

1 Review

## 2 Dietary patterns, skeletal muscle health and 3 sarcopenia in older adults

4 Antoneta Granic<sup>1-3,\*</sup>, Avan A Sayer<sup>1-3</sup> and Sian M Robinson<sup>1-3</sup>

5 <sup>1</sup> AGE Research Group, Institute of Neuroscience, The Medical School, Newcastle University, Newcastle  
6 upon Tyne NE2 4HH, UK; [antoneta.granic@newcastle.ac.uk](mailto:antoneta.granic@newcastle.ac.uk)

7 <sup>2</sup> NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and  
8 Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne NE4 5PL, UK  
9 [avan.sayer@newcastle.ac.uk](mailto:avan.sayer@newcastle.ac.uk) (A.A.S.); [sian.robinson@newcastle.ac.uk](mailto:sian.robinson@newcastle.ac.uk) (S.M.R.)

10 <sup>3</sup> Newcastle University Institute for Ageing, Newcastle upon Tyne NE2 4AX, UK  
11 [avan.sayer@newcastle.ac.uk](mailto:avan.sayer@newcastle.ac.uk) (A.A.S.); [sian.robinson@newcastle.ac.uk](mailto:sian.robinson@newcastle.ac.uk) (S.M.R.)

12 \* Correspondence: [sian.robinson@newcastle.ac.uk](mailto:sian.robinson@newcastle.ac.uk); Tel.: +44-0191-208-1744

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14  
15 **Abstract:** In recent decades, the significance of diet and dietary patterns (DPs) for skeletal muscle  
16 health has been gaining attention in ageing and nutritional research. Sarcopenia, a muscle disease  
17 characterised by low muscle strength, mass and function is associated with an increased risk of  
18 functional decline, frailty, hospitalisation and death. The prevalence of sarcopenia increases with age,  
19 and leads to high personal, social and economic costs. Finding adequate nutritional measures to  
20 maintain muscle health, preserve function and independence, for the growing population of older  
21 adults, would have important scientific and societal implications. Two main approaches have been  
22 employed to study the role of diet / DPs as a modifiable lifestyle factor in sarcopenia. An *a priori* or  
23 hypothesis-driven approach examines the adherence to pre-defined dietary indices such as the  
24 Mediterranean diet (MED) and Healthy Eating Index (HEI)—measures of diet quality—in relation to  
25 muscle health outcomes. *A posteriori* or data-driven approaches have used statistical tools—  
26 dimension reduction methods or clustering—to study DP-muscle health relationships. Both  
27 approaches recognise the importance of the whole diet and potential cumulative, synergistic, and  
28 antagonistic effects of foods and nutrients on ageing muscle. In this review, we have aimed to (i)  
29 summarise nutritional epidemiology evidence from four recent systematic reviews with updates  
30 from new primary studies about the role of DPs in muscle health, sarcopenia and its components; (ii)  
31 hypothesise about the potential mechanisms of ‘myoprotective’ diets, with MED as an example, and  
32 (iii) discuss the challenges facing nutritional epidemiology to produce the higher level evidence  
33 needed to understand the relationships between whole diets and healthy muscle ageing.  
34

35 **Keywords:** dietary patterns; nutrition; ‘myoprotective’ diet; Mediterranean diet; sarcopenia; muscle  
36 strength; muscle mass; muscle function; older adults.  
37

### 38 1. Introduction

39 The world’s population is getting older [1]. Population ageing has been regarded as one of the  
40 greatest accomplishments of humankind, but also as a societal challenge, to establish how to increase  
41 health span and create the potential for the added years of life to be characterised by good health and  
42 functioning [2]. Based on the 2017 report from the United Nations [1], the number of older adults  
43 aged 60 and over ( $\geq 60$ ) will increase worldwide from 962 million (or 1 in 8 people) in 2017 to 2.1  
44 billion (1 in 5) by the middle of the century. Advanced age is the main risk factor associated with the  
45 development of chronic diseases, such as cardiovascular, respiratory, neurological, and

46 musculoskeletal diseases. However, there is great heterogeneity in ageing and health in later life [3–  
47 5], which indicates opportunity for preventive strategies to increase healthspan [3]. Several  
48 environmental and lifestyle factors have been recognised to modify the ageing process [6], including  
49 physical activity [7,8] and diet [9–16].

50 The major threats to achieving a healthy lifespan are age-related physiological impairments in  
51 multiple organs, which lead to functional limitations, disability, reduced quality of life, and  
52 exacerbate the risk and severity of age-related chronic diseases [10]. Alterations in body composition  
53 characterised by a decrease in skeletal muscle mass and increase in body fat are among the most  
54 profound age-related changes [17,18]. These start in mid-adulthood and progress gradually  
55 thereafter. An estimated annual loss of muscle mass of 3% after the age of 60 is accompanied by a  
56 preferential loss of fast type II myofibres and their conversion into slow type I fibres, along with  
57 denervation of motor units and fat infiltration between and within the fibres [17,18]. Although the  
58 losses of muscle strength and power with ageing are even greater [19,20], longitudinal studies have  
59 shown a wide inter-individual variability in both muscle mass and strength decline in older adults  
60 [21,22]. This highlights the potential importance of modifiable risk factors such as physical activity,  
61 diet and nutrition as influences on muscle ageing [23–25].

62 Sarcopenia, a muscle disease characterised by low muscle strength, mass and quality [26,27] is  
63 associated with functional decline, poor quality of life, and increased mortality [28–32]. Sarcopenia  
64 has a complex aetiology that is not fully elucidated. Multifactorial environmental and genetic factors,  
65 including low grade chronic inflammation [33,34], insulin [35,36] and anabolic resistance [37–39],  
66 hormonal changes [40,41], mitochondrial dysfunction [36,42], oxidative stress [42,43], malnutrition  
67 [24,44–46], inactivity [47,48], and age-related chronic diseases [49–51], contribute to progressive and  
68 adverse changes in ageing muscle. Intervention studies suggest that some of these pathophysiological  
69 processes may be counteracted by ensuring adequate nutrition and exercise levels [38,42,47,48].

70 An extensive number of observational and intervention studies have used a single nutrient  
71 approach to investigate the relationship between diet and muscle health with ageing (e.g. protein  
72 or vitamin D with or without exercise; [44,52–54]). However, separating the influence of one dietary  
73 component from others, and understanding their interactions within a whole diet, on health  
74 outcomes is challenging. Only recently, studies using a whole diet approach have emerged to  
75 understand the role of diet / dietary patterns (DPs) in muscle health with ageing [55–59]. This  
76 approach acknowledges the complexity of human consumption in relation to health [60], and the  
77 complexity of understanding the effects of nutrient and bioactive components within a whole diet  
78 [61–63], when examining their influence on ageing muscle.

79 To date, two main methods have been used to explore the DP-muscle health link in  
80 epidemiological studies of muscle ageing: *a priori* (hypothesis-driven) and *a posteriori* (data driven)  
81 methods to identify DPs. DPs derived *a priori* are defined by a higher adherence to predefined dietary  
82 scores or indices (e.g. Mediterranean-style diet, MED [15,16,64], indices of diet quality (e.g. Healthy  
83 Eating Indices) [56]) that are based on current knowledge about what constitutes a healthy diet for,  
84 for example, cardiovascular and general health. Higher scores reflect a diet characterised by higher  
85 consumption of beneficial foods (e.g. fruits and vegetables, whole grains, lean meat, fish, nuts, low-  
86 fat dairy and olive oil) and their combination, and low consumption of nutrient-poor foods (e.g.  
87 refined grains, sweets, processed meats, and sources of trans fats) [65–67]. Conversely, the *a posteriori*  
88 method is purely exploratory, and uses all available dietary data to derive DPs, and may therefore  
89 better define the usual diet in a population, which may or may not relate to health outcomes. The *a*  
90 *posteriori* method utilises multivariate statistical tools (i.e. data reduction techniques), such as factor /  
91 principal component (PCA) and cluster analysis to explore DPs. These techniques are markedly  
92 different procedures but can be used in a complementary way to improve the interpretability of the  
93 results obtained from each method [68]. Reduced Rank Regression (RRR)—a newer hypothesis-  
94 driven approach, not yet used in nutritional epidemiology of muscle ageing [63,69]—identifies foods  
95 / food groups in a population that best explain the variation in *a priori* selected variables hypothesised  
96 to be independently associated with disease aetiology, such as nutrient intakes (e.g. protein or

97 vitamin D for muscle health) or biomarkers implied in disease pathogenesis (e.g. inflammatory  
98 cytokines).

99 Epidemiological investigation into DPs can contribute to a knowledge base for the development  
100 of interventions for optimal muscle ageing [56–59], and may inform nutritional public policy aimed  
101 to promote healthy ageing. Therefore, the purpose of this review is to (i) summarise current evidence  
102 in nutritional epidemiology from four recent systematic reviews (cut-off for inclusion April 2017)  
103 about the role of DPs in muscle health, sarcopenia and its components, and to update this evidence  
104 with new primary studies published since then; (ii) hypothesise about the potential mechanisms of  
105 a ‘myoprotective’ diet, with a focus on MED as an example, and (iii) discuss the challenges facing  
106 nutritional epidemiology to produce the higher level evidence needed to understand relationships  
107 between whole diets and healthy muscle ageing.

108

## 109 2. Evidence about the Role of Dietary Patterns in Muscle Ageing Studies

110

111 To our knowledge, there are four systematic reviews (publication years 2017–2018; cut-off for  
112 inclusion April 2017) that have examined evidence from nutritional epidemiology about the role of  
113 DPs in muscle health and function in older adults [56–59]. Only one examined the relationship  
114 between diet quality (defined both *a priori* and *a posteriori*) and components of sarcopenia; this,  
115 included studies that used various Healthy Eating Indices (e.g. HEI, Canadian HEI (C-HEI),  
116 Alternative HEI (AHEI), HEI-2005, Healthy Diet Indicator (HDI), Dietary Variety Score (DVS), Diet  
117 Quality Index-International (DQI-I)) along with region-specific DPs such as MED and Nordic diet  
118 (Nordic Diet Score, NDS) [56]. The remaining reviews [57–59] summarised the evidence from studies  
119 investigating the associations between MED and muscle health outcomes across the life course [57]  
120 and in older adults [58,59]—MED being a ‘healthy’ DP most frequently used in observational studies  
121 of muscle ageing and showing most consistent evidence, and thus hypothesised here to be  
122 ‘myoprotective’.

123

### 124 2.1. Dietary Patterns Derived A Priori: Example of Mediterranean Diet

125

#### 126 2.1.1. Main Characteristics of Mediterranean Diet

127 Of all healthy DPs determined *a priori*, MED has been most recognised because of its beneficial  
128 effects on various health outcomes, including survival, cardiovascular disease, cognitive health,  
129 frailty, and cancer [15,16,64,70–75]. A DP traditionally associated with populations living around the  
130 Mediterranean Sea in olive grove regions, MED is characterised by higher consumption of plant foods  
131 (fruits, vegetables, legumes, and cereals) and olive oil, moderate intake of fish, eggs, poultry and  
132 dairy foods, and low intake of red meats, with moderate consumption of red wine during meals [76].  
133 Declared by UNESCO (2010) [77] to be an Intangible Cultural Heritage of Humanity, MED as a  
134 lifestyle includes not only beneficial foods for health, but also intense physical work / exercise and  
135 tight social links through sharing of skills, knowledge, and traditions about, among others, crops,  
136 harvesting, fishing, food preservation, cooking, and food consumption [78]. Although the adherence  
137 to MED-style DPs has been assessed using different variants of MED indices (scores) [79,80] in  
138 various populations (including those living outside the Mediterranean basin), scientific consensus  
139 exists about the fundamental components of MED today [81]. The main principles of MED rest on its  
140 plant-based core, moderation in food consumption, and cultural and lifestyle elements such as  
141 cooking, conviviality, physical activity and adequate rest [81]. The benefits of MED for general health  
142 and quality-of-life have been recently been recognized in national dietary guidelines such as the 2015-  
143 2020 Dietary Guidelines for Americans [82].

144

#### 145 2.1.2. Systematic Reviews of Mediterranean Diet and Muscle Ageing: Summary of Evidence

146 In the last decade, a number of population-based cross-sectional and longitudinal studies have  
147 investigated the role of MED in skeletal muscle health (i.e. mass, strength, function, physical  
148 performance, and sarcopenia) in older adults. Along with general, cardiovascular, metabolic, and

149 cognitive health benefits, MED-style DPs may offer ‘*myoprotective*’ properties. Four recent systematic  
150 reviews (publication years 2017–2018) have synthesised the best available evidence exploring MED-  
151 muscle ageing links [56–59]. These reviews identified largely consistent positive associations with  
152 several muscle-related outcomes, especially with the measures of muscle functioning (Table 1), with  
153 these effects seen both in Mediterranean and non-Mediterranean populations. However, some  
154 challenges in understanding the MED pattern have been noted, including (i) a great variation in the  
155 MED indices used to define DP (exposure) in relation to different muscle outcomes across  
156 populations; (ii) variability in both the dietary and muscle-related assessments used to measure  
157 exposures and outcomes, respectively; (iii) differences between studies in the covariate factors  
158 employed to account for confounding, (iv) paucity of longitudinal studies, and (v) a small number of  
159 studies using sarcopenia as an outcome, compared with other age-related conditions [24]. Taken  
160 together, these limitations have contributed to the lack of more precise quantitative reviews of the  
161 effect of MED on sarcopenia and its components in older adults, particularly opportunities for using  
162 pooled data.

163 In a systematic review that investigated the relationship between MED and musculoskeletal  
164 health over the life course [57], 18 studies were selected, but only two explored the association  
165 between MED score (MDS, originally described by Trichopoulou et al. [70]) and muscle-related health  
166 in older adults [83,84]. The first of these was a prospective cohort study of over 2900 older men and  
167 women aged  $\geq 65$  living in Hong Kong [83]. In this study a 1-unit increase in MDS was not associated  
168 with prevalent or 4-year incident sarcopenia (defined by the Asian Working group for Sarcopenia  
169 algorithm [85]) after adjustment for socio-demographic, health and lifestyle variables. Despite some  
170 similarities between the Chinese diet and MED (e.g. higher intake of fruits and vegetables, and low  
171 intake of meats), the authors attributed the lack of association to a very low consumption of food  
172 groups traditional for MED in this cohort (e.g. legumes, nuts, olive oil, and wine). Because the MDS  
173 is a sum of nine or ten binary components representing food groups deemed to be either beneficial  
174 (scoring 1) or detrimental (scoring 0) for overall health, based on sex-specific median intakes, the  
175 cohort-specific medians in this study may not have represented healthy levels of intake. In contrast,  
176 the study of over 2500 women aged 18–79 from the TwinUK registry found that the percentage of fat-  
177 free mass (FFM/weight  $\times 100$ ) in women aged  $\geq 50$  was positively associated with the highest MDS  
178 quartile compared with the lowest quartile, and with a 13% difference in leg extension power  
179 between the extreme quartiles after adjustment for key covariates [84].

180 A review by McCure and Villani (2017) [59] synthesised the evidence from an additional eight  
181 studies, although much of this was cross-sectional (five cross-sectional, two longitudinal, and one  
182 cross-sectional and longitudinal), in older adults aged  $\geq 55$  [86–93]. MED was assessed using MDS  
183 (four studies) [86–89,93] and other MED score variants (e.g. Alternate Mediterranean Food Score,  
184 Mediterranean-type Diet Score) [88,90–93]. The muscle-related outcomes varied across the studies,  
185 from walking speed, lower body physical performance (Short Physical Performance Battery, SPPB),  
186 skeletal muscle mass, quality, and strength (grip strength) [86–88,90–93], and by several indices of  
187 sarcopenia [89]. The studies included older adults living in Mediterranean (e.g. Italy, Mediterranean  
188 islands) and non-Mediterranean regions (e.g. United States, Germany, Finland). The length of follow-  
189 up in the longitudinal studies was 3–9 years. All studies, both cross-sectional and longitudinal,  
190 reported benefits of adherence to MED, such that there was a lower risk of sarcopenic symptomology  
191 with greater adherence to MED [86–93]. Higher MED scores were associated with better muscle  
192 health and function [86,88–92], and reduced risk of decline in lower extremity functioning [87] and  
193 mobility [93].

194 For example, the study of over 550 women aged 65–72 living in Kuopio, Finland found that those  
195 in higher quartiles of MDS had faster walking speed, and greater lower body muscle quality (10 m-  
196 walking speed per leg lean mass) at baseline. Women in the lowest MDS quartile had a greater decline  
197 in relative skeletal muscle index (RSMI) and total lean mass (LM) over a 3-year follow-up compared  
198 with those in higher quartiles [89]. In the study of over 930 Italian men and women (Invecchiare in  
199 Chianti, InCHIANTI Study) aged  $\geq 65$  years, higher adherence to MED was associated with less  
200 decline in lower extremity performance (SPPB) over 3, 6 and 9-year follow-up [87]. Those with the

201 highest MDS (score 6-9) had about one point higher SPPB score at each follow-up compared to those  
202 with the lowest MDS (score  $\leq 3$ ) after adjustment for a set of covariates. Importantly, a one point  
203 decline in SPPB represents a clinically relevant change in lower body function. Additionally,  
204 participants with higher MED adherence had a 29% lower risk of developing mobility disability (a  
205 SPPB score of  $< 10$  points on the scale of 0-12) over the study period [87]. In the Health, Aging, and  
206 Body Composition Study (Health ABC) of over 2,200 participants aged 70-79, both usual and rapid  
207 20 m walking speed were higher in those with greater MED adherence (MDS 6-9). A higher MDS was  
208 associated with less decline in usual walking speed over 8 years after adjustment for key covariates,  
209 although this was attenuated by adjustment for total body fat percentage [93]. In contrast the  
210 association was not changed for MED adherence and rapid 20 m walking speed over the study  
211 period. Both of these longitudinal studies [87,93] used the same statistical approach and adjusted for  
212 a similar set of confounders, and have estimated MED exposure (MDS score) from food frequency  
213 questionnaires (FFQ); importantly they have also investigated the MED and muscle function  
214 relationship in Mediterranean [87] and non-Mediterranean populations [93]. Their findings provide  
215 strong support for MED; greater adherence to MED may help with mobility and slow the decline in  
216 lower body function in older adults.

217 The third systematic review and meta-analysis that investigated the relationship between MED,  
218 frailty, functional disability, and sarcopenia in older adults [58] included two additional prospective  
219 cohort studies [94,95] (publication year 2018). In the Senior-ENRICA study of over 1,600 older adults  
220 aged  $\geq 60$  years, higher adherence to MED assessed by MDS was not associated with the risk of  
221 mobility impairment and agility (defined using the Rosow and Breslau scale), or physical functioning  
222 decline (a  $\geq 5$ -point decline on the physical component of the 12-Item Short-Form Health Survey, SF-  
223 12) over 3-year follow-up [94]. However, when accordance to MED was assessed using the  
224 Mediterranean Diet Adherence Screener (MEDAS; a 14-component score used in the PREDIMED  
225 (PREvención con DIeta MEDiterránea) trial [64]), the highest MEDAS tertile was associated with 23-  
226 40% decreased odds for developing impairments in agility and mobility, and decrease in physical  
227 functioning [94]. In the Three-City-Bordeaux study of 560 initially non-frail older adults aged  $\geq 65$   
228 years, the highest MDS (score 6-9) was associated with a 55% reduced risk of developing mobility  
229 impairment (defined using the Rosow and Breslau scale), and a 56% lower risk of lower extremity  
230 impairment (chair stands) over 2-year follow-up [95].

231 The fourth systematic review included evidence from observational studies investigating the  
232 relationship between DPs defined *a priori* and *a posteriori* (including MED) and sarcopenia / elements  
233 of sarcopenia [56]. Two additional studies from InCHIANTI [96] and Senior-ENRICA cohorts [97]  
234 using MDS and MEDAS scores were included in this review, and reported similar findings as in  
235 Milanese et al. [87] and Struijk et al. [94]. Higher adherence to MED (MDS  $\geq 6$ ) was associated with  
236 a 51% lower risk of low walking speed compared with low adherence (MDS  $\leq 3$ ) after 6-year follow-  
237 up. There was no association between muscle strength (grip strength) and MDS [96]. Similarly, no  
238 significant association between MDS, grip strength and walking speed was observed in the ENRICA  
239 cohort, but belonging to the highest MEDAS tertile was associated with a 47% reduced risk of low  
240 walking speed [97].

241 Taken together, the reviews provide strong evidence for beneficial effects of MED, with better  
242 physical functioning, including lower body function (e.g. SPPB) and mobility (walking) observed  
243 across the studies, suggesting that higher adherence to MED-like DP may be 'myoprotective' in older  
244 adults. Differences in findings between some studies [e.g. 94] may illustrate the complexity in  
245 deriving Mediterranean-type DP, and the lack of a uniform operational definition for MED score.  
246 Debate continues about which components of MED should be included, which type (e.g. fat and  
247 grain), amounts and cut-offs for intake of food groups (e.g. alcohol) should be used in the score for  
248 the Mediterranean versus non-Mediterranean populations [98,99]. The current diet of the  
249 Mediterranean regions differs from the traditional MED originally described in Greece in 1960s [70].  
250 To understand and compare the influence that higher adherence to MED may have on skeletal muscle  
251 health in older adults, a univocal definition of MED and its dietary score based on modern

252 understanding of MED should be established [81], and which may possibly include non-traditional  
253 MED foods.

254

### 255 2.1.3. Mediterranean Diet and Muscle Ageing: Additional Evidence

256 To update the findings for the associations between MED and sarcopenia / components of  
257 sarcopenia, we conducted additional literature searches of peer-reviewed, full-length articles  
258 published in English since April 2017 (electronic databases searches of PubMed, MEDLINE,  
259 SCOPUS, and OVID; and cut-off for inclusion January 2019). We used the search strategy and key  
260 words similar to those described by McCure et al [59], and included observational studies (cross-  
261 sectional and prospective) in older adults aged  $\geq 60$  years that investigated MED and at least one  
262 muscle health outcome related to sarcopenia. We identified four more recent primary studies that  
263 investigated the role of MED in muscle health and function in older adults [100–103] (Table 1). In a  
264 study of 380 Spanish older adults aged 50–80, the highest quartile of MED (derived *a posteriori* by  
265 factor analysis) was positively associated with 30-s chair stands in men, and 6-min walking speed in  
266 women, but not with the measures of muscle strength (grip strength and arm curls) in both sexes.  
267 Additionally, men in the highest MED quartile needed less time to complete 8-foot TUG test and had  
268 faster 30-m gait speed compared to those in lower quartiles, whilst belonging to higher quartiles of  
269 ‘Westernized’ DP was associated with slower gait speed, lower body strength (chair rises), aerobic  
270 endurance (6-min walk test) and agility (8-foot TUG) in men and women [100]. Conversely, a cross-  
271 sectional study of 84 Italian older women found that those with higher grip strength ( $>20$ kg) had  
272 significantly higher PREDIMED scores determined from the 7-day food records, and were more  
273 likely to belong to the ‘high adherence’ PREDIMED group (score  $\geq 10$ ) [101]. In contrast, in the  
274 Helsinki Birth Cohort prospective study of over 960 community-dwelling older adults (mean age 61.6  
275 years), higher adherence to modified MDS at baseline was not associated with mobility limitations at  
276 10-year follow-up [102]. And, although a cross-sectional study of 117 type-2 diabetes patients aged  
277  $>60$ , recruited through the Center for Successful Aging with Diabetes at the Sheba Medical Center in  
278 Israel, found that those with higher adherence to MDS (score 5–9) had higher grip strength and  
279 reduced risk of falls, the associations did not persist in multi-variable analyses that adjusted for key  
280 covariates. However, there was a significant age by MDS interaction in this study, such that being in  
281 the highest tertile of MDS was associated with longer distance achieved in 6-minute walking test,  
282 faster time needed to complete 10-m walk and better balance score, but this was only found in  
283 patients aged  $\geq 75$  years [103] (Table 1).

284 In summary, the observational evidence from the additional primary studies reviewed, for the  
285 benefits of MED-type DPs for muscle health in older adults, is largely consistent with the findings of  
286 the systematic reviews. Whilst there are few studies that have investigated the role of MED (using  
287 MED scores) in the aetiology of sarcopenia [83,89], a number have explored the relationship between  
288 components of sarcopenia (e.g. grip strength, walking speed, muscle mass) and decline in physical  
289 function [e.g. 87,90,91,93,94,101–103]. Higher adherence to MED (assessed by MDS, PREDIMED score  
290 and other variants) were positively associated with lower extremity functioning, mobility and better  
291 walking speed over time [84,87,88,91,93–95,100,103], but not with measures of upper body muscle  
292 strength in most of the studies [91,96,97,100,103]. These results suggest that whilst MED may not  
293 improve muscle strength in older adults, higher adherence to MED-like DP may be beneficial for  
294 mobility and general physical functioning. However, as positive associations between muscle  
295 strength and MED have been observed in some studies (e.g. [101] in older women aged 60–85 using  
296 PREDIMED score) these need to be further explored to be replicated in other cohorts. Despite the  
297 gaps in current knowledge, MED may have the greatest potential to be ‘*myoprotective*’, although to  
298 reach a higher-level of evidence, internal and external validation of MED indices across prospective  
299 studies with longer follow-up taking a life course approach are needed to support future clinical trials  
300 of ‘*myoprotective*’ DPs in older adults.

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302

303

## 304 2.2. Dietary Patterns Derived A Priori: Example of Diet Quality Indices

305

306 The systematic review by Bloom et al (2018) [56] included eight studies that used 10 different  
307 indices of diet quality other than MED (e.g. HEI, C-HEI, AHEI, HEI-2005, DVS, HDI, DQI-I, NDS) in  
308 relation to sarcopenia / elements of sarcopenia in older adults (Table 1). Diet was assessed mostly by  
309 FFQ (five studies), followed by 24-hr recall and 3-day weighed food records. Muscle health-related  
310 outcomes varied from ASM, muscle strength (e.g. grip strength, knee extensor), physical performance  
311 (e.g. gait speed, senior fitness test, SPPB) to sarcopenia. Seven of the studies used dietary indices that  
312 are based on scientific evidence about DPs for general health, and compliance with population  
313 dietary guidelines for recommended reference intakes of nutrients (e.g. HEI and HEI-2005  
314 recommended by the Dietary Guidelines for Americans and the US Department of Agriculture [104]).  
315 Specifically, HEI (and the updated versions) has used a universal scoring metric and density  
316 approach to calculate amounts of a set of foods per 1,000 kcal to assess the quality of diet in the US  
317 population. HEI includes food groups that are culturally neutral; scores are given for total fruits and  
318 vegetables, whole and refined grains, total protein foods, seafood and plant-based protein foods,  
319 calories from solid fats, added sugar, sodium and alcohol [104]. The HEI is widely used in different  
320 research settings and in relation to an array of outcomes, including muscle health in older adults.

321 For example, in the National Health and Nutrition Examination Survey (NHANES 1999-2002)  
322 of over 2,000 older adults aged  $\geq 60$  years, diets with scores in the higher quartiles of HEI-2005 were  
323 associated with higher knee extension power and faster gait speed compared with the lowest HEI  
324 quartile. However, the associations were no longer significant after adjustment for physical activity  
325 [105]. In a study of community-dwelling older Australians (aged  $\geq 60$  years) lean mass and physical  
326 performance (SPPB) were not associated with HEI-total score, but in contrast, a weak positive  
327 association between lean mass in women and SPBB in men was observed when HDI was used to  
328 assess diet quality [106]. In a study of over 150 older adults (mean age at baseline 74.6 years) with  
329 type 2 diabetes, higher adherence to C-HEI was not associated with maintenance of muscle strength  
330 (grip strength, knee extensor and elbow flexor strength) over 3 years [107]. To date, only one study  
331 has examined the association between diet quality index (DQI-I) and the risk of sarcopenia. In a  
332 cohort of community-dwelling Chinese older adults aged  $\geq 65$ , men in the highest quartile of DQI-I  
333 had a 50% reduced risk of prevalent but not 4-year incident sarcopenia compared with those in the  
334 lowest quartile. No significant association between DQI-I and sarcopenia was observed in women  
335 [83].

336

### 337 2.2.1. Diet Quality Indices and Muscle Ageing: Additional Evidence

338 Using the literature search strategy described previously (Section 2.1.3), we identified four  
339 additional primary studies (three longitudinal and one cross-sectional) that used diet quality indices  
340 or region-specific diet scores in relation to muscle strength and function [102,108–110] in older adults  
341 aged  $\geq 60$  years at baseline (Table 1). In the Helsinki Birth Cohort study, the likelihood of developing  
342 mobility limitations was 58% lower in older adults in the highest tertile of NDS compared with those  
343 in the lowest tertile when assessed 10 years later [102]. The NDS included food groups that are more  
344 reflective of the diets consumed in the Nordic countries, such as berries, root and cruciferous  
345 vegetable, rye bread, and high intake of fish. In the same cohort, each 1-unit increase in NDS was  
346 associated with a 1.44 Newton (N) higher grip strength, and a 1.83 N higher leg strength in women,  
347 but not in men, at 10-year follow-up [108]. No associations were found with muscle mass in either  
348 sex [108]. In the British Regional Heart Study of over 1,200 men (mean age 66 at baseline), being in  
349 the highest category versus the lowest category of HDI (score 4-8 versus score 0-1) and Elderly  
350 Dietary Index (EDI; score 27-36 versus score 9-22) was associated with a 45% and a 50% reduced risk  
351 of mobility limitations, respectively 15 years later [109]. In a cross-sectional study of over 600 Korean  
352 older adults (aged  $\geq 65$  years) participating in the National Fitness Award project, higher  
353 Recommended Food Score (RFS) was positively associated with grip strength in women, but not in  
354 men. No associations were observed between the RFS and other physical performance tests,

355 including 2-min step test, TUG, figure-of-8 walk test, and arm curls. The study used a modified RFS  
356 to include foods characteristic of Korean diet such as seaweed [110].

357 In summary, the findings of the studies that used indices of diet quality in relation to  
358 components of sarcopenia included in the systematic reviews have been mixed; however, the positive  
359 findings for mobility / mobility limitations from the recent prospective studies need further  
360 exploration [102,108,109]. Most of the indices to date are based on a combination of foods and  
361 nutrients intake recommended to promote general health. The concept of 'diet quality' is  
362 multidimensional and heterogeneous, and there is a great variety across the scores regarding food  
363 groups and amounts [111]. There is a possibility that a 'diet quality' concept and what may constitute  
364 a healthy diet to protect other outcomes, such as cardiovascular health, may not be optimal for  
365 healthy muscle ageing. To test this hypothesis, additional evidence from prospective cohort studies  
366 with longer follow-up are needed, together with validation and greater harmonisation of diet quality  
367 indices across the populations.

### 368 369 2.3. Dietary Patterns Derived A Posteriori 370

371 The systematic review by Bloom et al (2018) [56] provided the most comprehensive synthesis of  
372 evidence from observational studies that used an *a posteriori* (data driven) approach to derive DPs,  
373 and to explore their relationship with sarcopenia [117] and its components of sarcopenia [112–  
374 116,118] (Table 2). Four cross-sectional [112,113,115,117] and three longitudinal studies [114,116,118]  
375 were included (duration of follow-up between 3.5 to 16 years) that used data reduction techniques  
376 (i.e. PCA / factor analysis [113–115,117,118], and clustering [112,116]) to derive DPs from dietary data  
377 assessed either by FFQ [113–115,117], 24-hour diet recall [112,116], or diet history [118]. Similar to the  
378 studies using MED scores for dietary exposures, muscle health-related outcomes varied across the  
379 studies from muscle mass [112], strength (grip strength) [113,116,118], physical performance (walking  
380 speed, chair rises, one-leg balance, TUG) [114–116,118], and sarcopenia [117]. Healthier DPs were  
381 generally described by higher intake of beneficial foods for overall health (e.g. higher intake of fruits  
382 and vegetables, fatty fish, and whole grains) in studies of Korean, British, and Spanish older adults.

383 Differences in how dietary exposures and muscle health outcomes were defined across the  
384 studies restricted a direct comparison of results. The review found limited evidence of a relationship  
385 between lean body mass and healthier DPs. However, in a study of over 1,400 Korean older adults  
386 aged 65 and over, a 'Westernized Korean' DP characterised by higher intake of bread, eggs, fish, milk,  
387 grains other than rice, and alcohol was associated with a 74% increased low appendicular skeletal  
388 mass (i.e. below ASM / weight reference value of 20-39; measured by DXA) compared with a  
389 'Traditional Korean' DP high in white rice but low in protein, fat, and milk products [112].

390 Inconsistent evidence has been found for associations between muscle strength (grip strength)  
391 and healthier DP [97,113,116]. A 'Prudent' DP, similar to a 'healthier' pattern defined by HEI, was  
392 associated with higher grip strength in older men and women participating in the Hertfordshire  
393 Cohort Study (HCS), which was partially explained by greater intake of fatty fish in men, but not in  
394 women [113]. Conversely, a 'Prudent diet' characterised by high intake of vegetables, potatoes, blue  
395 fish, meat, pasta, and olive oil was not associated with grip strength in the ENRICA cohort of Spanish  
396 older adults compared to 'Westernized' pattern high in refined bread, red and processed meats, and  
397 whole dairy products [118]. These findings were similar to the results reported in Struijk et al. [94]  
398 using MED score (MDS) in this cohort, showing the value of using a complementary DP methodology  
399 in the study of diet in relation to muscle health. In a cohort of very old adults (aged ≥85), The  
400 Newcastle 85+ Study, men belonging to a DP high in red meat, potatoes, and gravy ('High Red Meat')  
401 had lower grip strength and greater grip strength decline over a 5-year follow-up compared to those  
402 in a 'Low Meat' DP, a diet characterised by low intake of these foods, but higher intake of fruits, fish  
403 / seafood, whole grains / cereal products, dairy foods, and soups [116].

404 More consistent evidence has been reported for a relationship between less healthy DP and  
405 increased risk of decline in physical performance. For example, being in the highest tertile of a  
406 'Westernized pattern' was associated with an 85% increased risk of slow walking speed in the



407 ENRICA cohort [97]. This is consistent with a UK study of over 5,300 men aged  $\geq 60$ , in which being  
408 in the highest tertile of a 'Western-type' dietary pattern was associated with a 45% increased odds of  
409 slow walking speed compared with the lowest tertile, whilst no association between 8-foot walking  
410 speed and a 'Healthy-food' DP was observed [114]. Similarly, in the Newcastle 85+ Study, women  
411 belonging to a DP high in butter ('High Butter') had worse TUG performance compared to those in a  
412 'Low Meat' DP [119].

413 We are aware of only one cross-sectional [117] and one prospective study that investigated the  
414 association between DP derived *a posteriori* and sarcopenia [119]. In a cross-sectional study of 300  
415 Iranian older adults aged  $\geq 55$  years, those in the highest tertile of a MED-style DP identified using  
416 PCA (with high factor loadings for MED foods such as olives/olive oil, fruits, vegetables, nuts, whole  
417 grains, and fish) had a 58% reduced risk of prevalent sarcopenia. In this study, higher compared with  
418 lower adherence to the Western DP (with high factor loadings for tea, sugar, desserts and sweets,  
419 soy, and fast food) was not associated with sarcopenia [117]. In the community-dwelling participants  
420 from the Newcastle 85+ Study, belonging to a DP characterised by elements of a traditional British  
421 diet (high intake of butter, red meats, gravy, potato, vegetables, and sweets/desserts) was associated  
422 with a 2.4-fold increased risk of sarcopenia at 3-year follow-up compared with a DP in which more  
423 people ate unsaturated spreads and oils. A Traditional British DP was also associated with a 2.1-fold  
424 and a 5.4-fold increased risk of prevalent sarcopenia at baseline and 3-year follow-up, respectively  
425 even in participants with adequate protein intakes [119].

426

### 427 2.3.1. Dietary Patterns Derived *A Posteriori* and Muscle Ageing: Additional Evidence

428 We identified four additional primary studies (two longitudinal and two cross-sectional) that  
429 explored the relationship between DPs derived *a posteriori* (data-driven) and muscle health (cut-off  
430 for inclusion January 2019) [120–123] (Table 2). In the prospective Three-City Bordeaux Study of  
431 community-dwelling older adults aged  $\geq 67$  years, belonging to a 'Biscuits and snacking' cluster was  
432 associated with a 3-fold increase risk of mobility limitations (Rosow-Breslau scale) compared with a  
433 'Healthy' cluster (characterised by higher intake of fish in men and fruits in women) over 10 years  
434 [120]. Similarly, older Korean men (aged  $\geq 60$  years) belonging to a 'Healthy' DP (characterised by  
435 higher intake of fruits, vegetables, seaweed, mushrooms, legumes, whole grains, potatoes, fish, dairy  
436 products, eggs and red meat) had higher muscle mass compared to those belonging to a  
437 'Westernized' DP (high in fast food, rice cake, bread, noodles, rice, red meat, poultry, and soft drinks)  
438 [121]. In a cross-sectional study of over 500 Spanish older adults aged  $\geq 70$  years, three dietary clusters  
439 with a progressively worse adherence to dietary recommendations were identified using multiple  
440 correspondence and cluster analysis. A gradient effect of poor physical performance (TUG) was  
441 observed from cluster one to cluster three (poorest diet) [122]. This is also consistent with the findings  
442 from a cohort of British adults born in 1946 from the MRC National Survey of Health and  
443 Development (NSHD) study, in which diet quality identified by PCA at age 36, 43, 53, and 60–64 was  
444 associated with better physical performance at age 60–64 years. In particular, higher diet quality  
445 scores characterised by higher intakes of fruit, vegetables, and wholegrain bread at age 60–64 were  
446 associated with faster chair rise speed and better balance [123].

447 Although emerging, the evidence from studies employing an *a posteriori* approach to derive DPs  
448 in relation to muscle ageing has been mixed (Table 2). The strongest evidence has been found between  
449 westernized DPs and impairments in mobility and physical performance. The westernized diets may  
450 have increased the risk of poor physical functioning via potential effects on myofibre quality and  
451 composition [17,18], and increasing the pathophysiological processes implicated in sarcopenia and  
452 functional decline, including fat infiltration [124,125], inflammation [33,34,126–128], oxidative stress  
453 [128,129], and insulin resistance [130–132].

454 To characterise '*myoprotective*' diets in older adults, harmonisation of the findings across well-  
455 designed prospective cohort studies with longer follow-up and a life course approach [123] that use  
456 complimentary DP methodology to investigate the diet-muscle health relationships will be essential  
457 to enable meaningful pooled analyses, currently lacking for sarcopenia and its components [58]. Of  
458 all DPs that are either hypothesis or data-driven, only one meta-analysis has been conducted with

459 MED and functional disability (defined by SPPB, the Rosow and Breslow scale, and SF-12 scores) and  
460 frailty as outcomes [58]. Although showing most consistent evidence for components of sarcopenia  
461 related to muscle function, studies investigating MED and sarcopenia were scarce and had different  
462 methodological design, thus limiting meaningful comparison [58].  
463

Accepted Version

464 **Table 1.** *A priori* dietary patterns and muscle health: summary of evidence

Ref.	Study design/duration	Participants/setting	Measure of muscle health/function	Dietary assessment	Findings
<b>Summary of systematic reviews<sup>a</sup></b>					
[57] <sup>b</sup>	1 longitudinal / 4 years [83];  1 cross-sectional [84];	older adults (aged ≥65), Hong Kong [83];  women (aged ≥50), the TwinUK registry [84];	prevalent and incident sarcopenia [83];  muscle mass and leg explosive power [84]	FFQ / MDS score [83,84];	→association between MDS and sarcopenia [83];  ↑association between %FFM and higher MDS, ↑leg extension power with ↑MDS [84];  <u>Systematic review conclusion:</u> inconclusive evidence for the role of MED in musculoskeletal health across the life course;
[59] <sup>b</sup>	1 mixed (longitudinal and cross-sectional) / 3 years [89];  2 longitudinal [87,93] / 9 and 8 years, respectively;  5 cross-sectional [86,88,90–92];	women (aged 65-72), Kupio, Finland [89];  older adults (aged ≥65), the InCHIANTI Study, Italy [87];  older adults (aged 70-79), the Health ABC Study, US [93];	10-m walking speed, chair rises, one leg stance, knee extension, grip strength, squat, LBMQ [89];  SPPB [87];  20-m walking speed (usual and rapid) [93];	3-day food record / MDS [89];  FFQ / MDS score [87,93];	↑association between MDS walking speed, LBMQ and squat test, lowest MDS quartile associated with greater loss of relative skeletal muscle and lean mass, no other associations [89];  ↑association between MDS and SPPB at baseline, higher MDS associated with less decline in SPPB at 3-, 6-, 9-year follow-up, higher MDS associated with lower risk of mobility disability, and slower decline in mobility [87];  higher MDS associated with higher usual and rapid walking speed, and less decline in rapid walking speed [93];  <u>Systematic review conclusion:</u> lower risk of sarcopenic symptomatology with higher adherence to MED;
[58] <sup>b</sup>	2 longitudinal [94,95] / 3 and 2 years, respectively;	older adults (aged ≥60), the Senior-ENRICA, Madrid, Spain [94];	physical function limitations (Rosow and Breslau scale, SF-12) [94];	diet history / MDS, MEDAS [94];  FFQ / MDS [95];	→association between MDS, mobility impairment and agility (Rosow and Breslau scale), →association between MDS and physical function decline (SF-12), the highest tertile of MEDAS associated with the

older adults (aged ≥65), the Three-City-Bordeaux Study, France [95]; modified frailty phenotype (Rosow and Breslau scale, chair stands) [95]; decreased risk of developing agility, mobility, and physical functioning impairments [94]; the highest MDS associated with the reduced risk of developing mobility and lower extremity impairments [95];

Systematic review conclusion: higher adherence to MED associated with the lower risk of frailty and functional impairment, →association between MED and sarcopenia in cohort studies, ↑association between MED and sarcopenia in cross-sectional studies;

[56] <sup>b,d</sup>	2 longitudinal [96,97] <sup>b</sup> / 6 and 3.5 years, respectively <sup>b</sup> ;	older adults (aged ≥65), the InCHIANTI, Italy [96];	grip strength, walking speed (over 15 feet) [96];	FFQ / MDS score [96]; diet history / MDS, MEDAS score [97];	higher MDS associated with the reduced risk of developing low walking speed, →association between MDS and grip strength [96];
	2 cross-sectional [105,106] <sup>d</sup> ;	older adults (aged ≥60), the Senior-ENRICA, Madrid, Spain [97];	grip strength, 3-m walking speed [97];	24-hr multi-pass dietary recall / HEI-2005 [105];	→association between MDS, walking speed and grip strength, but the highest MEDAS tertile associated with reduced risk of low walking speed [97];
	2 longitudinal [83,107] <sup>d</sup> / 4 and 3 years, respectively;	older adults (aged ≥60), NHANES 1999-2002, US [105];	knee extensor power, 20-foot gait speed [105];	FFQ / HEI, HDI [106];	↑association between HEI-2005, knee extension power and gait speed, but attenuated by physical activity [105];
		older adults (aged ≥60), the Falls Risk and Osteoporosis Longitudinal Study, Australia [106];	lean mass, SPPB [106];	FFQ / DQ-I [83];	→association between lean mass, SPPB and HEI, ↑weak association between lean mass and HDI (women), and SPPB and HDI (men) [106];
		older adults (aged ≥65), Hong Kong [83];	prevalent and incident sarcopenia [83];	three 24-hr dietary recalls / C-HEI [107];	the highest quintile of DQ-I associated with the reduced risk of prevalent sarcopenia (men), →association between DQ-I and 4-year incident sarcopenia (men and women) [83];
		older adults (mean age 74.6 years), NuAge	grip strength, knee extensor, and elbow flexor strength [107];		→association between C-HEI and muscle strength (grip strength, knee extensor, elbow flexor) maintenance over 3 years [107];

cohort, Quibeck, Canada  
[107];

**Systematic review conclusion:** Strong observational evidence for the association between 'healthier' diets and lower risk of decline in physical performance, but not for decline in muscle strength;

<b>Additional evidence<sup>e</sup></b>					
[100] <sup>b,d</sup>	cross-sectional;	older adults (aged 55-80 (men), and 60-80 (women)), Balearic Islands and Madrid, Spain;	physical fitness (grip strength, 30-s arm curls, 30-s chair stand, 8-foot TUG, 30-m gait speed, 6-min walk test);	FFQ / MED and Westernized DP / factor analysis;	↑association between the highest quartile of MED and 30-s chair stands (men), and 6-min walking speed (women), →association between MED and muscle strength (grip strength and arm curls) in both sexes, the highest MED quartile associated with less time to complete TUG test and 30-m gait speed (men), higher quartiles of a 'Westernized' DP associated with slower gait speed, lower body strength (chair rises), agility (8-foot TUG) and aerobic endurance (6-min walk test) in both sexes;
[101] <sup>b</sup>	cross-sectional;	older women (aged 60-85), the PERSSILAA study, Campania Region, Italy;	grip strength;	7-day food records / PREDIMED score;	women with higher grip strength had higher PREDIMED scores and were more likely to belong to the 'high adherence' PREDIMED group (score ≥10);
[102] <sup>b,d</sup>	longitudinal / 10 years;	older adults (mean age 61.6 years), the Helsinki Birth Cohort Study, Finland;	mobility limitations;	FFQ / mMDS / NDS;	→association between mMDS and mobility limitations at 10-year follow-up, the highest tertile of NDS associated with the lower risk of developing mobility limitations;
[103] <sup>b</sup>	cross-sectional;	type-2 diabetes patients (aged >60 years), the Center for Successful Aging, Diabetes at Sheba Medical Center, Israel;	Berg balance test, TUG, 6-min walk test, 10-m walk test, four square step test, 30-s chair stand, grip strength;	FFQ / MDS;	↑association between MDS and grip strength, but not after adjustment for key covariates, age × MDS interaction: the highest MDS tertile associated with longer distance achieved in 6-min walking test, faster time 10-m walk, and better balance score in those aged ≥75 years;
[108] <sup>b</sup>	longitudinal / 10 years;	older adults (aged >60), the Helsinki Birth Cohort Study, Finland;	grip strength, leg strength, lean body mass	FFQ / MDS;	↑association between grip strength and NDS (women) at 10-year follow-up, →associations between NDS and muscle mass in both sexes;

[109] <sup>d</sup>	longitudinal / 15 years;	older men (aged 66 at baseline) / the British Regional Heart Study, UK;	mobility limitations (going up or down stairs or walking 400 yards);	FFQ / HDI / EDI;	the highest HDI and EDI category at baseline associated with the reduced risk of mobility limitations 15 years later;
[110] <sup>d</sup>	cross-sectional;	older adults (aged ≥65), the National Fitness Award project, the Ministry of Culture, Sports, and Tourism, South Korea;	fitness tests (2-min step test, TUG, figure-of-8 walk test, grip strength, arm curls);	FFQ / RFS;	↑association between RFS and grip strength (women), →association between RFS and other physical performance tests;

Evidence summary for studies with *a priori* DPs: higher adherence to MED associated with better lower extremity functioning, mobility, better walking speed and less decline over time; inconclusive evidence for muscle strength; mixed evidence for Diet Quality Indices and sarcopenia / elements of sarcopenia; emerging evidence for ↑association between 'healthier' DP and mobility / mobility limitations.

465 <sup>a</sup>Summary of selected observational studies from the systematic reviews described in Sections 2.1.2, 2.1.3 (Mediterranean diet), 2.2 and 2.2.1 (Diet Quality Indices) (publication years  
466 2017-2018; cut-off for inclusion April 2017). <sup>b</sup>Reviews and studies using Mediterranean diet indices only. <sup>c</sup>Not described in detail in this review. <sup>d</sup>Studies using Diet Quality Indices  
467 and region-specific *a priori* diet scores. <sup>e</sup>Cut-off for inclusion January 2019. ↑: positive association; →: no association;  
468 C-HEI, Canadian-Healthy Eating Index; DQ-I, Diet Quality Index-International; DP, dietary pattern; EDI, Elderly Dietary Index; %FFM, percent fat free mass; FFQ, Food Frequency  
469 Questionnaire; HDI, Healthy Diet Indicator; HEI, Healthy Eating Index; HEI-2005, Healthy Eating Index-2005; Health ABC Study, the Health, Aging, and Body Composition Study;  
470 InCHIANTI Study, the Invecchiare in Chianti Study; LBMQ, lower body muscle quality; MDS, Mediterranean Diet Score; MED, Mediterranean diet; MEDAS, Mediterranean Diet  
471 Adherence Screener; NHANES 1999-2002, the National Health and Nutrition Examination Survey 1999-2002; NuAge Study, the Quebec Longitudinal Study on Nutrition and  
472 Aging; PERSSILAA, the PERsonalised ict Supported Services for Independent Living and Active Ageing; PREDIMED, the Prevención con Dieta Mediterránea; RFS, Recommended  
473 Food Score; SPPB, Short Physical Performance Battery; TUG, Timed Up-and-Go Test.

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486 **Table 2.** *A posteriori* dietary patterns and muscle health: summary of evidence

Ref.	Study design/duration	Participants/setting	Measure of muscle health/function	Dietary assessment	Findings
<b>Summary of systematic review<sup>a</sup></b>					
[56]	4 cross-sectional [112,113,115,117];  3 longitudinal [114,116,118] / 3.5 to 16 years;	older adults (aged ≥65), the KNHANES, South Korea [112];  older adults (aged 59-73), the Hertfordshire Cohort Study, UK [113];  older adults (mean age 68 years), the Hertfordshire Cohort Study, UK [115];  older adults (aged ≥55), Tehran, Iran [117];  older adults (aged ≥60 at the final follow-up) [114];  older adults (aged ≥85), the Newcastle 85+ Study, UK [116];  older adults (aged ≥60), the Senior-ENRICA, Madrid, Spain [118];	appendicular skeletal muscle mass [112];  grip strength [113];  short SPPB (3-m walk test, 5 chair rises, one-legged standing balance [115];  8-feet walking speed [114];  sarcopenia [117];  grip strength, TUG [116];  grip strength, 3-m walking speed [118];	24-hr dietary recall / clustering analysis [112];  FFQ / PCA [113–115,117];  24-hr dietary recall / cluster analysis [116];  diet history / PCA [118];	a ‘Westernized Korean’ DP associated with increased abnormalities in lean mass compared with a ‘Traditional Korean’ DP [112];  ↑association between ‘Prudent diet’ and grip strength, but partly explained by fatty fish consumption in men and not in women [113];  →association between diet and SPPB in men, higher ‘Prudent diet’ score associated with better 3-m walk time chair stands and balance in women, but not after adjustment for key covariates [115];  the highest tertile of a ‘MED-like’ DP associated with the reduced risk of sarcopenia, but →association between a ‘Westernized’ DP and sarcopenia [117];  →association between a ‘Healthy-foods’ DP and physical function, the highest tertile of a ‘Western-type’ DP associated with the increased risk of poor physical function [114];  men belonging to ‘High Red Meat’ DP had worse GS at baseline, and greater GS decline over 5 years [116];  →association between a ‘Prudent diet’ and grip strength, a ‘Westernized’ DP associated with slow walking speed [118];

					<u>Systematic review conclusion:</u> the evidence for the association between 'healthier' diets, physical performance and muscle strength has been mixed;
<b>Additional evidence<sup>b</sup></b>					
[119]	longitudinal / 3 years;	older adults (aged ≥85), the Newcastle 85+ Study, UK;	sarcopenia;	24-hr dietary recall / cluster analysis;	'Traditional British' DP associated with the increased risk of sarcopenia at baseline and 3-year follow-up in older adults with good protein intake;
[120]	longitudinal / 10 years;	older adults (aged ≥67), the Three-City Bordeaux Study, France;	mobility limitations (Rosow-Breslau scale);	FFQ / hybrid clustering method;	'Biscuits and snacking' cluster associated with a 3-fold increased risk of mobility restriction compared with a 'healthy cluster' in men; →association between clusters and mobility in women;
[121]	cross-sectional;	older adults (aged ≥60), the KNHNES 2008-2011, South Korea;	appendicular skeletal muscle mass;	FFQ / factor analysis;	a 'Healthy' DP associated with higher muscle mass in men, but not in women;
[122]	cross-sectional;	older adults (aged ≥70), Gipuzkoa, Spain;	TUG;	FFQ / multiple correspondence and cluster analysis;	three DPs with progressively worse adherence to dietary recommendations; a gradient effect of DPs in relation to TUG;
[123]	longitudinal / 60-64 years;	British 1946 birth cohort, the MRC National Survey of Health and Development study, UK;	chair rises, TUG, and standing balance (at age 60-64);	prospective 5-day food diaries (completed in 1982, 1989, 1999, and 2006-2010) / PCA;	↑association between a 'healthier' DP at ages 36, 43, 53, and 60-64 and physical performance at age 60-64;

Evidence summary for studies with *a posteriori* DPs: mixed evidence for 'healthier' DPs and components of sarcopenia; higher adherence to 'Westernized' DPs associated with impairments in mobility and physical performance.

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<sup>a</sup>Summary of selected observational studies described in Sections 2.2. <sup>b</sup>Summary of observational studies described in Section 2.3.1. ↑: positive association; →: no association; DP, dietary pattern; FFQ, food frequency questionnaire; PCA, principal component analysis; KNHANES, Korea National Health and Nutrition Examination Survey; TUG, Timed Up-and-Go Test.



#### 490 2.4. Similarities and Differences between the Findings of Dietary Patterns and Muscle Ageing Studies

491 Direct comparisons of the associations (positive and negative) between DPs (derived *a priori* or  
492 *a posteriori*) and muscle health / function in observational studies summarised in the latest reviews  
493 [56–59] and presented here are limited for several reasons. The studies varied by the (i) dietary  
494 assessments used to measure the exposure (from FFQs, 24-hr recalls to weighed food records); (ii)  
495 methods employed to derive DPs (MED indices being the commonest approach followed by diet  
496 quality indices); (iii) assessments used to measure the outcomes (sarcopenia and its components); (iv)  
497 muscle health / function outcomes (from body composition and muscle mass (ASM), muscle strength  
498 (grip strength, knee and elbow extensor strength), physical performance (gait speed, SPPB, senior  
499 fitness test, mobility impairment and agility, physical components of SF-12)); (v) covariates selected  
500 to adjust for confounding; (vi) populations under study, including differences in age, background  
501 diet and nutritional status; and (vii) study designs (more cross-sectional than longitudinal). To our  
502 knowledge, the role of DPs in sarcopenia prevalence and incidence has been investigated only in the  
503 following four studies [83,89,117,119] in Chinese [83], Nordic [89], Iranian [117] and British [119] older  
504 adults, warranting further investigations. A growing literature on DPs recognises the importance of  
505 a whole food approach to understand synergistic, antagonistic, and cumulative effects of nutrients  
506 and other food components in muscle health with ageing. However, how the complex concept of a  
507 ‘healthy diet for muscle health’ has been addressed varies significantly across studies, from MED and  
508 various HELs (hypothesis driven and based on general health) to data-driven approaches that  
509 describe whole diets in a population. Most studies have used several muscle-related outcomes, but  
510 only a few employed different methods within studies to derive DPs to provide complementary  
511 findings [e.g. 83,97,106].

512 The most consistent results were observed with MED-type DPs (derived *a priori* or *a posteriori*)  
513 in relation to physical functioning (lower extremity functioning, mobility, walking speed) in the  
514 populations living in the Mediterranean and non-Mediterranean regions [84,87,88,91,93–95,100,121].  
515 Regardless of differences across the studies in conceptualisation of MED (MDS or PREDIMED score,  
516 *a posteriori*-derived MED DP) and physical function outcomes, the similarity in the findings suggest  
517 that this DP may be ‘myoprotective’ in different populations of older adults. Therefore, the potential  
518 ‘myoprotective’ mechanisms that may underpin the effect of MED on muscle are explored in Section  
519 3. Conversely, the most consistent evidence obtained from a *a posteriori* method implies that higher  
520 adherence to westernized DP is a strong risk factor for impaired mobility and physical performance  
521 [97,100,113,116,121], which in turn might indicate lack of consumption of foods that characterise the  
522 MED pattern. Inconclusive results were observed with DPs and other components of sarcopenia,  
523 including muscle mass and muscle strength. More research and cross-validation of the finding are  
524 needed to understand the DP-sarcopenia relationship using well-defined cohorts of older adults with  
525 longer follow-up, which will allow for data harmonisation and pooled analyses of DP effects on  
526 muscle health and function and to define of an ‘optimal’ diet for prevention of sarcopenia.

527 Based on the evidence reviewed here, MED may have the best profile foods with ‘myoprotective’  
528 properties, and may provide a blueprint for designing DPs for muscle health in older adults in the  
529 future to include not only consideration of the type of classic MED foods but also their amount and  
530 ratio. Specifically, the traditional MED is characterized by higher intake of plant foods and olive oil  
531 (sources of vitamins, minerals, fibre, phytochemicals, healthy fatty acids, and protein), and moderate  
532 to low intake of animal-based foods, when compared with westernized DPs. The sources, amounts  
533 and ratio of the profile foods in MED may translate into favorable nutrient profiles for muscle health  
534 and function. However, there may be debate about how certain elements of MED align with current  
535 nutritional guidelines [e.g. 133,134] or expert opinion about nutrient needs for muscle health [44,52].  
536 These may include a somewhat lower protein intake (when expressed as either percentage of total  
537 energy, or g/kg of body weight (actual or ideal) [135]) than recommended for older adults for muscle  
538 health [44,52], and low vitamin D intake [discussed in 133]. Therefore, when designing an ‘optimal’  
539 diet for prevention of sarcopenia around MED, there may be other aspects of healthy diet such as  
540 optimal protein intake for muscle health in older adults [44] that also need to be considered.

### 541 3. Potential Mechanisms of Myoprotective Dietary Patterns in Older Adults

542 In recent years, a number of systematic / narrative reviews and opinion articles have discussed  
543 the potential role of nutrition, nutritional supplements (e.g. protein supplements, vitamin D, n-3 fatty  
544 acids, creatine, etc.), and nutrients from foods (e.g. dairy protein and magnesium) in muscle ageing  
545 and sarcopenia [e.g. 23–25,55,136–149]. Fewer reviews have examined relationships between whole  
546 foods (e.g. fruits and vegetables, dairy, meats) [150–154] and DPs (e.g. MED; diet quality defined by  
547 dietary indices) and muscle health in older adults [56–59]. Many have hypothesised potential  
548 mechanisms by which nutrients (supplemented or from diet) may influence sarcopenia and age-  
549 related functional decline, although recognising the gaps in understanding based on current  
550 knowledge. For example, in a review about nutritional influences on muscle ageing Welch [139]  
551 evaluated established, less established and potential nutritional factors implicated in the main  
552 biomechanisms of age-related muscle loss. Whilst protein, essential amino acids (EAA), and leucine  
553 (mostly in combination with exercise) have been recognised as established factors, current  
554 understanding about the role of vitamin D, antioxidant nutrients (vitamin C, E, carotenoids), minerals  
555 and trace elements (e.g. selenium, zinc, potassium, magnesium, iron, phosphorus) in muscle loss is  
556 less established. Conversely, the associations between dietary acid-base load (alkaline diets), dietary  
557 fat (type, composition and ratio), and bioactive compounds (nitrate, curcumin, antioxidant  
558 compounds in olive oil) are the least established, although recognised as potential factors relevant  
559 for muscle ageing [139]. Other nutritional factors and novel dietary candidates for muscle health  
560 suggested to contribute to healthy muscle ageing include dairy bioactive components, ursolic acid,  
561 phytochemicals nitrate-rich foods, and amino acid metabolites and precursors [23,25,136,137]—  
562 acting via a number of mechanisms including anti-inflammatory, anti-oxidative, and anabolic-  
563 promoting functions.

564 While much of the epidemiological research has focused on dietary intakes, there is also  
565 evidence of differences in nutrient status related to muscle health. For example, nutrient intake and  
566 biochemical nutrient status for a number of nutrients differs between sarcopenic and non-sarcopenic  
567 older adults regardless of energy intake, suggesting the importance of diet quality and nutrient  
568 density in the whole diet / DP for muscle health [155,156]. In the Maastricht Sarcopenia Study of 227  
569 older adults aged  $\geq 65$  years, those with sarcopenia had 10–18% lower intake of five nutrients (n-3 fatty  
570 acids, vitamin B<sub>6</sub>, folic acid, vitamin E, and magnesium), and their biochemical markers for n-6 fatty  
571 acid (linoleic acid) were 7% lower and homocysteine levels 27% higher compared with non-  
572 sarcopenic older adults. The groups did not differ in energy intake [155]. In the PROVIDE study, a  
573 multi-centre randomized controlled trial of vitamin D and leucine-enriched whey protein  
574 supplements for sarcopenia conducted with 380 older adults aged  $\geq 65$  years, those with sarcopenia  
575 had ~6% lower protein intake (g/kg body weight), ~33% lower vitamin D, ~22% low vitamin B<sub>12</sub>, and  
576 ~2–6% lower intake of magnesium, phosphorus and selenium compared with those without  
577 sarcopenia. But of all biochemical markers examined, only serum concentration of vitamin B<sub>12</sub> was  
578 ~15% lower in sarcopenic older adults. Again, energy intake was similar in both groups [156].

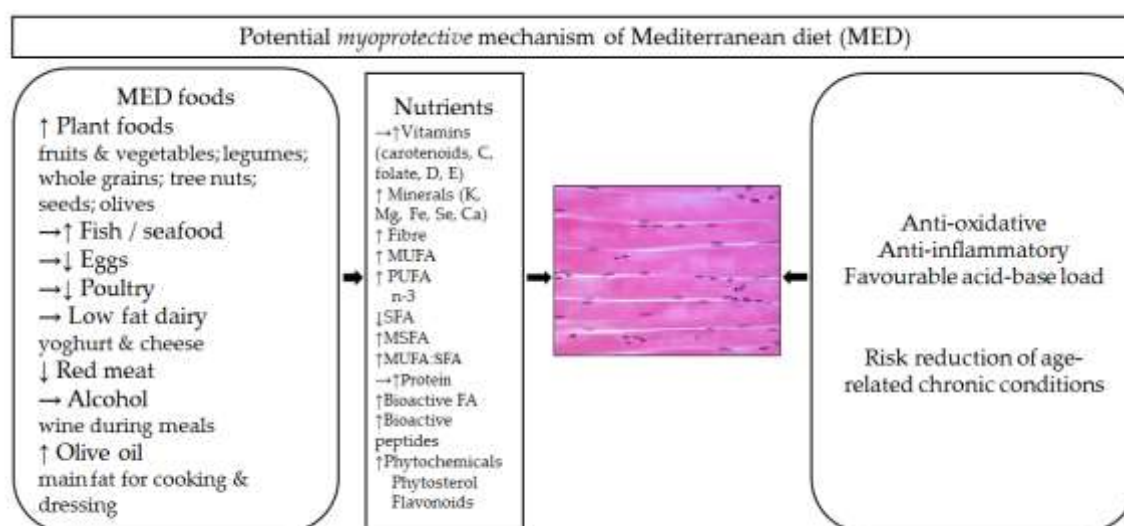
579 These findings (and the results from the studies of DPs) suggest that combined actions (probably  
580 synergistic, cumulative, and antagonistic) of a number of macro- and micronutrients, together with  
581 other food components within the food matrix rather than a single nutrient may be important for  
582 muscle mass, strength and function in older adults. Higher intake of beneficial foods in a healthy diet  
583 may provide not only sufficient energy, but also adequate levels of relevant ‘myoprotective’ nutrients  
584 and bioactive compounds per calorie. The interaction between the nutrients acting upon the aged  
585 muscle may help to preserve or improve myofibre quantity and quality by counteracting  
586 pathophysiology of sarcopenia [34,36–39,128,129,131].

#### 587 588 3.1. Potential Myoprotective Mechanisms of Healthy Dietary Patterns: Example of Mediterranean Diet

589  
590 MED is recommended for healthy ageing and chronic disease risk reduction, not only because  
591 of higher intake of specific foods (e.g. plant-based foods, extra virgin olive oil) and nutrients (e.g.  
592 monounsaturated fatty acids (MUFAs) from olive oil, and PUFAs from fish), but as a healthy eating

593 pattern that as a whole exerts important health benefits [133], including those that may be  
 594 'myoprotective'. Figure 1. depicts hypothesised 'myoprotective' effects of the complex combination of  
 595 nutrients within a variety of foods in MED on aged muscle, which may be indirect and direct. The  
 596 indirect 'myoprotective' mechanisms of MED may act through a reduction in risk of age-related chronic  
 597 conditions (e.g. cardiovascular diseases, diabetes, polypharmacy) that are associated with either  
 598 induction or worsening of sarcopenic symptomatology [157–159]. MED may also act directly by  
 599 ameliorating processes that have been implicated in sarcopenia (i.e. oxidative stress [129,130],  
 600 inflammation [33,34,126–128], insulin resistance [130–132], and metabolic acidosis [reviewed in  
 601 23,24,139,160,161] (Figure 1).

602 Oxidative stress or accumulation of reactive oxygen and nitrogen species (ROS/NRS) in aged  
 603 muscle leads to impaired cellular homeostasis and damage to key cell macromolecules such as  
 604 proteins, lipids, and nucleic acid, affecting their structure and function [reviewed in 127,129]. An  
 605 excess of free radicals is pathologic and the inability of endogenous antioxidant enzymes to neutralise  
 606 their detrimental effects on organelles and biomolecules in myofibres has been implicated in the loss  
 607 of muscle mass, quality and function [128,129]. Diet rich in exogenous antioxidants vitamins (e.g.  
 608 vitamin E, C, carotenoids), minerals (zinc, copper, iron, selenium, magnesium) [149], and  
 609 phytochemicals [162] from fruits, vegetables, olive oil and nuts such as MED can help in restoring the  
 610 redox homeostasis [163] in the muscle, and counteract ROS/NRS-induced damage. Antioxidants act  
 611 as scavengers of excess free radicals produced by several organelles in myofibres, and help maintain  
 612 neuromuscular integrity and function that is changed with ageing [164]. However, because older  
 613 myofibres benefit from the production of low-dose ROS to improve endogenous antioxidant system  
 614 and cellular repair capacity during, for example, nonexhaustive exercise and lifelong physical  
 615 activity, excess intake of antioxidant supplementation may be counteractive and cause reductive  
 616 stress [reviewed in 25,165,166]. Conversely, MED may provide the right combination of antioxidants  
 617 in the amounts beneficial to redox homeostasis in physically active older adults, thus improving  
 618 function.  
 619



620

621 **Figure 1.** Hypothesised 'myoprotective' effect of Mediterranean diet (MED). Because of higher (↑) intake of  
 622 plant-based foods, olive oil as a main source of fat, moderate-to-high (→↑) intake of fatty fish, moderate-  
 623 to-low (→↓) intake of poultry and eggs, moderate (→) intake of dairy (mostly from yoghurt and cheese),  
 624 low (↓) intake of red meats and meat products, and moderate intake of red wine during meals, MED is a  
 625 potential source of bioactive nutrients that may act synergistically, antagonistically, and cumulatively on  
 626 the ageing muscle and may be 'myoprotective'. Potential 'myoprotective' effects of MED may work through  
 627 its higher anti-oxidative and anti-inflammatory capacity, and favourable acid-base load (directly) and by  
 628 reducing the risk of age-related conditions related to sarcopenia (indirectly). MUFA, monounsaturated

629 fatty acids; PUFA, polyunsaturated fatty acids. Skeletal muscle image adapted from:  
630 <https://teaching.ncl.ac.uk/bms>  
631

632 In addition to modulating redox balance, antioxidants in MED may affect signaling pathways  
633 and transcriptional factors such as nuclear factor  $\kappa$ B (NK- $\kappa$ B) [167], which are responsible for the  
634 expression of pro-inflammatory cytokines, including interleukin 6 and 8 (IL-6 and IL-8) [167] and  
635 tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) [168]. Ageing is associated with a 2-4-fold increase in pro-  
636 inflammatory mediators in serum or plasma, which can both induce and exacerbate age-related  
637 pathologies [167], including loss of muscle mass and function [33,34,126–128]. Besides chronic  
638 disorders and subclinical infections, several factors have been recognised to contribute to chronic  
639 low-grade inflammation (inflammageing), including increases in adipose tissue, hormonal changes,  
640 dysregulation of the immune system at the organ level [168]; and oxidative stress, mitochondrial  
641 dysfunction, glycation, telomere attrition, cell senescence, epigenetic modifications at the cellular  
642 level [169]. Furthermore, inflammatory mediators (e.g. IL-6 and TNF- $\alpha$ ) interfere with anabolic  
643 signaling by, for example, downregulating insulin and insulin-like growth factor-1 (IGF-1), and  
644 affecting muscle protein synthesis (MPS) after a meal or exercise [170,171]. Muscle insulin resistance  
645 may also arise in the presence of a high fatty acid availability and fat accumulation within the fibres,  
646 with induction of intracellular inflammation [172].

647 It has been proposed that inflammatory markers may act not only as common risk factors for the  
648 most age-related chronic conditions, but also provide a link between lifestyle factors, chronic diseases  
649 (including sarcopenia), and physiological changes with ageing [168]. Several dietary components in  
650 a healthy DP may have anti-inflammatory properties [172], and the lack of them may negatively  
651 influence muscle ageing. Anti-inflammatory effects of MED for muscle health may be achieved  
652 through higher intake of n-3 PUFA (fatty fish) and MUFA (olive oil). For example, a positive  
653 association between fatty fish intake and grip strength has been reported in older adults from the  
654 Hertfordshire Cohort Study—each additional portion of fatty fish was associated with a 0.43 kg  
655 increase in grip strength in men and a 0.48 kg increase in grip strength women [113]. In a 24-week  
656 intervention study involving 63 women (aged 65-70), a healthy diet rich in n-3 PUFAs (achieved  
657 through higher fish / seafood intake of  $\geq 500$  g/week) in combination with resistance exercise (RE),  
658 resulted in a 23% increase in type IIA muscle fibres, and downregulation of genes involved in  
659 inflammation and upregulation of regulators of growth response in the muscle [173], when compared  
660 with RE alone. Combining RE with a diet characterised by low n-6 to n-3 PUFA ratio ( $<2$ ) and keeping  
661 total fat energy intake mainly from MUFA and PUFA (and accord with MED) may counteract age-  
662 related changes in fast myofibres. A traditional MED provides about 36-40% of total energy intake  
663 from fat (7-10% from saturated fats, 19-25% from MUFA, and 3-6% from PUFA) [133], because of  
664 higher consumption of olive oil, moderate to lower intake of dairy and meats compared to Western  
665 DPs. The beneficial effects of MED-like DPs on muscle function and physical performance compared  
666 to westernized DPs [e.g. 84,87,88,91,93–95,100] may be attributed to anti-inflammatory properties of  
667 its fat content and composition [162].

668 Better balance in the dietary acid-base load and potential reduction of diet-induced metabolic  
669 acidosis is another beneficial element of MED 'myoprotective' mechanism that may be involved in  
670 muscle ageing and sarcopenia. Metabolic acidosis is a major cause of muscle loss in patients with  
671 chronic kidney disease, and MED has been recently recommended in clinical guidelines as a strategy  
672 for chronic kidney disease prevention [174]. Because MED is more plant-based, higher in fibre and  
673 lower in meats and dairy, it has potential to be less acidic. Although limited, research has shown that  
674 alkaline diets have positive effects on lean muscle mass in healthy older adults [reviewed in  
675 23,24,139,160,161,175].

676 In conclusion, MED may be beneficial for muscle health by simultaneously affecting several  
677 processes involved in sarcopenia and other age-related diseases, and not limited to oxidative stress  
678 and inflammation (Figure 1).

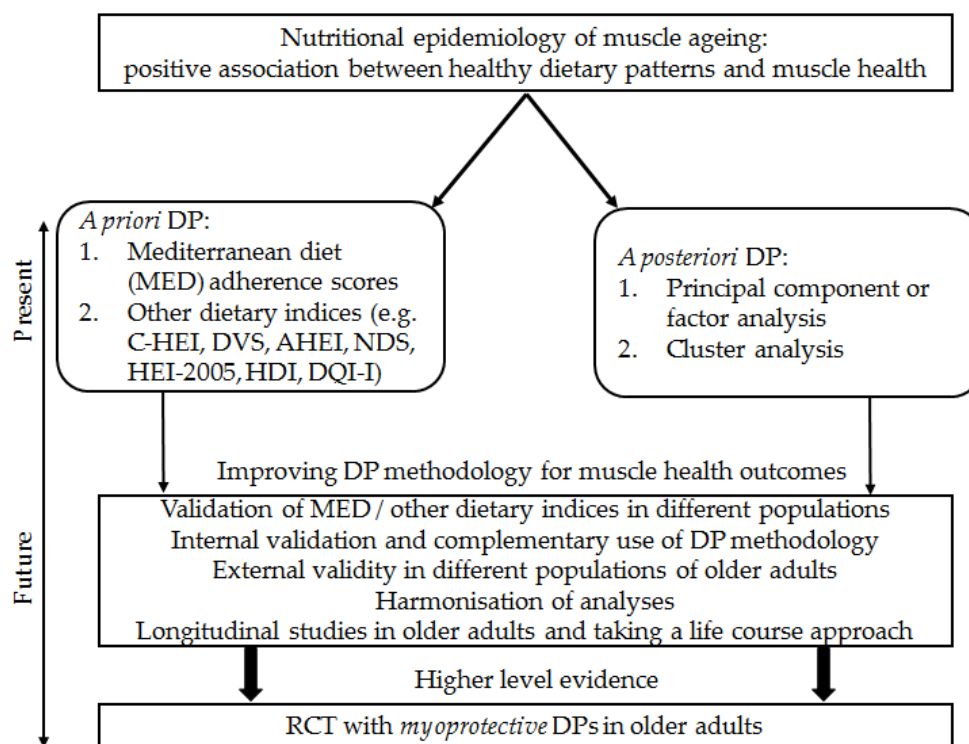
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#### 681 4. Challenges Facing Dietary Patterns Research in Nutritional Epidemiology of Muscle Ageing

682 Similar to research involving other health outcomes (e.g. cognition [176]), testing diet-muscle  
683 health hypothesis using DP methodology faces several challenges. Figure 2 describes current  
684 approaches in nutritional epidemiology of muscle ageing and suggestions for improving DP  
685 methodology aimed to achieve a higher level of evidence in the future. For example, regardless of  
686 positive associations between MED and physical performance in older adults from the Mediterranean  
687 and non-Mediterranean regions reported in several studies, different MED indices have to be cross-  
688 validated, and should be based on the latest scientific understanding of MED [81]. DP methodology  
689 is flexible and complementary techniques have been developed [67–69], but not all of them have been  
690 employed to test DP-muscle ageing hypothesis. Specifically, the RRR method not yet used in the  
691 studies of muscle ageing will allow investigation of DPs that maximally explain the variation in other  
692 response variables relevant for muscle health (e.g. protein and beneficial fatty acids) that are  
693 hypothesised to be associated with aetiology of sarcopenia and will provide mechanistic insights [69].  
694 Harmonising the operational definitions of sarcopenia [26,85,175,177] and understanding of the  
695 concepts of ‘healthy’ diets for muscle health across the well-conducted prospective studies with  
696 longer follow-up will build on current scientific knowledge about the role of whole diet in muscle  
697 ageing. Although the research focus of most observational studies on diet and sarcopenia has been  
698 later life, there is evidence for benefits of a life course approach when investigating factors affecting  
699 sarcopenia. This includes the role of early nutrition in determining peak muscle strength in mid-  
700 life and consequent rate of muscle mass / strength decline in later life [178,179].

701 The proposed ‘*myoprotective*’ potential of a healthy DP such as MED may be viewed as a sum of  
702 the different effects of multiple, distinct component, which do not act in isolation [180], and may vary  
703 across the regions (e.g. Mediterranean and non-Mediterranean regions) and over time [76,81].  
704 Different compounds in the whole diet associated with better muscle health may have multifactorial  
705 effects through different mechanisms of action (including effects on single, multiple or more general  
706 pathways), which may be also influenced by heterogeneous nature of sarcopenic muscle in older  
707 adults.

708 In summary, to reach a higher-level evidence, harmonisation, validation (internal and external)  
709 of DPs, and complementary use of DP methodology in longitudinal / cohort studies of ageing with  
710 longer follow-up taking a life course approach in different populations is needed to gather  
711 information that will aid design of future randomised controlled trials (RCTs) with ‘*myoprotective*’  
712 diets (Figure 2).



713 **Figure 2.** Dietary pattern-muscle health hypothesis investigation in nutritional epidemiology of muscle  
 714 ageing faces several challenges to reach a higher level evidence. AHEI, Alternative Healthy Eating Index;  
 715 DVS, Dietary Variety Score; DP, dietary pattern; HDI, Healthy Diet Indicator; HEI-2005, Healthy Eating  
 716 Index 2005; DQI-I, Diet Quality Index-International; MED, Mediterranean diet; NDS, Nordic Diet Score.

## 717 5. Conclusions

718 Muscle health is an integral part of healthy ageing. In recent years, diet / nutrition as a modifiable  
 719 risk factor has been extensively investigated in relation to several aspects of muscle health, including  
 720 muscle mass, strength, and physical performance. The evidence from nutritional epidemiology to  
 721 date suggests a positive association between healthier DPs such as MED and muscle function,  
 722 including physical performance and mobility decline in older adults. MED may exert 'myoprotective'  
 723 effects through different mechanisms of action arising from multiple dietary components and  
 724 pathways. Although there are few studies of sarcopenia, observational studies examining the role of  
 725 whole diet are emerging, and show a lower risk of sarcopenia in association with healthier diets.  
 726 However, much of the current evidence is limited to cross-sectional studies and for some outcomes,  
 727 such as muscle strength, findings are mixed. To date, only one meta-analysis has been conducted that  
 728 investigated the protective role of MED in functional disability in older adults [64]. There are  
 729 therefore clear gaps in knowledge. To reach a higher level of evidence, cross-validation and  
 730 harmonisation of the methods to define dietary patterns are needed, together with studies of different  
 731 populations of older adults with longer follow-up taking a life course approach, which may inform  
 732 the design of future clinical trials.

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742

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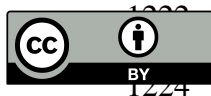
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