity and Frailty

There is ample evidence showing that physical activity and exercise supports healthy aging. Adequate physical activity reduces the risk for multiple diseases, such as various cancers, cardiovascular diseases, obesity and type 2 diabetes [73]. In addition, adequate physical activity is associated with reduces risk for falls, disability, activities of daily living (ADL) dependency, institutionalization and hospitalization and, as such, declines the frailty risk at an older age. Unfortunately, frail individuals tend to have low physical activity levels. Using the NHANES data Kehler and Theou demonstrated that frail individuals are less likely to meet physical activity guidelines and show prolonged bouts of sedentary time [74]. An increase in physical activity or exercise training would significantly improve skeletal muscle mass, strength, physical performance, cognitive performance, and psychological wellbeing and has been shown to be a very promising intervention to counteract frailty [75].

Resistance-type exercise training is a very effective intervention to counteract physical frailty as it initiates muscle hypertrophy and improvements in muscle strength and physical performance [76–81]. A meta-analysis of 49 randomized intervention studies showed that after an average of 20.5 weeks of resistance-type exercise training, elderly people gained 1.1 kg (CI: 0.9–1.2) of lean body mass [82]. Furthermore, an additional meta-analysis showed that elderly people improved maximal leg press strength by $29 \pm 2\%$ and leg extension strength by $33 \pm 2\%$ after an average of 18 weeks of resistance-type exercise training [82]. Endurance-type exercise training may also be effective to counteract frailty as it improves mitochondrial biosynthesis, maximal aerobic capacity as well as maximal walking speed in frail older adults [83,84]. The combination of both resistance-type and endurance-type exercise training, however, may be superior to counteract frailty as compared to resistance-type or endurance-type exercise training alone [83,85], although more studies are needed to confirm this. A large study study ($n = 1634$) in this field is the Lifestyle Interventions and Independence for Elders (LIFE) study [86].

This study showed that a combination of resistance, endurance, flexibility and balance exercises is highly effective to counteract physical frailty and prevent mobility disability [86]. But not only physical components of frailty may be improved after exercise, also cognitive performance, mood, emotion, and social networking were improved after multicomponent exercise interventions in frail individuals [87,88]. Based on the available evidence, recommendations for frail older people should include a progressive program of both resistance, endurance, flexibility and balance exercises to prevent and/or counteract both the physical and multiple component frailty phenotype [84].

4.2. Protein and Exercise

It has been suggested that exercised muscles become more sensitive to nutrients, allowing more of the available amino acids to be synthesized into skeletal muscle protein. In sedentary, mostly frail elderly subjects, however, the sensitivity of skeletal muscle tissue to anabolic stimuli such as physical activity or protein intake might be reduced [89–91]. To illustrate, postprandial rates of muscle protein synthesis were significantly reduced by 26% after a 14-day reduction in physical activity in older adults [89]. To overcome this anabolic resistance, a combination of exercise with increased protein intake seems to be the most plausible strategy. In fact, Pennings et al. showed that resistance exercise after dietary protein provision resulted in a 28% increase in muscle protein synthesis in older adults [92]. In a long-term study, Tieland et al. showed that 24-week protein supplementation (15 g milk protein twice daily provided at breakfast and lunch) combined with resistance training increased muscle mass, strength, and physical performance in frail elderly participants [93]. Furthermore, they were also able to show the benefits of protein and exercise on cognitive performance in frail subjects [94]. These findings also have been shown in multiple meta-analysis, showing an effect of protein supplementation during exercise on muscle mass and strength in older adults [95–97]. In contrast, however, Chale et al. could not replicate the beneficial effects of dietary protein supplementation (40 g milk protein per day) during resistance exercise in mobility-limited, frail older adults [98] and also a few systematic reviews were not able to show benefits of protein during exercise [99,100]. A possible explanation for the apparent differences between studies might be the used dietary strategy and the population included in the trials. For example, the amount, timing of protein provision and the source of protein differs between studies and may be of critical importance to find significant results. In addition, those participants who are malnourished may be more susceptible to an increase in protein intake compared to those who have a protein intake well above the recommended daily allowance ($RDA > 0.8\text{--}1.0\text{ g/kg/d}$). Also hospitalized subjects, migrants, sarcopenic-obese subjects or elderly in rehabilitation who may have suboptimal nutritional intakes may benefit from additional protein intakes during exercise training. Clearly, more research is warranted in those frail populations allowing us to gain better insight in the potential benefits of additional protein intake during exercise on muscle mass, strength, physical performance and frailty indices, and, as such, support healthy aging, even for the very frail.

5. Discussion

To prevent frailty, research has focused on factors that contribute to the development of frailty. Nutrition and physical activity are factors closely related to frailty. Most efforts so far have been spent on understanding the association between protein intake with or without physical activity and physical aspects of frailty. Far less is known on the association between protein intake and the broader concept of frailty, covering in addition to the physical domain: cognition, mood, social health and comorbidity. We, therefore, performed a narrative review to investigate the association between protein, physical activity and the broader concept of frailty. We identified several observational studies, clinical trials, systematic reviews, and meta-analysis that described the association and effect of protein, with or without physical activity, with/on physical frailty. Most, but not all, find that low protein intake is associated with a higher prevalence and incidence of frailty. Concluding that especially in combination with physical activity optimal dietary protein intake can help to prevent or ameliorate physical frailty. Far less is known on the broader concept of frailty and its association with protein and physical activity.

The few studies that do look into this association find a clear beneficial effect of physical activity but no conclusions regarding protein intake can yet be made. Similar, for other important aspects of frailty including mood, cognition, and comorbidity the number of studies are limited and results are inconclusive.

At this moment there is an ongoing debate on the effect of protein on health domains and the associated recommendations for intake. On one hand, the suggested increase in dietary protein intake for elderly people (up to 1.5 g/kg/bw) may be beneficial for some health outcomes including skeletal muscular health and weight maintenance but on the other hand long term consumption of high protein (2 g/kg/bw) has been associated with adverse effects including renal, digestive, and vascular abnormalities [70]. Future research should focus on including broader measures of frailty and health to better understand the long term beneficial and possible harmful effects of high dietary protein consumption. In addition, more knowledge is required on several aspects.

First, to optimize dietary protein intake to improve muscle mass, physical functioning, and physical frailty, the amount of protein per meal should be considered. Dietary protein intake in frail elderly at breakfast (on average 10 g), lunch (on average 15 g) or prior to sleep (on average 5 g) may be insufficient to maximally stimulate muscle protein synthesis rates as frail elderly people could be resistant to such low anabolic stimuli [101,102]. Indeed, compelling evidence shows that older adults have lower muscle protein synthesis rates than their younger peers when consuming low (e.g., 10–20 g) amounts of protein per meal [101,102]. This age-related decline in protein synthesis could be explained by low physical activity, blood flow, testosterone or estrogen levels and increased inflammation and/or insulin resistance [103,104]. Therefore, a stronger stimulus, i.e., higher protein (>25–30 g) per meal may be needed to optimize dietary protein synthesis and support muscle growth in frail elderly people [105].

Second, the source of protein may be important for frailty. Sources that are rich in essential amino acids (EAA) are suggested to be superior to stimulate muscle protein synthesis in comparison to sources that are lower in EAA [106,107]. Especially, sources that are rich in the essential amino acid leucine, that provides a key signal to initiate muscle protein synthesis. Mainly animal protein sources are rich in EAA and leucine and may, therefore, be the preferred source for frail elderly people [106–108]. However, not all studies do observe stronger beneficial effects of animal protein than for plant protein on frailty outcomes [37,109,110]. It could be that proteins from animal food sources are in theory more beneficial for muscle health, but also related to a less optimal dietary pattern (e.g., high in red meat and saturated fats) and positive energy balance. A diet high in plant proteins is generally associated with a more optimal dietary pattern which could beneficially influence frailty. Indeed, several observational studies suggest that a healthy dietary pattern is associated with lower physical frailty prevalence and incidence [36,111–113]. Similar, with changes in population and dietary recommendations that have led to a tremendous increase in the demand for protein, mainly from animal sources [114], we have to consider the sustainability of protein consumption. An increase in proteins from animal food sources is associated with increased greenhouse gas emissions and overutilization of water. This further highlights the importance to find sustainable and healthy solutions to optimize protein consumption in elderly people.

Third, in addition to the amount of protein, also the timing of protein ingestion may be important to optimize dietary protein intake in frail elderly people. Indeed, some intervention studies [115,116] but not all [117–119], showed that distributing protein intake evenly throughout the day better stimulates muscle protein synthesis and compared to an unequal protein distributed intake. Especially, long term, well-controlled intervention trials are needed to identify the optimal protein amount, sources and distribution for physically frail older adults. Fourth, we observed that most studies are performed among relatively healthy often Caucasian individuals. Far less is known on for example the optimal dietary protein requirement in frail elderly people with or without the combination of physical activity.

In conclusion, numerous well-performed studies show a beneficial effect of protein intake, especially in combination with physical activity on several aspects of frailty including physical frailty,

bone health and risk factors associated with weight loss and maintenance. Nevertheless, the overall effect of protein intake on multidimensional frailty currently not well understood and should be further investigated. Furthermore, research should focus on protein amount, timing/distribution and source to better understand the relation between protein intake, physical activity, and frailty.

Author Contributions: All authors have made substantial contributions to the conception of the work and drafting of the manuscript (J.D.S., E.O., P.J.M.W., M.T.). All authors approved the submitted version and agree to be personally accountable for the authors' own contribution and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the authors was not personally involved, are appropriately investigated, resolved, and documented in the literature (J.D.S., E.O., P.J.M.W., M.T.).

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Clegg, A.; Young, J.; Iliffe, S.; Rikkert, M.O.; Rockwood, K. Frailty in elderly people. *Lancet* **2013**, *381*, 752–762. [[CrossRef](#)]
2. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in older adults: Evidence for a phenotype. *J. Gerontol. A Biol. Sci. Med. Sci.* **2001**, *56*, M146–M156. [[CrossRef](#)] [[PubMed](#)]
3. Rockwood, K.; Mitnitski, A. Frailty in relation to the accumulation of deficits. *J. Gerontol. A Biol. Sci. Med. Sci.* **2007**, *62*, 722–727. [[CrossRef](#)] [[PubMed](#)]
4. Mitnitski, A.B.; Mogilner, A.J.; Rockwood, K. Accumulation of deficits as a proxy measure of aging. *Sci. World J.* **2001**, *1*, 323–336. [[CrossRef](#)] [[PubMed](#)]
5. Bouillon, K.; Kivimaki, M.; Hamer, M.; Sabia, S.; Fransson, E.I.; Singh-Manoux, A.; Gale, C.R.; Batty, G.D. Measures of frailty in population-based studies: An overview. *BMC Geriatr.* **2013**, *13*, 64. [[CrossRef](#)]
6. Drubbel, I.; de Wit, N.J.; Bleijenberg, N.; Eijkemans, R.J.; Schuurmans, M.J.; Numans, M.E. Prediction of adverse health outcomes in older people using a frailty index based on routine primary care data. *J. Gerontol. A Biol. Sci. Med. Sci.* **2013**, *68*, 301–308. [[CrossRef](#)] [[PubMed](#)]
7. de Vries, N.M.; Staal, J.B.; van Ravensberg, C.D.; Hobbelen, J.S.; Olde Rikkert, M.G.; Nijhuis-van der Sanden, M.W. Outcome instruments to measure frailty: A systematic review. *Ageing Res. Rev.* **2011**, *10*, 104–114. [[CrossRef](#)]
8. Schoufour, J.D.; Ehteld, M.A.; Evenhuis, H.M. Comparing two frailty concepts among older people with intellectual disabilities. *Eur. J. Ageing* **2017**, *14*, 63–79. [[CrossRef](#)]
9. Gabrovec, B.; Veninsek, G.; Samaniego, L.L.; Carriazo, A.M.; Antoniadou, E.; Jelenc, M. The role of nutrition in ageing: A narrative review from the perspective of the European joint action on frailty—ADVANTAGE JA. *Eur. J. Intern. Med.* **2018**, *56*, 26–32. [[CrossRef](#)]
10. de Haas, S.C.M.; de Jonge, E.A.L.; Voortman, T.; Graaff, J.S.; Franco, O.H.; Ikram, M.A.; Rivadeneira, F.; Kieft-de Jong, J.C.; Schoufour, J.D. Dietary patterns and changes in frailty status: The Rotterdam study. *Eur. J. Nutr.* **2018**, *57*, 2365–2375. [[CrossRef](#)]
11. Goisser, S.; Guyonnet, S.; Volkert, D. The Role of Nutrition in Frailty: An Overview. *J. Frailty Aging* **2016**, *5*, 74–77. [[PubMed](#)]
12. Kobayashi, S.; Suga, H.; Sasaki, S.; Three-Generation Study of Women on Diets and Health Study Group. Diet with a combination of high protein and high total antioxidant capacity is strongly associated with low prevalence of frailty among old Japanese women: A multicenter cross-sectional study. *Nutr. J.* **2017**, *16*, 29. [[CrossRef](#)] [[PubMed](#)]
13. Bartali, B.; Frongillo, E.A.; Bandinelli, S.; Lauretani, F.; Semba, R.D.; Fried, L.P.; Ferrucci, L. Low nutrient intake is an essential component of frailty in older persons. *J. Gerontol. A Biol. Sci. Med. Sci.* **2006**, *61*, 589–593. [[CrossRef](#)] [[PubMed](#)]
14. Beasley, J.M.; Shikany, J.M.; Thomson, C.A. The role of dietary protein intake in the prevention of sarcopenia of aging. *Nutr. Clin. Pract.* **2013**, *28*, 684–690. [[CrossRef](#)] [[PubMed](#)]
15. Coelho-Junior, H.J.; Milano-Teixeira, L.; Rodrigues, B.; Bacurau, R.; Marzetti, E.; Uchida, M. Relative Protein Intake and Physical Function in Older Adults: A Systematic Review and Meta-Analysis of Observational Studies. *Nutrients* **2018**, *10*, 1330. [[CrossRef](#)]

16. Bauer, J.M.; Verlaan, S.; Bautmans, I.; Brandt, K.; Donini, L.M.; Maggio, M.; McMurdo, M.E.; Mets, T.; Seal, C.; Wijers, S.L.; 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*, 740–747. [[CrossRef](#)]
17. Tieland, M.; van de Rest, O.; Dirks, M.L.; van der Zwaluw, N.; Mensink, M.; van Loon, L.J.; de Groot, L.C. Protein supplementation improves physical performance in frail elderly people: A randomized, double-blind, placebo-controlled trial. *J. Am. Med. Dir. Assoc.* **2012**, *13*, 720–726. [[CrossRef](#)]
18. Lesourd, B. Protein undernutrition as the major cause of decreased immune function in the elderly: Clinical and functional implications. *Nutr. Rev.* **1995**, *53*, S86–S94. [[CrossRef](#)]
19. Shams-White, M.M.; Chung, M.; Du, M.; Fu, Z.; Insogna, K.L.; Karlsen, M.C.; LeBoff, M.S.; Shapses, S.A.; Sackey, J.; Wallace, T.C.; et al. Dietary protein and bone health: A systematic review and meta-analysis from the National Osteoporosis Foundation. *Am. J. Clin. Nutr.* **2017**, *105*, 1528–1543. [[CrossRef](#)]
20. Wallace, T.C.; Frankenfeld, C.L. Dietary Protein Intake above the Current RDA and Bone Health: A Systematic Review and Meta-Analysis. *J. Am. Coll. Nutr.* **2017**, *36*, 481–496. [[CrossRef](#)]
21. Le Couteur, D.G.; Solon-Biet, S.; Cogger, V.C.; Mitchell, S.J.; Senior, A.; de Cabo, R.; Raubenheimer, D.; Simpson, S.J. The impact of low-protein high-carbohydrate diets on aging and lifespan. *Cell Mol. Life Sci.* **2016**, *73*, 1237–1252. [[CrossRef](#)] [[PubMed](#)]
22. Soultoukis, G.A.; Partridge, L. Dietary Protein, Metabolism, and Aging. *Ann. Rev. Biochem.* **2016**, *85*, 5–34. [[CrossRef](#)] [[PubMed](#)]
23. Tieland, M.; Borgonjen-Van den Berg, K.J.; van Loon, L.J.; de Groot, L.C. Dietary protein intake in community-dwelling, frail, and institutionalized elderly people: Scope for improvement. *Eur. J. Nutr.* **2012**, *51*, 173–179. [[CrossRef](#)] [[PubMed](#)]
24. Tieland, M.; Borgonjen-Van den Berg, K.J.; Van Loon, L.J.; de Groot, L.C. Dietary Protein Intake in Dutch Elderly People: A Focus on Protein Sources. *Nutrients* **2015**, *7*, 9697–9706. [[CrossRef](#)] [[PubMed](#)]
25. Morley, J.E.; Argiles, J.M.; Evans, W.J.; Bhasin, S.; Cella, D.; Deutz, N.E.; Doehner, W.; Fearon, K.C.; Ferrucci, L.; Hellerstein, M.K.; et al. Nutritional recommendations for the management of sarcopenia. *J. Am. Med. Dir. Assoc.* **2010**, *11*, 391–396. [[CrossRef](#)] [[PubMed](#)]
26. Deutz, N.E.; Bauer, J.M.; Barazzoni, R.; Biolo, G.; Boirie, Y.; Bosy-Westphal, A.; Cederholm, T.; Cruz-Jentoft, A.; Krznaric, Z.; Nair, K.S.; et al. Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group. *Clin. Nutr.* **2014**, *33*, 929–936. [[CrossRef](#)]
27. Rogers, N.T.; Marshall, A.; Roberts, C.H.; Demakakos, P.; Steptoe, A.; Scholes, S. Physical activity and trajectories of frailty among older adults: Evidence from the English Longitudinal Study of Ageing. *PLoS ONE* **2017**, *12*, e0170878. [[CrossRef](#)] [[PubMed](#)]
28. Stephan, A.J.; Strobl, R.; Muller, M.; Holle, R.; Autenrieth, C.S.; Thorand, B.; Linkohr, B.; Peters, A.; Grill, E. A high level of household physical activity compensates for lack of leisure time physical activity with regard to deficit accumulation: Results from the KORA-Age study. *Prev. Med.* **2016**, *86*, 64–69. [[CrossRef](#)]
29. Blodgett, J.; Theou, O.; Kirkland, S.; Andreou, P.; Rockwood, K. The association between sedentary behaviour, moderate-vigorous physical activity and frailty in NHANES cohorts. *Maturitas* **2015**, *80*, 187–191. [[CrossRef](#)]
30. Brinkman, S.; Voortman, T.; Kieft-de Jong, J.C.; van Rooij, F.J.A.; Ikram, M.A.; Rivadeneira, F.; Franco, O.H.; Schoufour, J.D. The association between lifestyle and overall health, using the frailty index. *Arch. Gerontol. Geriatr.* **2018**, *76*, 85–91. [[CrossRef](#)]
31. Peel, N.M.; McClure, R.J.; Bartlett, H.P. Behavioral determinants of healthy aging. *Am. J. Prev. Med.* **2005**, *28*, 298–304. [[CrossRef](#)] [[PubMed](#)]
32. Verspoor, E.; Voortman, T.; Rooij van, F.J.A.; Rivadeneira, F.; Franco, O.H.; Kieft-de Jong, J.C.; Schoufour, J.D. Macronutrient intake and its associations with frailty: The Rotterdam Study. Submitted.
33. Woo, J.; Chan, R.; Leung, J.; Wong, M. Relative contributions of geographic, socioeconomic, and lifestyle factors to quality of life, frailty, and mortality in elderly. *PLoS ONE* **2010**, *5*, e8775. [[CrossRef](#)] [[PubMed](#)]
34. Veronese, N.; Stubbs, B.; Noale, M.; Solmi, M.; Rizzoli, R.; Vaona, A.; Demurtas, J.; Crepaldi, G.; Maggi, S. Adherence to a Mediterranean diet is associated with lower incidence of frailty: A longitudinal cohort study. *Clin. Nutr.* **2018**, *37*, 1492–1497. [[CrossRef](#)] [[PubMed](#)]

35. Rahi, B.; Colombet, Z.; Gonzalez-Colaco Harmand, M.; Dartigues, J.F.; Boirie, Y.; Letenneur, L.; Feart, C. Higher Protein but Not Energy Intake Is Associated with a Lower Prevalence of Frailty among Community-Dwelling Older Adults in the French Three-City Cohort. *J. Am. Med. Dir. Assoc.* **2016**, *17*, 672.e7–672.e11. [[CrossRef](#)] [[PubMed](#)]
36. Shikany, J.M.; Barrett-Connor, E.; Ensrud, K.E.; Cawthon, P.M.; Lewis, C.E.; Dam, T.T.; Shannon, J.; Redden, D.T.; Osteoporotic Fractures in Men (MrOS) Research Group. Macronutrients, diet quality, and frailty in older men. *J. Gerontol. A Biol. Sci. Med. Sci.* **2014**, *69*, 695–701. [[CrossRef](#)]
37. Schoufour, J.D.; Franco, O.H.; Kiefte-de Jong, J.C.; Trajanoska, K.; Stricker, B.; Brusselle, G.; Rivadeneira, F.; Lahousse, L.; Voortman, T. The association between dietary protein intake, energy intake and physical frailty—Results from the Rotterdam Study. *Br. J. Nutr.* **2019**, *121*, 393–401. [[CrossRef](#)]
38. Tieland, M.; Franssen, R.; Dullemeijer, C.; van Dronkelaar, C.; Kyung Kim, H.; Ispoglou, T.; Zhu, K.; Prince, R.L.; van Loon, L.J.C.; de Groot, L. The Impact of Dietary Protein or Amino Acid Supplementation on Muscle Mass and Strength in Elderly People: Individual Participant Data and Meta-Analysis of RCT's. *J. Nutr. Health Aging* **2017**, *21*, 994–1001. [[CrossRef](#)] [[PubMed](#)]
39. Bhasin, S.; Apovian, C.M.; Travison, T.G.; Pencina, K.; Moore, L.L.; Huang, G.; Campbell, W.W.; Li, Z.; Howland, A.S.; Chen, R.; et al. Effect of Protein Intake on Lean Body Mass in Functionally Limited Older Men: A Randomized Clinical Trial. *JAMA Intern. Med.* **2018**, *178*, 530–541. [[CrossRef](#)]
40. Wright, F.; Boyle, S.; Baxter, K.; Gilchrist, L.; Nellaney, J.; Greenlaw, N.; Forde, L. Understanding the relationship between weight loss, emotional well-being and health-related quality of life in patients attending a specialist obesity weight management service. *J. Health Psychol.* **2013**, *18*, 574–586. [[CrossRef](#)]
41. Watson, N.A.; Dyer, K.A.; Buckley, J.D.; Brinkworth, G.D.; Coates, A.M.; Parfitt, G.; Howe, P.R.C.; Noakes, M.; Murphy, K.J. Comparison of two low-fat diets, differing in protein and carbohydrate, on psychological wellbeing in adults with obesity and type 2 diabetes: A randomised clinical trial. *Nutr. J.* **2018**, *17*, 62. [[CrossRef](#)] [[PubMed](#)]
42. Jackson, S.E.; Steptoe, A.; Beeken, R.J.; Kivimaki, M.; Wardle, J. Psychological changes following weight loss in overweight and obese adults: A prospective cohort study. *PLoS ONE* **2014**, *9*, e104552. [[CrossRef](#)] [[PubMed](#)]
43. Ahmad, W.; Taggart, F.; Shafique, M.S.; Muzafar, Y.; Abidi, S.; Ghani, N.; Malik, Z.; Zahid, T.; Waqas, A.; Ghaffar, N. Diet, exercise and mental-wellbeing of healthcare professionals (doctors, dentists and nurses) in Pakistan. *PeerJ* **2015**, *3*, e1250. [[CrossRef](#)] [[PubMed](#)]
44. Meegan, A.P.; Perry, I.J.; Phillips, C.M. The Association between Dietary Quality and Dietary Guideline Adherence with Mental Health Outcomes in Adults: A Cross-Sectional Analysis. *Nutrients* **2017**, *9*, 238. [[CrossRef](#)] [[PubMed](#)]
45. Goodwin, J.S.; Goodwin, J.M.; Garry, P.J. Association between nutritional status and cognitive functioning in a healthy elderly population. *JAMA* **1983**, *249*, 2917–2921. [[CrossRef](#)] [[PubMed](#)]
46. La Rue, A.; Koehler, K.M.; Wayne, S.J.; Chiulli, S.J.; Haaland, K.Y.; Garry, P.J. Nutritional status and cognitive functioning in a normally aging sample: A 6-y reassessment. *Am. J. Clin. Nutr.* **1997**, *65*, 20–29. [[CrossRef](#)] [[PubMed](#)]
47. Roberts, R.O.; Roberts, L.A.; Geda, Y.E.; Cha, R.H.; Pankratz, V.S.; O'Connor, H.M.; Knopman, D.S.; Petersen, R.C. Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. *J. Alzheimers Dis.* **2012**, *32*, 329–339. [[CrossRef](#)]
48. Jakobsen, L.H.; Kondrup, J.; Zellner, M.; Tetens, I.; Roth, E. Effect of a high protein meat diet on muscle and cognitive functions: A randomised controlled dietary intervention trial in healthy men. *Clin. Nutr.* **2011**, *30*, 303–311. [[CrossRef](#)]
49. Fischer, K.; Colombani, P.C.; Langhans, W.; Wenk, C. Carbohydrate to protein ratio in food and cognitive performance in the morning. *Physiol. Behav.* **2002**, *75*, 411–423. [[CrossRef](#)]
50. Kaplan, R.J.; Greenwood, C.E.; Winocur, G.; Wolever, T.M. Dietary protein, carbohydrate, and fat enhance memory performance in the healthy elderly. *Am. J. Clin. Nutr.* **2001**, *74*, 687–693. [[CrossRef](#)]
51. Walker, T.B.; Smith, J.; Herrera, M.; Lebegue, B.; Pinchak, A.; Fischer, J. The influence of 8 weeks of whey-protein and leucine supplementation on physical and cognitive performance. *Int. J. Sport Nutr. Exerc. Metab.* **2010**, *20*, 409–417. [[CrossRef](#)] [[PubMed](#)]

52. van der Zwaluw, N.L.; van de Rest, O.; Tieland, M.; Adam, J.J.; Hiddink, G.J.; van Loon, L.J.; de Groot, L.C. The impact of protein supplementation on cognitive performance in frail elderly. *Eur. J. Nutr.* **2014**, *53*, 803–812. [[CrossRef](#)] [[PubMed](#)]
53. Lindseth, G.N.; Lindseth, P.D.; Jensen, W.C.; Petros, T.V.; Helland, B.D.; Fossum, D.L. Dietary Effects on Cognition and Pilots' Flight Performance. *Int. J. Aviat. Psychol.* **2011**, *21*, 269–282. [[CrossRef](#)] [[PubMed](#)]
54. Attuquayefio, T.; Stevenson, R.J. A systematic review of longer-term dietary interventions on human cognitive function: Emerging patterns and future directions. *Appetite* **2015**, *95*, 554–570. [[CrossRef](#)] [[PubMed](#)]
55. Canevelli, M.; Lucchini, F.; Quarata, F.; Bruno, G.; Cesari, M. Nutrition and Dementia: Evidence for Preventive Approaches? *Nutrients* **2016**, *8*, 144. [[CrossRef](#)]
56. Westerterp-Plantenga, M.S.; Lemmens, S.G.; Westerterp, K.R. Dietary protein—Its role in satiety, energetics, weight loss and health. *Br. J. Nutr.* **2012**, *108*, S105–S112. [[CrossRef](#)]
57. Santesso, N.; Akl, E.A.; Bianchi, M.; Mente, A.; Mustafa, R.; Heels-Ansdell, D.; Schunemann, H.J. Effects of higher- versus lower-protein diets on health outcomes: A systematic review and meta-analysis. *Eur. J. Clin. Nutr.* **2012**, *66*, 780–788. [[CrossRef](#)]
58. Westerterp-Plantenga, M.S.; Rolland, V.; Wilson, S.A.; Westerterp, K.R. Satiety related to 24 h diet-induced thermogenesis during high protein/carbohydrate vs. high fat diets measured in a respiration chamber. *Eur. J. Clin. Nutr.* **1999**, *53*, 495–502. [[CrossRef](#)]
59. Verreijen, A.M.; Engberink, M.F.; Houston, D.K.; Brouwer, I.A.; Cawthon, P.M.; Newman, A.B.; Tylavsky, F.A.; Harris, T.B.; Weijs, P.J.; Visser, M. Dietary protein intake is not associated with 5-y change in mid-thigh muscle cross-sectional area by computed tomography in older adults: The Health, Aging, and Body Composition (Health ABC) Study. *Am. J. Clin. Nutr.* **2019**, *109*, 535–543. [[CrossRef](#)]
60. Drummen, M.; Tischmann, L.; Gatta-Cherifi, B.; Adam, T.; Westerterp-Plantenga, M. Dietary Protein and Energy Balance in Relation to Obesity and Co-morbidities. *Front. Endocrinol.* **2018**, *9*, 443. [[CrossRef](#)]
61. Pedersen, A.N.; Kondrup, J.; Borsheim, E. Health effects of protein intake in healthy adults: A systematic literature review. *Food Nutr. Res.* **2013**, *57*, 21245. [[CrossRef](#)] [[PubMed](#)]
62. Huntriss, R.; Campbell, M.; Bedwell, C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: A systematic review and meta-analysis of randomised controlled trials. *Eur. J. Clin. Nutr.* **2018**, *72*, 311–325. [[CrossRef](#)] [[PubMed](#)]
63. Richter, C.K.; Skulas-Ray, A.C.; Champagne, C.M.; Kris-Etherton, P.M. Plant protein and animal proteins: Do they differentially affect cardiovascular disease risk? *Adv. Nutr.* **2015**, *6*, 712–728. [[CrossRef](#)] [[PubMed](#)]
64. Schwingshackl, L.; Hoffmann, G. Long-term effects of low-fat diets either low or high in protein on cardiovascular and metabolic risk factors: A systematic review and meta-analysis. *Nutr. J.* **2013**, *12*, 48. [[CrossRef](#)]
65. Cam, A.; de Mejia, E.G. Role of dietary proteins and peptides in cardiovascular disease. *Mol. Nutr. Food Res.* **2012**, *56*, 53–66. [[CrossRef](#)] [[PubMed](#)]
66. Hu, F.B. Protein, body weight, and cardiovascular health. *Am. J. Clin. Nutr.* **2005**, *82*, 242S–247S. [[CrossRef](#)] [[PubMed](#)]
67. Rizza, W.; Veronese, N.; Fontana, L. What are the roles of calorie restriction and diet quality in promoting healthy longevity? *Ageing Res. Rev.* **2014**, *13*, 38–45. [[CrossRef](#)]
68. Mitchell, S.E.; Delville, C.; Konstantopelos, P.; Hurst, J.; Derous, D.; Green, C.; Chen, L.; Han, J.J.; Wang, Y.; Promislow, D.E.; et al. The effects of graded levels of calorie restriction: II. Impact of short term calorie and protein restriction on circulating hormone levels, glucose homeostasis and oxidative stress in male C57BL/6 mice. *Oncotarget* **2015**, *6*, 23213–23237. [[CrossRef](#)]
69. Wu, J.; Zeng, R.; Huang, J.; Li, X.; Zhang, J.; Ho, J.C.; Zheng, Y. Dietary Protein Sources and Incidence of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Studies. *Nutrients* **2016**, *8*, 730. [[CrossRef](#)] [[PubMed](#)]
70. Wu, G. Dietary protein intake and human health. *Food Funct.* **2016**, *7*, 1251–1265. [[CrossRef](#)] [[PubMed](#)]
71. Schwingshackl, L.; Hoffmann, G. Comparison of high vs. normal/low protein diets on renal function in subjects without chronic kidney disease: A systematic review and meta-analysis. *PLoS ONE* **2014**, *9*, e97656. [[CrossRef](#)] [[PubMed](#)]

72. Alferink, L.J.; Kieft-de Jong, J.C.; Erler, N.S.; Veldt, B.J.; Schoufour, J.D.; de Kneeg, R.J.; Ikram, M.A.; Metselaar, H.J.; Janssen, H.; Franco, O.H.; et al. Association of dietary macronutrient composition and non-alcoholic fatty liver disease in an ageing population: The Rotterdam Study. *Gut* **2019**, *68*, 1088–1098. [[CrossRef](#)] [[PubMed](#)]
73. Daskalopoulou, C.; Stubbs, B.; Kralj, C.; Koukounari, A.; Prince, M.; Prina, A.M. Physical activity and healthy ageing: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Res. Rev.* **2017**, *38*, 6–17. [[CrossRef](#)] [[PubMed](#)]
74. Kehler, D.S.; Theou, O. The impact of physical activity and sedentary behaviors on frailty levels. *Mech. Ageing Dev.* **2019**, *180*, 29–41. [[CrossRef](#)] [[PubMed](#)]
75. Catalan-Matamoros, D.; Gomez-Conesa, A.; Stubbs, B.; Vancampfort, D. Exercise improves depressive symptoms in older adults: An umbrella review of systematic reviews and meta-analyses. *Psychiatry Res.* **2016**, *244*, 202–209. [[CrossRef](#)] [[PubMed](#)]
76. Bemben, D.A.; Palmer, I.J.; Bemben, M.G.; Knehans, A.W. Effects of combined whole-body vibration and resistance training on muscular strength and bone metabolism in postmenopausal women. *Bone* **2010**, *47*, 650–656. [[CrossRef](#)] [[PubMed](#)]
77. Candow, D.G. The impact of nutritional and exercise strategies for aging bone and muscle. *Appl. Physiol. Nutr. Metab.* **2008**, *33*, 181–183. [[CrossRef](#)] [[PubMed](#)]
78. Fiatarone, M.A.; O'Neill, E.F.; Ryan, N.D.; Clements, K.M.; Solares, G.R.; Nelson, M.E.; Roberts, S.B.; Kehayias, J.J.; Lipsitz, L.A.; Evans, W.J. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N. Engl. J. Med.* **1994**, *330*, 1769–1775. [[CrossRef](#)]
79. Meredith, C.N.; Frontera, W.R.; O'Reilly, K.P.; Evans, W.J. Body composition in elderly men: Effect of dietary modification during strength training. *J. Am. Geriatr. Soc.* **1992**, *40*, 155–162. [[CrossRef](#)]
80. Rosendahl, E.; Lindelof, N.; Littbrand, H.; Yifter-Lindgren, E.; Lundin-Olsson, L.; Haglin, L.; Gustafson, Y.; Nyberg, L. High-intensity functional exercise program and protein-enriched energy supplement for older persons dependent in activities of daily living: A randomised controlled trial. *Aust. J. Physiother.* **2006**, *52*, 105–113. [[CrossRef](#)]
81. Verdijk, L.B.; Gleeson, B.G.; Jonkers, R.A.; Meijer, K.; Savelberg, H.H.; Dendale, P.; van Loon, L.J. Skeletal muscle hypertrophy following resistance training is accompanied by a fiber type-specific increase in satellite cell content in elderly men. *J. Gerontol. A Biol. Sci. Med. Sci.* **2009**, *64*, 332–339. [[CrossRef](#)] [[PubMed](#)]
82. Peterson, M.D.; Sen, A.; Gordon, P.M. Influence of resistance exercise on lean body mass in aging adults: A meta-analysis. *Med. Sci. Sports Exerc.* **2011**, *43*, 249–258. [[CrossRef](#)] [[PubMed](#)]
83. Pasanen, T.; Tolvanen, S.; Heinonen, A.; Kujala, U.M. Exercise therapy for functional capacity in chronic diseases: An overview of meta-analyses of randomised controlled trials. *Br. J. Sports Med.* **2017**, *51*, 1459–1465. [[CrossRef](#)] [[PubMed](#)]
84. Marzetti, E.; Calvani, R.; Tosato, M.; Cesari, M.; Di Bari, M.; Cherubini, A.; Broccatelli, M.; Saveria, G.; D'Elia, M.; Pahor, M.; et al. Physical activity and exercise as countermeasures to physical frailty and sarcopenia. *Ageing Clin. Exp. Res.* **2017**, *29*, 35–42. [[CrossRef](#)]
85. Villareal, D.T.; Aguirre, L.; Gurney, A.B.; Waters, D.L.; Sinacore, D.R.; Colombo, E.; Armamento-Villareal, R.; Qualls, C. Aerobic or Resistance Exercise, or Both, in Dieting Obese Older Adults. *N. Engl. J. Med.* **2017**, *376*, 1943–1955. [[CrossRef](#)]
86. Pahor, M.; Guralnik, J.M.; Ambrosius, W.T.; Blair, S.; Bonds, D.E.; Church, T.S.; Espeland, M.A.; Fielding, R.A.; Gill, T.M.; Groessl, E.J.; et al. Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE study randomized clinical trial. *JAMA* **2014**, *311*, 2387–2396. [[CrossRef](#)]
87. Espeland, M.A.; Lipska, K.; Miller, M.E.; Rushing, J.; Cohen, R.A.; Verghese, J.; McDermott, M.M.; King, A.C.; Strotmeyer, E.S.; Blair, S.N.; et al. Effects of Physical Activity Intervention on Physical and Cognitive Function in Sedentary Adults With and Without Diabetes. *J. Gerontol. A Biol. Sci. Med. Sci.* **2017**, *72*, 861–866. [[CrossRef](#)]
88. Tarazona-Santabalbina, F.J.; Gomez-Cabrera, M.C.; Perez-Ros, P.; Martinez-Arnau, F.M.; Cabo, H.; Tsaparas, K.; Salvador-Pascual, A.; Rodriguez-Manas, L.; Vina, J. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. *J. Am. Med. Dir. Assoc.* **2016**, *17*, 426–433. [[CrossRef](#)]

89. Breen, L.; Stokes, K.A.; Churchward-Venne, T.A.; Moore, D.R.; Baker, S.K.; Smith, K.; Atherton, P.J.; Phillips, S.M. Two weeks of reduced activity decreases leg lean mass and induces “anabolic resistance” of myofibrillar protein synthesis in healthy elderly. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 2604–2612. [[CrossRef](#)]
90. Burd, N.A.; Wall, B.T.; van Loon, L.J. The curious case of anabolic resistance: Old wives’ tales or new fables? *J. Appl. Physiol.* **2012**, *112*, 1233–1235. [[CrossRef](#)]
91. Katsanos, C.S.; Kobayashi, H.; Sheffield-Moore, M.; Aarsland, A.; Wolfe, R.R. Aging is associated with diminished accretion of muscle proteins after the ingestion of a small bolus of essential amino acids. *Am. J. Clin. Nutr.* **2005**, *82*, 1065–1073. [[CrossRef](#)] [[PubMed](#)]
92. Pennings, B.; Koopman, R.; Beelen, M.; Senden, J.M.; Saris, W.H.; van Loon, L.J. 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*, 322–331. [[CrossRef](#)] [[PubMed](#)]
93. Tieland, M.; Dirks, M.L.; van der Zwaluw, N.; Verdijk, L.B.; van de Rest, O.; de Groot, L.C.; van Loon, L.J. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: A randomized, double-blind, placebo-controlled trial. *J. Am. Med. Dir. Assoc.* **2012**, *13*, 713–719. [[CrossRef](#)] [[PubMed](#)]
94. van de Rest, O.; van der Zwaluw, N.L.; Tieland, M.; Adam, J.J.; Hiddink, G.J.; van Loon, L.J.; de Groot, L.C. Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: Secondary analysis of a randomized, double-blind, placebo-controlled trial. *Mech. Ageing Dev.* **2014**, *136–137*, 85–93. [[CrossRef](#)] [[PubMed](#)]
95. Cermak, N.M.; Res, P.T.; de Groot, L.C.; Saris, W.H.; van Loon, L.J. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: A meta-analysis. *Am. J. Clin. Nutr.* **2012**, *96*, 1454–1464. [[CrossRef](#)] [[PubMed](#)]
96. Liao, C.D.; Tsao, J.Y.; Wu, Y.T.; Cheng, C.P.; Chen, H.C.; Huang, Y.C.; Chen, H.C.; Liou, T.H. Effects of protein supplementation combined with resistance exercise on body composition and physical function in older adults: A systematic review and meta-analysis. *Am. J. Clin. Nutr.* **2017**, *106*, 1078–1091. [[CrossRef](#)] [[PubMed](#)]
97. Hou, L.; Lei, Y.; Li, X.; Huo, C.; Jia, X.; Yang, J.; Xu, R.; Wang, X. Effect of Protein Supplementation Combined with Resistance Training on Muscle Mass, Strength and Function in the Elderly: A Systematic Review and Meta-Analysis. *J. Nutr. Health Aging* **2019**, *23*, 451–458. [[CrossRef](#)] [[PubMed](#)]
98. Chale, A.; Cloutier, G.J.; Hau, C.; Phillips, E.M.; Dallal, G.E.; Fielding, R.A. 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*, 682–690. [[CrossRef](#)] [[PubMed](#)]
99. Thomas, D.K.; Quinn, M.A.; Saunders, D.H.; Greig, C.A. Protein Supplementation Does Not Significantly Augment the Effects of Resistance Exercise Training in Older Adults: A Systematic Review. *J. Am. Med. Dir. Assoc.* **2016**, *17*, 959.e1–959.e9. [[CrossRef](#)] [[PubMed](#)]
100. Beaudart, C.; Dawson, A.; Shaw, S.C.; Harvey, N.C.; Kanis, J.A.; Binkley, N.; Reginster, J.Y.; Chapurlat, R.; Chan, D.C.; Bruyere, O.; et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: Systematic review. *Osteoporos Int.* **2017**, *28*, 1817–1833. [[CrossRef](#)]
101. Wall, B.T.; Gorissen, S.H.; Pennings, B.; Koopman, R.; Groen, B.B.; Verdijk, L.B.; van Loon, L.J. Aging Is Accompanied by a Blunted Muscle Protein Synthetic Response to Protein Ingestion. *PLoS ONE* **2015**, *10*, e0140903. [[CrossRef](#)] [[PubMed](#)]
102. Churchward-Venne, T.A.; Murphy, C.H.; Longland, T.M.; Phillips, S.M. Role of protein and amino acids in promoting lean mass accretion with resistance exercise and attenuating lean mass loss during energy deficit in humans. *Amino Acids* **2013**, *45*, 231–240. [[CrossRef](#)] [[PubMed](#)]
103. Wall, B.T.; Dirks, M.L.; Snijders, T.; van Dijk, J.W.; Fritsch, M.; Verdijk, L.B.; van Loon, L.J. Short-term muscle disuse lowers myofibrillar protein synthesis rates and induces anabolic resistance to protein ingestion. *Am. J. Physiol. Endocrinol. Metab.* **2016**, *310*, E137–E147. [[CrossRef](#)] [[PubMed](#)]
104. Boirie, Y. Fighting sarcopenia in older frail subjects: Protein fuel for strength, exercise for mass. *J. Am. Med. Dir. Assoc.* **2013**, *14*, 140–143. [[CrossRef](#)] [[PubMed](#)]
105. Jarzagueta, M.; Polakof, S.; David, J.; Migne, C.; Joubrel, G.; Efstathiou, T.; Remond, D.; Mosoni, L.; Dardevet, D. A meal with mixed soy/whey proteins is as efficient as a whey meal in counteracting the age-related muscle anabolic resistance only if the protein content and leucine levels are increased. *Food Funct.* **2018**, *9*, 6526–6534. [[CrossRef](#)]

106. Lord, C.; Chaput, J.P.; Aubertin-Leheudre, M.; Labonte, M.; Dionne, I.J. Dietary animal protein intake: Association with muscle mass index in older women. *J. Nutr. Health Aging* **2007**, *11*, 383–387. [[PubMed](#)]
107. Volpi, E.; Kobayashi, H.; Sheffield-Moore, M.; Mittendorfer, B.; Wolfe, R.R. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. *Am. J. Clin. Nutr.* **2003**, *78*, 250–258. [[CrossRef](#)]
108. Devries, M.C.; McGlory, C.; Bolster, D.R.; Kamil, A.; Rahn, M.; Harkness, L.; Baker, S.K.; Phillips, S.M. Leucine, Not Total Protein, Content of a Supplement Is the Primary Determinant of Muscle Protein Anabolic Responses in Healthy Older Women. *J. Nutr.* **2018**, *148*, 1088–1095. [[CrossRef](#)]
109. Kobayashi, S.; Asakura, K.; Suga, H.; Sasaki, S. Three-generation Study of Women on, D.; Health Study, G. High protein intake is associated with low prevalence of frailty among old Japanese women: A multicenter cross-sectional study. *Nutr. J.* **2013**, *12*, 164. [[CrossRef](#)]
110. Beasley, J.M.; LaCroix, A.Z.; Neuhouster, M.L.; Huang, Y.; Tinker, L.; Woods, N.; Michael, Y.; Curb, J.D.; Prentice, R.L. Protein intake and incident frailty in the Women’s Health Initiative observational study. *J. Am. Geriatr. Soc.* **2010**, *58*, 1063–1071. [[CrossRef](#)]
111. Bollwein, J.; Diekmann, R.; Kaiser, M.J.; Bauer, J.M.; Uter, W.; Sieber, C.C.; Volkert, D. Dietary quality is related to frailty in community-dwelling older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* **2013**, *68*, 483–489. [[CrossRef](#)] [[PubMed](#)]
112. Talegawkar, S.A.; Bandinelli, S.; Bandeen-Roche, K.; Chen, P.; Milaneschi, Y.; Tanaka, T.; Semba, R.D.; Guralnik, J.M.; Ferrucci, L. 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*, 2161–2166. [[CrossRef](#)] [[PubMed](#)]
113. Leon-Munoz, L.M.; Guallar-Castillon, P.; Lopez-Garcia, E.; Rodriguez-Artalejo, F. Mediterranean diet and risk of frailty in community-dwelling older adults. *J. Am. Med. Dir. Assoc.* **2014**, *15*, 899–903. [[CrossRef](#)] [[PubMed](#)]
114. Wu, G.; Fanzo, J.; Miller, D.D.; Pingali, P.; Post, M.; Steiner, J.L.; Thalacker-Mercer, A.E. Production and supply of high-quality food protein for human consumption: Sustainability, challenges, and innovations. *Ann. N. Y. Acad. Sci.* **2014**, *1321*, 1–19. [[CrossRef](#)] [[PubMed](#)]
115. Areta, J.L.; Burke, L.M.; Ross, M.L.; Camera, D.M.; West, D.W.; Broad, E.M.; Jeacocke, N.A.; Moore, D.R.; Stellingwerff, T.; Phillips, S.M.; et al. Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. *J. Physiol.* **2013**, *591*, 2319–2331. [[CrossRef](#)] [[PubMed](#)]
116. Mamerow, M.M.; Mettler, J.A.; English, K.L.; Casperson, S.L.; Arentson-Lantz, E.; Sheffield-Moore, M.; Layman, D.K.; Paddon-Jones, D. Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. *J. Nutr.* **2014**, *144*, 876–880. [[CrossRef](#)] [[PubMed](#)]
117. Gingrich, A.; Spiegel, A.; Kob, R.; Schoene, D.; Skurk, T.; Hauner, H.; Sieber, C.C.; Volkert, D.; Kiesswetter, E. Amount, Distribution, and Quality of Protein Intake Are Not Associated with Muscle Mass, Strength, and Power in Healthy Older Adults without Functional Limitations-An enable Study. *Nutrients* **2017**, *9*, 1358. [[CrossRef](#)] [[PubMed](#)]
118. Farsijani, S.; Payette, H.; Morais, J.A.; Shatenstein, B.; Gaudreau, P.; Chevalier, S. Even mealtime distribution of protein intake is associated with greater muscle strength, but not with 3-y physical function decline, in free-living older adults: The Quebec longitudinal study on Nutrition as a Determinant of Successful Aging (NuAge study). *Am. J. Clin. Nutr.* **2017**, *106*, 113–124. [[CrossRef](#)]
119. Farsijani, S.; Morais, J.A.; Payette, H.; Gaudreau, P.; Shatenstein, B.; Gray-Donald, K.; Chevalier, S. 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. [[CrossRef](#)] [[PubMed](#)]

