

Mediterranean Diet attenuates risk of frailty and sarcopenia: New insights and future directions

Rebecca McClure¹, Anthony Villani¹

¹ School of Health and Sport Sciences, University of the Sunshine Coast, Queensland Australia

Abstract

Sarcopenia and physical frailty are associated with progressive disability and predictive of negative health outcomes. Dietary interventions are considered the cornerstone in the management of sarcopenic symptomatology and physical frailty. However few studies have investigated preventative strategies. Moreover, most studies have focused on the efficacy of individual nutrients or supplements rather than dietary patterns. The Mediterranean Diet (MedDiet) is a dietary pattern that provides evidence for an association between diet quality, healthy ageing and disease prevention. The purpose of this paper was to examine, synthesise and develop a narrative review of the current literature, investigating the potential benefits associated with adherence to a MedDiet and attenuation of physical frailty and sarcopenic symptomatology in older adults. We also explored the underlying mechanisms underpinning the potential benefits of the MedDiet on ameliorating physical frailty and sarcopenic symptomatology. Synthesis of the reviewed literature is suggestive of a decreased risk of physical frailty and sarcopenic symptomatology with greater adherence to a MedDiet. We identified the anti-inflammatory and high antioxidant components of the MedDiet as two potential biological mechanisms involved. Due to a lack of evidence from RCTs to support the proposed physiological mechanisms, we suggest investigating these observations in older adults with type 2 diabetes (T2DM) whom are vulnerable to physical frailty and disability. A number of biological mechanisms describing the pathway to disability in older adults with T2DM have been postulated with many of these mechanisms potentially mitigated with dietary interventions involving the MedDiet. Exploring these mechanisms with the use of well-designed, longer-term dietary intervention studies in older adults with an increased vulnerability to physical frailty and sarcopenia is warranted.

Address for correspondence: Dr Anthony Villani; School of Health and Sport Sciences, University of the Sunshine Coast, Maroochydore Qld 4558 Australia; Tel: +61 7 5456 3546; E-mail: avillani@usc.edu.au

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Introduction

Global trends in population ageing are pronounced and historically unprecedented leading to an increased need to promote healthy ageing. It is estimated that approximately one-quarter of the population in the United Kingdom (UK), Australia and in the United States (US) will be aged 65 years and older by 2050 [1, 2]. Of greatest concern is the potential threat for loss of independence and the subsequent economic impact associated with healthcare services utilised by older people. A major cause of loss of independence, institutionalization and disability amongst older adults is an age-related decline in skeletal muscle mass (SMM) and function,

a geriatric muscle wasting syndrome termed sarcopenia [3-5].

Ageing is associated with changes in body composition that typically favours a reduction in muscle size and quality. Specifically, losses in lean body mass occur at a rate of approximately 1-2% per year following the fifth decade of life [6]. The aetiology of an age-related reduction in SMM is multifactorial and is thought to be attributable to a range of factors including type II muscle fiber atrophy [7-9], mitochondrial dysfunction [10, 11] and an accumulation of intramuscular fat [12, 13]. Moreover, such disturbances in the architecture of skeletal muscle favour a loss of muscle strength and quality [14-16]. With less muscle mass, muscle strength and muscle function are compromised.

Current evidence suggests that muscle strength declines more rapidly than the concomitant loss of SMM, with muscle strength declining by ~1.5% per year between the fifth and sixth decade of life, further accelerating thereafter [13, 17-19]. This evidence supports the hypotheses that muscle quality is more strongly associated with physical disability and risk of institutionalization relative to muscle mass alone [20-25].

Sarcopenia, meaning poverty of flesh, is characterized by a progressive and generalized loss of SMM and function associated with ageing [4, 26, 27]. A number of consensus groups have established operational definitions and diagnostic criterion cut-offs for the sarcopenic phenotype to include measures of physical performance and grip strength in addition with low SMM [3, 4, 26, 28-30]. Frailty however is a multidimensional syndrome associated with diminished strength, endurance and reduced physiological functioning increasing an individual's vulnerability to stressors and increasing the risk of adverse health outcomes, including mortality [31-34]. Akin to sarcopenia, different diagnostic criteria have been validated to identify frail older adults which mainly refer to two conceptual models: the frailty index proposed by Rockwood et al [35] and the physical frailty phenotype proposed by Fried et al [36]. Most recently, a simple five question FRAIL scale has been developed which has greater application in the clinical setting [33, 37]. Both sarcopenia and the physical frailty phenotype are associated with loss of independence, institutionalization, progressive disability and predictive of major negative health-related outcomes, including mortality [38]. Given the number of key physiological mechanisms implicated in the pathogenesis of both geriatric muscle wasting conditions [39], sarcopenia may be considered a biological substrate for the development of the physical frailty phenotype and provide a physiological pathway in the development of negative health-related outcomes [34]. Despite this overlap, not all frail persons are sarcopenic and not all sarcopenic persons are frail [40]. Irrespective of the lack of a widely accepted operationalization of these geriatric conditions, both sarcopenia and physical frailty share physique commonalities (i.e. low SMM) and clinical symptomology including slow gait speed, weakness and impaired balance. Therefore, effective treatment and preventative strategies are paramount to facilitate improved health outcomes and enhance quality of life.

Nutrition and physical activity interventions are cornerstones for the management of sarcopenic symptomology and physical frailty [40-43]. Both aerobic and resistance training attenuates the loss of lean body mass, increases muscle strength and ameliorates frailty in older adults [42-44]. Numerous

dietary interventions have been extensively investigated, though most studies have focused on the efficacy of individual nutrients or supplements rather than dietary patterns [45-49]. However, it is plausible that many dietary factors, including individual nutrients and other non-nutrient bioactive constituents, individually and collectively, influence skeletal muscle functioning and body composition. The Mediterranean Diet (MedDiet) is an example of a dietary pattern that provides evidence for an association between diet quality and healthy ageing [50-53]. There is evidence suggesting that greater adherence to a MedDiet is associated with substantial reductions in the risk of several major age-related diseases including cardiovascular disease (CVD) [54], overall cancer risk [55], type 2 diabetes mellitus (T2DM) [56-58] and cognitive decline [59, 60].

Despite the wealth of available literature on the MedDiet and healthy ageing, dietary intervention studies investigating the relationship between the MedDiet, physical frailty and sarcopenic symptomology are scant. Therefore, the purpose of this review is to provide a coherent overview of the best available evidence from a selective framework of key studies examining the following: 1) the association between adherence to MedDiet pattern, physical frailty and sarcopenic symptomology; 2) underlying mechanisms underpinning the potential benefits of the MedDiet on ameliorating physical frailty and sarcopenic symptomology; and 3) future directions and feasibility of exploring these observations with the use of robust dietary interventions. Peer reviewed literature included in this narrative review were identified through searches of publications listed in electronic databases including MEDLINE, EMBASE, OVID and PubMed. All electronic databases were searched commencing in January 2017 ceasing in April 2017. Searches were limited to full-length articles, written in the English language, men and/or women ≥ 55 years and publications that assessed one or more parameters that relate to the physical frailty phenotype or sarcopenic symptomology, including body composition, skeletal muscle strength and physical performance. Titles and abstracts of articles were examined using the following key words: "Mediterranean Diet", "Mediterranean-style diet", "frailty", "sarcopenia", "mobility", "gait speed", "walking speed", "muscle mass", "muscle strength", "muscle performance", "older adults", "ageing" and "elderly". This review aims to obtain the highest level of evidence possible; therefore given the notable absence of randomised controlled trials (RCTs), prospective observational studies and cross-sectional studies were included, whereas letters, opinions, editorials, abstracts, dissertations and review papers

were excluded. For the purpose of the present review, we only included studies that assessed adherence to the MedDiet or MedDiet pattern rather than individual constituents of the dietary pattern.

Assessing adherence to a Mediterranean diet

The traditional MedDiet is the dietary pattern prevailing among the people of the olive growing regions of the Mediterranean basin before the mid-1960s. The pioneering Seven Countries Study suggested that this dietary pattern was associated with reduced risk of coronary heart disease relative to northern European countries and the United States after a 25 year follow-up [61, 62]. The traditional dietary pattern is characterized by a high consumption of vegetables, fruit, legumes, nuts and unprocessed cereals, and a moderate consumption of fish, shellfish, eggs and wine (typically during meals) [63-66]. Moreover, the total dietary lipid intake was high (30-40% of total energy intake) with extra-virgin olive oil (EVOO) used as the major culinary fat. On the contrary, consumption of red meats, processed meats, meat products, vegetable oils, processed cereals, dairy products (with the exception of long-preserved cheeses) and butter was very low and infrequent [63-66]. The nutrient profile of the MedDiet includes a high monounsaturated:saturated fat ratio, a high intake of alpha-linolenic acid, a lower ratio of omega-6/omega-3 fatty acids, moderate ethanol intake, high intakes of dietary fiber, vitamins, minerals, antioxidants and a range of non-nutritive compounds including polyphenols, carotenoids and flavonoids; moreover, the intake of animal protein in the traditional MedDiet was low [67-69].

Over the past several decades, research on dietary intake and its relationship with disease has shifted from the study of individual nutrients or single foods, to the evaluation of whole-dietary patterns, as a determinant of disease risk [50]. The MedDiet pattern fits well within the current paradigm of assessing dietary patterns rather than isolated foods or nutrients. However, the MedDiet pattern has evolved from the original definition introduced by Ancel Keys in the Seven Countries Study [61, 62]. Therefore, to attain a greater understanding of the mechanisms associated with the proposed health benefits of the MedDiet, adherence to the dietary pattern must be quantified. Dietary patterns can be defined in a number of ways including general principals and descriptions of the diet, *a priori* scoring systems, *a posteriori* dietary pattern formation, dietary pyramids or by food and nutrient analysis [53, 65-67, 70, 71]. Over the past several years, adherence to the MedDiet has been estimated mainly through the creation of diet quality indices such as *a priori* scoring systems as they

simplify analysis of adherence to the diet in relation to different primary health outcomes [50, 67, 72].

Adherence to the Mediterranean Diet, Physical Frailty and Sarcopenic Symptomology

Study Characteristics

A total of 14 full-text articles published between 2008 and 2017 were identified, and fulfilled the search criteria for this review. However, four full-text articles were duplicate publications: two studies were reported on four occasions in separate articles [73-76]. Therefore a total of 12 studies were included in this narrative review (see Table 1). There were five longitudinal cohort studies [74, 76-79] and seven cross-sectional studies [80-85]. Two studies originated from Italy [76, 86], Germany [80, 82] and USA [78, 84], with one study coming from Greece [85], Spain [74], United Kingdom [83], Iran [81], China [77] and Finland [79]. Sample sizes ranged from 192 to 2983 participants.

There were five studies that assessed physical frailty or physical function [74, 76, 77, 80, 84]. Physical frailty was largely assessed using the Fried et al [36] diagnostic criteria that includes self-reported weight loss, exhaustion, low grip strength, slow gait speed and low physical activity. However, the study conducted by Chan et al [77] assessed physical frailty using the 5-item FRAIL scale proposed by Morley et al [37] that includes diagnostic criteria including fatigue, resistance, ambulation, illnesses and weight loss. Zbeida et al [84] assessed physical function in two separate cohorts (US National Health and Nutrition Survey (NHANES) and the Israeli National Health and Nutrition Survey) using the Physical Function Questionnaire used as a component of the NHANES protocol and the Katz et al [87] scale which includes activities of daily living including the ability to dress, shower, sit-to-stand from a chair, eat and use the toilet. Objective measurements including gait speed and muscle strength were also collected [84]. In a separate analysis of the InCHIANTI study [88], Milanese et al [73] assessed physical functioning using the Short Physical Performance Battery (SPPB) [89] which evaluates lower extremity function by measuring three domains of physical function that mimic activities of daily living: 1) balance; 2) usual gait speed; 3) chair stands.

A total of seven studies assessed sarcopenia or elements of sarcopenic symptomology [78, 79, 81-83, 85, 86]. Two studies [79, 81] identified sarcopenia using the diagnostic algorithm established by the

European Working Group on Sarcopenia in Older People (EWGSOP) which defines sarcopenia as loss of function (either gait speed or grip strength) in the presence of low SMM or appendicular skeletal muscle (ASM) [4]. One study [82] assessed body composition using Dual Energy X-ray Absorptiometry (DXA) to derive ASM, calculated as the sum of lean soft tissue mass in both arms and legs [90] and further adjusted by BMI to establish the ASM index calculated using the formula, ASM/BMI [91, 92]. Tyrovolas et al [85] however assessed ASM using a predictive equation proposed by Lee et al [93] to determine the ASM index. Isometric hand-grip strength, gait speed or both were assessed in the remaining three studies [78, 83, 86].

The majority of studies (n = 10) used a variety of different *a priori* scoring systems to assess adherence to the MedDiet [74, 76-80, 82, 84-86]. The most commonly used diet quality index was the

Mediterranean Diet Score (MDS) developed by Trichopoulou et al [94], used in six studies [74, 76-79, 84]. Three studies [82, 85, 86] assessed adherence to the MedDiet using dietary assessment tools developed in accordance with the MedDiet pyramid [95-97]. Bollwein et al [80] assessed dietary adherence using the alternate Mediterranean food (MED) score developed by Fung et al [98] which is an adaptation of the MDS developed by Trichopoulou et al [94] for application in non-Mediterranean populations. Two studies [81, 83] applied data-driven (*a posteriori*) approaches including Principal Component Analysis (PCA) to characterize dietary patterns from dietary data collected by Food Frequency Questionnaires (FFQ). For each of the studies included in this review, the dietary assessment tool used to assess adherence to the MedDiet is presented in Table 1.

Table 1: Characteristics of included studies investigating the association between adherence to a Mediterranean dietary pattern, physical frailty and sarcopenic symptomology

Study	Study population	Study design (follow-up)	Sample size	Mean age (SD)	Dietary adherence tool	Efficacy	Major findings
Physical frailty							
Chan et al 2015 [77]	Community dwelling older adults, China	Longitudinal (4 years)	2724	71.8 (4.8)	MDS	-	No association between adherence to a MedDiet and incident frailty was observed
León-Muñoz et al 2014 [74]	Community dwelling older adults, Spain	Longitudinal (3.5 years)	1815	Mean age of entire cohort not reported; all participants ≥ 60 years	MDS and MEDAS	↑	An increasing adherence to a MedDiet was associated with decreasing risk of frailty
León-Muñoz et al 2015 [75]							
Zbeida et al 2014 [84]	Community dwelling older adults, United States	Cross-sectional (no follow-up)	2791	Mean age of entire cohort not reported; all participants ≥ 60 years	MDS	↑	Greater adherence to a MedDiet is associated with better physical functioning
Talegawkar et al 2012 [76]	Community dwelling older adults, Italy	Longitudinal (6 years)	690	73.0 (6.2)	MDS	↑	Adherence to a MedDiet was inversely associated with the development of frailty
Milaneschi et al 2011 [73]							
Bollwein et al 2012 [80]	Community dwelling older adults, Germany	Cross-sectional (no follow-up)	192	83.0 (4.2)	MED	↑	Adherence to a MedDiet is associated with lower odds of frailty, in particular of the frailty criteria low walking speed and low physical activity

Sarcopenic Symptomology							
Isanejad et al 2017 [79]	Community dwelling older women, Finland	Cross-sectional & Longitudinal (3 years)	554	Mean age of entire cohort not reported; all participants ≥ 60 years	MDS	↑	Women with lower adherence to a MedDiet lost more relative skeletal muscle (as defined by relative skeletal muscle index) and total body lean mass compared to those with higher adherence over the 3-year follow-up. At baseline, women with higher adherence had a faster walking speed (10 m) and greater lower body muscle quality
Tyrovolas et al 2016 [85]	Community dwelling older adults from 21 Mediterranean Islands	Cross-sectional (no follow-up)	2663	Mean age of entire cohort not reported; all participants ≥ 65 years	MedDietScore	↑	Skeletal muscle mass was positively associated with the successful ageing score
Fougère et al 2016 [86]	Community dwelling older adults, Italy	Cross-sectional (no follow-up)	304	86.3 (6.8)	MSDPS	↑	Higher adherence to a MedDiet was associated with higher lower-limb physical performance (SPPB >7). However, no association was found for grip strength
Nikolov et al 2015 [82]	Community dwelling older adults, Germany	Cross-sectional (no follow-up)	1509	68.2 (3.7)	mMedTypeDiet score	↑	Higher adherence to a MedDiet was associated with a positive effect on ALM/BMI in women
Hashemi et al 2015 [81]	Community dwelling older adults, Iran	Cross-sectional (no follow-up)	300	66.8 (7.7)	PCA from dietary data collected by FFQ to define a Mediterranean dietary pattern	↑	Adherence to the MedDiet is associated with lower odds of sarcopenia
Shahar et al 2012 [78]	Community dwelling older adults, United States	Longitudinal (8 years)	2225	Mean age of entire cohort not reported; all participants ≥ 70 years	MDS	↑	Walking speed over 8 years was faster in participants with higher adherence to the MedDiet at baseline
Robinson et al 2008 [83]	Community dwelling older adults, United Kingdom	Cross-sectional and retrospective cohort study (no follow-up)	2983	Mean age of entire cohort not reported; all participants ≥ 60 years	PCA from dietary data collected by FFQ to define a "Prudent" dietary pattern	↑	A greater Prudent Diet Score was positively associated with an increase in isometric hand-grip strength

Abbreviations: MedDiet, Mediterranean Diet; MDS, Mediterranean Diet Score; MEDAS, Mediterranean Diet Adherence Screener Score; MED, Alternate Mediterranean Food Score; MedDietScore, Mediterranean Diet Score; MSDPS, Mediterranean Diet Score; mMedTypeDiet, Mediterranean-type Diet Score; PCA, Principal Component Analysis; FFQ, Food Frequency Questionnaire; SPPB, Short Physical Performance Battery; ALM, Appendicular Lean Mass; BMI, Body Mass Index; ↑, MedDiet attenuated physical frailty or sarcopenic symptomology; -, MedDiet had no effect.

Adherence to a Mediterranean Diet and Physical Frailty

Four out of five studies [74, 76, 80, 84] reported that greater adherence to a MedDiet is associated with lower risk of physical frailty and slower decline of physical functioning over time. Results from two longitudinal cohort studies reported that greater adherence to a MedDiet was inversely associated with the development of physical frailty [74, 76]. Longitudinal analysis from the InCHIANTI study [88] showed that greater adherence to a MedDiet at baseline (defined as MDS score ≥ 6) was associated with lower odds of developing frailty after a 6 year follow-up (OR = 0.30; 95% CI: 0.14–0.66) [76]. This inverse relationship was also observed for individual components of the physical frailty phenotype including low physical activity (OR = 0.62; 95% CI: 0.40–0.96) and gait speed (OR = 0.48; 95% CI: 0.27–0.86). However, no associations were observed for feelings of exhaustion and low muscle strength [76]. In a separate analysis of the InCHIANTI study [88] Milaneschi et al [73] reported that participants with higher adherence to a MedDiet (defined as MDS score ≥ 6) were less likely to have mobility disability at baseline (defined as SPPB score <10) even after adjustments for age, gender, energy intake, BMI, MMSE score, physical activity, instrumental activities of daily living, depressive symptoms, number of chronic diseases and medications (OR = 0.50; 95% CI: 0.30–0.82; $p = 0.006$). Milaneschi et al [73] further reported that participants with greater adherence to a MedDiet experienced significantly less decline in SPPB scores over time (3-year follow-up: 0.9 points higher (SE = 0.2, $p \leq 0.001$); 6-year follow-up: 1.1 points higher (SE = 0.3, $p = 0.0002$); 9-year follow-up: 0.9 points higher (SE = 0.4, $p = 0.03$)). Using two dietary assessment instruments (MDS and MEDAS) León-Muñoz et al [74] reported that over a mean follow-up period of 3.5 years, an increasing adherence to a MedDiet was associated with decreasing risk of physical frailty. Compared with individuals in the lowest tertile of the MEDAS score, those in the highest tertile were associated with a lower risk of physical frailty (OR = 0.55; 95% CI: 0.35–0.86; $p = 0.009$); however, in the adjusted analyses for all confounders, the association was weakened (OR = 0.65; 95% CI: 0.40–1.04; $p = 0.07$) [74]. Alternatively when using the MDS as an adherence tool, an increasing adherence to a MedDiet was associated with a progressively reduced risk of frailty in the adjusted analyses for all confounders (Tertile 2: OR = 0.59; 95% CI: 0.37–0.95; $p \leq 0.05$; Tertile 3: OR = 0.48; 95% CI: 0.30–0.77; $p = 0.002$) [74]. These investigators also reported that a higher MEDAS score was inversely associated with gait speed and unintentional weight loss; whereas participants in the highest tertile of the MDS had a lower risk of exhaustion, low physical activity, unintentional weight loss and grip strength (non-significant, data not reported) [74]. In contrast, a prospective cohort study

from China reported no association between adherence to a MedDiet and incidence of physical frailty after a 4-year follow-up in 2724 older adults aged ≥ 65 years [77].

In a cross-sectional study of 192 community-dwelling older adults from Germany, Bollwein et al [80] reported that greater adherence to a MedDiet, as assessed by the MED score, was associated with a decreased risk of physical frailty (OR = 0.26; 95% CI: 0.07–0.98). The investigators also reported a linear trend in the odds ratios, indicative of a graded effect of this observation (Quartile 2: OR = 1.04; 95% CI: 0.36–3.05; Quartile 3: OR = 0.37; 95% CI: 0.11–1.32; Quartile 4: OR = 0.19; 95% CI: 0.05–0.82; p for trend = 0.011). Akin to Talegawkar et al [76] Bollwein et al [80] also reported an inverse relationship for individual components of the physical frailty phenotype including low physical activity ($p \leq 0.001$), unintentional weight loss ($p = 0.03$) and gait speed ($p = 0.04$). These investigators also reported no associations between adherence to a MedDiet, feelings of exhaustion and low muscle strength [80]. Similarly, in a cross-sectional analysis of two separate cohorts (NHANES and the Israeli National Health and Nutrition Survey) Zbeida et al [84] reported that greater adherence to a MedDiet in the NHANES cohort (defined as MDS score ≥ 6) was associated with a faster gait speed ($p \leq 0.001$), better muscle strength ($p = 0.002$), and a higher physical function score ($p = 0.001$) compared with individuals in the lowest tertile; this observation however was only present for physical functioning when assessed against the Israeli National Health and Nutrition Survey cohort [84].

Adherence to a Mediterranean Diet and Sarcopenic Symptomology

Diagnosis of Sarcopenia

Two studies [79, 81] evaluated adherence to a MedDiet and identified the proportion of sarcopenic individuals within the cohort. Using PCA to characterize dietary patterns from dietary data collected on $n = 300$ elderly Iranian men and women, Hashemi et al [81] reported that greater adherence to a MedDiet pattern was associated with a decrease in the proportion of sarcopenic individuals from 21% in the first tertile, 20% in the second tertile to 12% in the third tertile. Similarly, in a cohort of $n = 554$ postmenopausal elderly women derived from the Osteoporosis Risk Factor and Prevention-Fracture Prevention Study (OSTPRE-FPS), Isanejad et al [79] reported similar observations in the prevalence of sarcopenia across categories of adherence when using the MDS. However, these observed differences in the prevalence of sarcopenia across adherence categories in both studies were not statistically significant [79, 81]. When adjusted for all

confounders, Hashemi et al [81] reported that those participants in the top tertile of the MedDiet pattern were 60% less likely to be sarcopenic compared with those in the lowest tertile (OR = 0.40; 95% CI: 0.17–0.97; $p = 0.04$) [81]. In contrast, this observation was not shown by Isanejad et al [79] (OR = 0.93; 95% CI: 0.38–1.48; $p = 0.960$). However, in a separate analysis of body composition data, Isanejad et al [79] showed that women in the lowest quartile of adherence to a MedDiet had a lower relative skeletal muscle index (RSMI) ($P_{\text{trend}} = 0.001$) and total body SMM ($P_{\text{trend}} = 0.001$) compared with those in higher quartiles over the 3-year follow-up.

Body Composition

Two studies [82, 85] evaluated the relationship between adherence to a MedDiet and body composition outcomes. In a cross-sectional analysis of $n = 1509$ community-dwelling older adults in Germany, Nikolov et al [82] reported that higher adherence to a MedDiet, as assessed by the mMedTypeDiet score, was significantly associated with a higher ALM/BMI ratio in female participants only compared with moderate or low adherence (High adherence: $0.64 \pm 0.1\text{kg/m}^2$; Moderate adherence: $0.61 \pm 0.1\text{kg/m}^2$; Low adherence: $0.62 \pm 0.1\text{kg/m}^2$; $p = 0.004$). In contrast, Tyrovolas et al [85] investigated determinants of healthy ageing including a range of socio-demographic characteristics, dietary habits, psychological and physical activity status, and their potential influence on body composition in $n = 2663$ community-dwelling older adults from 21 Mediterranean islands. To determine adherence to a MedDiet, the MedDietScore was used [95]. Adherence to a MedDiet was one of ten components used to establish a successful ageing index which was represented as the cumulative score of the ten components [85]. The investigators reported that after adjusting for confounders, including adherence to a MedDiet, ASM index was significantly greater ($P < 0.001$) in participants with a higher successful ageing index; however, no direct association between adherence to a MedDiet and ASM index was observed [85].

Muscle Strength and Gait Speed

Three studies [78, 83, 86] reported that greater adherence to a MedDiet was associated with improved muscle functioning. In the Health, Aging, and Body Composition (Health ABC) prospective cohort study, Shahar et al [78] reported that participants with greater adherence to a MedDiet (defined as MDS score ≥ 6) at baseline demonstrated a significantly better gait speed when assessed over a 20-m course (Usual gait speed: High adherence; 1.19 ± 0.19 m/s; Moderate adherence; 1.16 ± 0.21 m/s; Low adherence; 1.15 ± 0.19 m/s, $p = 0.02$; Rapid gait speed: High adherence; 1.65 ± 0.30 m/s; Moderate adherence; 1.59 ± 0.32 m/s; Low adherence; 1.55 ± 0.30 m/s, $p = 0.001$). Furthermore, the

investigators also reported that after 8-years of follow-up, usual and rapid 20-m walking speed declined in all three MedDiet adherence categories; however, participants who reported greater adherence performed better at all follow-up periods [78]. In a cross-sectional analysis of $n = 304$ older adults from Italy, Fougere et al [86] reported a positive association between higher adherence to a MedDiet and lower limb functioning as assessed by the SPPB (SPPB score ≥ 7); however, this association did not exist with isometric hand-grip strength [86]. Using a FFQ based on the European Prospective Investigation into Cancer and Nutrition questionnaire [99] Robinson et al [83] used PCA to describe a “prudent” dietary pattern (PruDiet) characterized by high consumption of fruit, vegetables, whole-grain cereals, and fatty fish and low consumption of white bread, chips, sugar, and full-fat dairy products. The investigators reported that a greater PruDiet score was positively associated with an increase in isometric hand-grip strength (Men: 0.18; 95% CI: 0.01–0.35kg; $p = 0.04$; Women: 0.27; 95% CI: 0.13–0.42kg; $p < 0.001$). Specifically, in males a higher consumption of fruit, fatty fish, and breakfast cereals but lower intake of meat was associated with higher isometric hand-grip strength. In women, higher grip strength was also associated with higher consumption of fruit and fatty fish, but there was no association with breakfast cereals or meat consumption [83]. Moreover, vegetable consumption in women only was also positively associated with an increase in isometric hand-grip strength [83]. However, the investigators reported that the most important association between dietary intake and grip strength amongst men and women was with fatty fish (Men: 0.43; 95% CI: 0.13–0.74kg; $p = 0.005$; Women: 0.48; 95% CI: 0.24–0.72kg; $p < 0.001$) [83].

Underlying Mechanisms Underpinning the Potential Benefits of the Mediterranean Diet on Ameliorating Physical Frailty and Sarcopenic Symptomology

The pathophysiology of physical frailty and sarcopenia is complex and multifactorial. It is widely thought that the most important influences associated with the aetiology include, but not limited to, a reduction of anabolic hormones (testosterone, growth hormone, insulin-like growth factor-I (IGF-I)), muscular disuse, increased circulating concentrations of pro-inflammatory cytokines (particularly TNF- α and IL-6), oxidative stress due to the accumulation of free radicals, mitochondrial dysregulation of muscle cells, a decline in the number of α -motoneurons and low vitamin-D status [100–104]. Although a number of dietary interventions have previously been investigated for their efficacy in the management and/or prevention of physical frailty and sarcopenia [45–49], the role of dietary protein often receives much attention. Dietary protein intake stimulates muscle protein synthesis (MPS) and facilitates postprandial muscle protein accretion [105]. Moreover,

the need for more dietary protein with ageing is in part due to a compromised ability to efficiently utilize amino acids for MPS, resulting in a blunted muscle protein synthetic response to an anabolic stimuli, a phenomenon termed anabolic resistance [105, 106]. As of consequence, evidence based recommendations for protein intake in older adults have recently been published [107, 108]. Despite the potential role of dietary protein in relation to muscle preservation and function, an important determinant of MPS is not only an adequate intake of dietary protein but also the signalling of anabolic molecules [109]. The presence of marked systemic inflammation and oxidative stress, two key pathological features of physical frailty and sarcopenia, both play a role in suppressing regulatory molecules involved in MPS [109, 110]. The tightly regulated balance between pro-oxidant and antioxidant defence systems is altered with ageing because of a reduction in endogenous anti-oxidative enzymes leading to an increased reactive oxygen species (ROS) load inducing oxidative damage of mitochondrial DNA and a greater propensity to trigger cellular apoptosis [11, 109, 111]. Pro-inflammatory cytokines activate many altered metabolic pathways associated with skeletal muscle wasting, including increased proteolysis and myocyte apoptosis [112, 113]. Specifically, both TNF- α and IL-6 are known to be elevated with ageing [114] and play a role in stimulating muscle proteolysis and myocyte apoptosis [113, 115].

The belief that a single nutrient could lower the risk of physical frailty and/or sarcopenia is perhaps somewhat optimistic. For example, plasma levels of antioxidants, in particular carotenoids and polyphenols, are inversely associated with physical frailty and sarcopenic symptomology [116-120]. Similar observations have been found for fruit and vegetable intake [121-123]. Although observational evidence suggests adherence to "healthier" dietary patterns such as the MedDiet appears to attenuate physical frailty and sarcopenic symptomology, the exact mechanisms of this remains poorly understood and relatively unexplored. Although no such mechanism has clearly been identified, examining the potential role of the MedDiet or important constituents of the dietary pattern on systemic inflammation and oxidative stress may help to explain the underlying mechanisms involved.

From a theoretical standpoint, the most compelling theory relates to the powerful synergism of nutrients, their potential influence on skeletal muscle function and body composition, and their role in attenuating the physiological mechanisms previously identified as important mediators in the aetiology of physical frailty and sarcopenia. A MedDiet pattern emphasises a high consumption of vegetables, fruit, legumes, unprocessed grains, nuts, EVOO and a moderate intake of fish and shellfish [63-66]. The high fruit and vegetable intake, coupled with EVOO and nuts, add mechanistic benefits provided by their polyphenolic

and high antioxidant content. For example carotenoids and polyphenols are known to be efficient quenchers of singlet oxygen, as well as potent scavengers of other ROS, inhibit lipid peroxidation and modulate redox-sensitive transcription factors involved in the up-regulation of pro-inflammatory cytokines [124-126]. Vitamin C is a water-soluble vitamin that represents a first-line antioxidant defence in plasma. It is a powerful inhibitor of lipid peroxidation and regenerates vitamin E in lipoproteins and cellular membranes [127]. Vitamin E is a major lipid-soluble antioxidant that prevents lipid peroxidation in lipoproteins and may serve to protect against muscle atrophy by combating oxidative stress and protecting the muscle against oxidative insults [128].

Previous studies involving participants at high risk of CVD have shown that adherence to MedDiet pattern independently dampens, or is inversely associated with pro-inflammatory cytokines, including TNF- α and IL-6 [98, 129-133]. Moreover, long chain omega-3 (n-3) fatty acids, eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA, 22:3n-6) found in fatty fish, are also recognized for their potent anti-inflammatory properties [134, 135]. Marine n-3 fatty acids exert a range of anti-inflammatory actions including a decreased production of the pro-inflammatory cytokines, TNF- α and IL-6 [136, 137]. In a cross-sectional analysis of the of the InCHIANTI study [88] Abbatecola et al [138] reported that n-3 fatty acid concentrations were associated with a shorter time to complete a 7-m walk, independent of multiple confounders; at the 3-year follow-up, baseline n-3 fatty acid concentrations continued to be inversely associated with the development of impaired physical performance, as assessed by the SPPB (OR: 0.21; 95% CI: 0.08-0.53; p = 0.001) [138]. Smith et al [139] previously published novel evidence supporting the efficacy of n-3 fatty acid supplementation on its role in increasing muscle anabolic signalling activity and stimulating MPS above basal post-absorptive values in older adults. In a recently published RCT, Smith et al [140] further showed that a 6-month n-3 fatty acid intervention, without exercise, had statistical and clinically beneficial effects on attenuating sarcopenic symptomology by increasing thigh muscle volume (3.6%; 95% CI: 0.2-7.0%), hand-grip strength (2.3kg; 95% CI: 0.8-3.7kg) and upper/lower body 1-RM muscle strength (4.0%; 95% CI: 0.8-7.3%) (all p <0.05). Furthermore, Rodacki et al [141] previously reported that n-3 fatty acid supplementation augments exercise induced changes in muscle strength and physical performance. Despite the exact mechanisms being unclear, the investigators of these studies identified that the anabolic effects of n-3 fatty acids are independent of any significant influence on inflammation. Rather, they likely involve alterations in both anabolic and catabolic pathways, improved mitochondrial functioning and biogenesis, neuroprotection and motor-neuron excitability properties [139-141].

Although much of the evidence proposed so far is based on individual nutrients contained within a MedDiet pattern, the plausibility to support a causal role of the MedDiet in attenuating physical frailty and sarcopenic symptomology should consider that the synergistic relationship of nutrients is likely to be greater than the influence of single nutrients on skeletal muscle functioning and body composition. Given the nutrient profile of the MedDiet, mechanistic benefits including a reduction in oxidative stress and pro-inflammatory cytokines, provide plausible mechanisms linking adherence to a MedDiet pattern and attenuation of physical frailty and/or sarcopenic symptomology in older adults.

Implications for Future Research and Conclusions

Unfortunately there is a lack of available evidence from RCTs to support the proposed physiological mechanisms and establish causality primarily due to the progressive nature of physical frailty and sarcopenia. Longer term RCTs with sufficient power and length of time may pose difficulties with dietary adherence. Moreover, whether a traditional MedDiet intervention is feasible among western cultures in a way that promotes lifestyle and dietary reform is currently unknown. In an attempt to accommodate for potential barriers impacting dietary adherence (i.e. palatability, availability, convenience, cost and culture) it has been suggested that the development of a “westernised” MedDiet that is matched with the traditional MedDiet in terms of nutrient content would seem a more feasible approach [142, 143]. Irrespective, given the evidence associated with the MedDiet and healthy ageing [50-53], a pragmatic approach may include adopting a MedDiet pattern to attenuate physical frailty and sarcopenia with advanced age. Moreover, it would be prudent to investigate this causal relationship amongst older adults who are more vulnerable to physical frailty and sarcopenia, such as older adults with T2DM [144-146]. In addition to the various micro and macrovascular diseases which contribute to disability amongst patients with T2DM, in older people with diabetes, physical frailty and sarcopenia are now emerging as a third category of complications [144-146]. Numerous observational studies have reported that older adults with T2DM are at risk of an accelerated decline SMM, muscle strength and/or higher odds of impaired physical functioning relative to their nondiabetic counterparts [147-158]. Despite the plethora of evidence, the biological mechanisms are uncertain and still under investigation. A number of biological mechanisms describing the pathway to disability have been postulated including insulin resistance, hyperglycaemia, chronic inflammation, oxidative stress, excess adiposity and physical inactivity [144, 145, 159]. Many of these proposed mechanisms are, at least partially, modifiable with dietary interventions involving the MedDiet. For example, recent

meta-analyses of RCTs have shown that when comparing with a variety of control diets, a Mediterranean style diet has beneficial effects on glycemic control, weight loss and cardiovascular risk factors among individuals with T2DM [160, 161]. Furthermore, recent results from the long term MEDITA trial showed that when compared with a standard low-fat diet, a Mediterranean diet ameliorates the inflammatory response and improves endothelial functioning in persons with T2DM [162, 163]. Therefore, the efficacy of a MedDiet pattern in a cohort of older adults whom are vulnerable to an accelerated decline in SMM and function warrants future investigation.

To the best of our knowledge, this review is the first of its kind to examine the potential benefits associated with the MedDiet on attenuating physical frailty and sarcopenic symptomology in older adults. Synthesis of the reviewed literature is suggestive of a decreased risk of physical frailty and sarcopenic symptomology with greater adherence to a MedDiet. Despite being unable to establish causality due to the observational study design of each of the reviewed studies, the present review highlights the relevance of examining whole dietary patterns and their influence on SMM and function. A MedDiet pattern emphasises a high consumption of vegetables, fruit, legumes, unprocessed cereals, nuts, EVOO and a moderate intake of fish and shellfish and has a unique nutritional profile rich in monounsaturated and n-3 fatty acids, vitamins, minerals, antioxidants and non-nutritive compounds including polyphenols, carotenoids and flavonoids. Synergistically, the interaction between these nutrients may exert multifactorial benefits on body composition and skeletal muscle functioning by reducing oxidative stress and pro-inflammatory cytokines. Although clinical intervention studies are scant, investigating this hypothesis using short-term RCTs may be superfluous due to the progressive nature of geriatric muscle wasting syndromes. On the other hand, older adults with T2DM are at greater risk of a decline in SMM, physical dysfunction and disability. Therefore, exploring these observations with the use of well-designed, longer-term dietary intervention studies in older adults with an increased vulnerability to physical frailty and sarcopenia is warranted.

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Authors Contributions

Both authors contributed to this work. RM conducted the literature search, completed data extraction, interpreted the findings and prepared the manuscript. AV contributed to data extraction,

interpretation of the findings and preparation of the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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