Special Article

Relationship between the Mediterranean dietary pattern and musculoskeletal health in children, adolescents, and adults: systematic review and evidence map

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Context: *An understanding of the modifiable effects of diet on bone and skeletal muscle mass and strength over the life course will help inform strategies to reduce age-related fracture risk. The Mediterranean diet is rich in nutrients that may be important for optimal musculoskeletal health.* ***Objective:*** *The aim of this systematic review was to investigate the relationship between a Mediterranean diet and musculoskeletal outcomes (fracture, bone density, osteoporosis, sarcopenia) in any age group.* ***Data Sources:*** *Ten electronic databases were searched.* ***Study Selection:*** *Randomized controlled trials and prospective cohort studies that investigated a traditional Mediterranean diet, published in any language, were eligible. Studies using other designs or other definitions of the Mediterranean diet were collated separately in an evidence map.* ***Data Extraction:*** *Details on study design, methods, population, dietary intervention or exposure, length of follow-up, and effect on or association with musculoskeletal outcomes were extracted.* ***Results:*** *The search yielded 1738 references. Data from eligible randomized controlled trials ($n = 0$) and prospective cohort studies ($n = 3$) were synthesized narratively by outcome for the systematic review. Two of these studies reported on hip fracture incidence, but results were contradictory. A third study found no association between the Mediterranean diet and sarcopenia incidence.* ***Conclusions:*** *Overall, the systematic review and evidence map demonstrate a lack of research to understand the relationship between the Mediterranean diet and musculoskeletal health in all ages.* ***Systematic Review Registration:*** *PROSPERO registration number IDCRD42016037038.*

INTRODUCTION

Bone fractures in older adults are a substantial public health problem, predicted to be compounded in the future by an increasingly aging population.[1,2] Health and social care costs associated with age-related fractures are considerable; in 2005, the combined annual expenditure was estimated at €32 billion for European countries,[3] projected to increase to €37 billion by 2025.[2] To help reduce the incidence of age-related fractures, a better understanding of the effects of modifiable factors, such as diet, on bone and

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muscle health over the life course is needed to inform strategies.

Fall-related fracture risk increases with age.[4,5] Causes are multiple, the most noteworthy being age-related deterioration of both bone and skeletal muscle health. It is well established that low bone mass and microarchitectural deterioration of bone tissue, characteristic of osteoporosis, increases susceptibility to low-impact fragility fractures.[6] However, more recently, the relevance of loss of skeletal muscle mass or strength to bone health has been recognized, with evidence of associations between low skeletal muscle mass, low strength, or low physical performance and outcomes of osteoporosis or low bone mineral density, falling, and fractures.[7–11] Risk of falling can be attributed in part to muscle-related factors that include impaired balance, reduced agility, and diminished grip strength. Additionally, skeletal muscle may provide a physical protective barrier to reduce the impact of falls. There is a mechanical interrelationship between skeletal muscle and bone that may affect fracture risk. Bone tissue is responsive to the mechanical load of skeletal muscle contraction,[12] and thus a decline in muscle function could result in a deterioration in bone health.[13,14] Emerging research also suggests there is a biochemical interrelationship whereby skeletal muscle secretes endocrine factors that stimulate bone growth and repair.[12,13] When sarcopenia (characterized by age-related, progressive, generalized loss of skeletal muscle mass and strength) and osteoporosis coexist, as they commonly do,[10,11] fracture risk increases.[8]

Sarcopenia was identified in the late 1980s,[15] but definitions and diagnostic cutoff points continue to be debated.[16–19] Related terms such as dynapenia, referring to age-related loss of power and muscle strength,[20] and myopenia, used to define clinically relevant muscle wasting occurring at any age,[21] are also emerging. In this review, the definition of sarcopenia is that used by the European Working Group on Sarcopenia in Older People: "the presence of low skeletal muscle mass with low skeletal muscle function (either low muscle strength or low physical performance)."[17] This combination of skeletal muscle outcomes is also used in definitions proposed by other working groups.[22–24] Since interplay exists between bone and muscle, it is logical to investigate the musculoskeletal system, rather than the skeletal system alone, when seeking to develop strategies to reduce fracture risk in later life. Furthermore, musculoskeletal influences earlier in life must be considered. Bone mass and skeletal muscle mass and strength reach a peak in early adulthood before declining, and so the health of bone and skeletal muscle in later life may be determined not only by the extent of the decline but also by levels attained in childhood and adolescence.[25,26] A computer modeling study suggests that peak bone mineral density may be the principal factor influencing the timing of onset of development of osteoporosis.[27]

An important modifiable factor affecting the musculoskeletal system is diet.[25,28,29] An understanding of the role of individual nutrients in maintaining bone and skeletal muscle health is advantageous, yet nutrients are not eaten in isolation. When consumed together over a period of time, nutrients can have interactive and cumulative effects. It is thus relevant to investigate overall dietary patterns to explain the effects of nutrition on health. Of particular interest is the influence of the Mediterranean diet, a predominantly plant-based diet with moderate intakes of fish; low intakes of meat, dairy, and saturated fats; olive oil as the main source of dietary fat; and regular but moderate alcohol intake.[30] Although the Mediterranean diet has been broadly described, variations exist in the food groups and nutrient components included in associated adherence indices used by different researchers. These variations must therefore be taken into account when comparing studies.[31]

The Mediterranean diet is rich in antioxidants such as vitamin C, carotenoids, and selenium and in minerals such as magnesium, which recent studies have suggested may affect muscle health.[28] Similarly, phytoestrogens, antioxidants, potassium, magnesium, and vitamins K and C, found in such a diet, may be important for reducing the risk of osteoporosis and fracture.[32] Accumulating evidence from systematic reviews indicates wider health benefits of the Mediterranean diet,[33] notably the positive associations with reduced risk of coronary heart disease,[34,35] stroke,[36] diabetes,[37,38] and all-cause mortality.[39] Studies investigating the relationship between this diet and musculoskeletal health might therefore be expected. At the time of conducting this research, only 1 previous review of studies investigating the effects of a Mediterranean diet on musculoskeletal health (bone outcomes only) had been carried out,[40] and this did not use a priori–defined methods.

The aim of this study was therefore to identify, evaluate, and synthesize the research evidence pertaining to the relationship between the Mediterranean diet and musculoskeletal outcomes in children, young people, and adults.

Objectives

The first objective of this systematic review was to conduct a systematic search for studies of any design that have investigated the relationship between a Mediterranean diet (by any definition) and musculoskeletal outcomes, and to map the nature of that research by summarizing the types of participants, diets, and outcomes investigated. The purpose of this broad evidence map is to inform future investigators of the existing evidence base and information gaps.

The second objective was to use established methodology[41] to undertake a systematic review of a subset of studies identified in the evidence map that fulfil tighter inclusion criteria. Evidence from RCTs was used to determine the effects of a diet that follows the core principles of a traditional Mediterranean diet, when compared with any other dietary pattern, on outcomes of: fracture incidence (primary objective), fracture risk score, osteopenia and osteoporosis incidence, bone mineral density, bone mineral content, bone turnover markers, sarcopenia incidence or combined outcomes of skeletal muscle mass plus skeletal muscle strength or physical performance where sarcopenia incidence/prevalence is not reported. Evidence from prospective cohort studies was used to determine the association between a diet that follows the core principles of a traditional Mediterranean diet and the above outcomes when adjusted for established or potential confounders.

The third objective was to examine the characteristics of Mediterranean diet adherence assessment scores to ensure that standard Mediterranean diet definitions were used in the studies included in this systematic review.

METHODS

The study protocol was registered on April 1, 2016, with the PROSPERO International Prospective Register of Systematic Reviews, registration ID CRD42016037038.[42] The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist[43] was used to guide reporting (see Table S1 in the Supporting Information online).

Defining the Mediterranean diet

In research settings, a large number of indices are used to define and operationalize the Mediterranean diet.[38,39] While a Mediterranean diet by any definition was of interest in the evidence map (objective 1), the focus of the systematic review (objective 2) was solely on studies that investigated a diet most closely representing what is traditionally termed a Mediterranean diet. In order to define this diet at the outset (objective 3), the 23 Mediterranean diet adherence indices previously identified by Shaw (2015)[44] were examined, and the food categories and scoring approach used in each of the indices was noted, including whether higher consumption is treated as positive (encouraged) or is restricted. These findings were considered alongside the findings of 2 reviews: a systematic review that had tabulated the food categories and scoring methods of Mediterranean diet adherence indices used in prospective cohort studies investigating a range of health outcomes,[39] and a separate evaluation of 22 Mediterranean diet adherence indices that was published subsequent to the work undertaken for this paper.[31] All 3 evaluations confirmed there is a lack of uniformity between indices in the number of food categories, food category groupings (eg, fruit and nuts can be treated independently or grouped together in 1 category), the description of foods within categories (eg, dairy vs full-fat dairy), and the scoring approaches used.

In this systematic review, the Mediterranean diet was defined as a diet that explicitly addressed, as a minimum, the 8 core food categories most frequently cited across the indices: vegetables, fruit, legumes, cereals, fish, meat, dairy, and dietary fat used in food preparation and cooking. Alcohol, listed in most diet adherence scores, was not considered a core category because this systematic review had no age restrictions and alcohol consumption is not assessed in children. Variation in the food descriptors used within a core category was allowed; for example, meat, red meat, and/or processed meat were all accepted in the meat category, and olive oil, monounsaturated fatty acids (MUFAs) to polyunsaturated fatty acids (PUFAs) to saturated fatty acids (SFAs) ratio, and MUFA or PUFA to SFA ratio were all accepted in the dietary fat category.[30,45] Quantities of food intake from each core category had to comply with the broad, indicative criteria shown in Table 1. For example, for a diet to be defined as a Mediterranean diet, the vegetable intake, which is encouraged and treated as positive across all dietary indices, needed to be high, defined here as greater than or equal to either a minimum number of recommended servings (varies across studies and indices) or the sex-specific median of the study population.

The resultant criteria to define a Mediterranean diet for the systematic review allowed some leeway on types of foods while ensuring that diets that differed markedly from the traditionally defined Mediterranean diet were excluded.

Identifying studies

A search of 10 databases (MEDLINE, Embase, CINAHL, Cochrane Library databases, LILACS [Literatura Latino Americana em Ciências da Saúde], Web of Science, CAB Abstracts, International Standard RCT Number [ISRCTN] Registry, WHO International Trials Registry Platform [ICTRP], and ProQuest Dissertations & Theses) was performed on December 8, 2015, to identify studies eligible for inclusion in the evidence map and systematic review using a combination of indexing and free text terms related to Mediterranean diet or associated adherence scores (intervention and exposure terms) and bone or muscle

Table 1 **PICOS criteria for inclusion of studies in the evidence map and systematic review**

Parameter	Evidence map	Systematic review
Participants	People of any age, in any country, with any clinical condition, whose meals were either self-provided or provided as part of care in a residential home	
Intervention diet (interventional studies)	Participants advised to follow a dietary pattern labeled as "Mediterranean," with or without provision of foods; diet not to have been modified for weight loss (such diets can alter dietary patterns); co-interventions such as exercise allowed, provided they were administered to all groups	Inclusion criteria were the same as those for the evidence map, but in addition, advice about MD to have addressed at least 8 core food categories, as follows: high consumption encouraged[a] for (1) fruit, (2) vegetables, (3) legumes, (4) cereals, and (5) fish; high consumption discouraged[b] for (6) meat and (7) dairy; and, for (8) dietary fat, low consumption[b] of SFAs, or a high ratio of MUFAs and/or PUFAs to SFAs, or olive oil as the predominant dietary fat encouraged; MD enhancements, such as provision of supplementary olive oil, allowable if relevant to MD and in food form
Comparator diet (interventional studies)	Advice to follow usual diet or any dietary pattern other than MD, or no dietary advice	
Assessment of exposure to MD	A priori assessment, using any MD adherence index, or a posteriori assessment, using methods such as exploratory principal component analysis to identify commonly consumed combinations of foods that are then designated as comprising a MD	A priori assessment only[c], using an MD adherence index that addresses at least 8 core food categories, with scores favoring high consumption of (1) vegetables, (2) fruit, (3) legumes, (4) cereals, and (5) fish; low to moderate consumption of (6) meat and (7) dairy; and, for (8) dietary fat, low consumption of SFAs or a high ratio of MUFAs and/or PUFAs to SFAs, or consumption of olive oil as the predominant fat used in cooking or food preparation
Outcomes	Fracture incidence (primary outcome), fracture risk score, osteoporosis or osteopenia incidence, BMD, BMC, bone turnover markers, sarcopenia or dynapenia or myopenia incidence, skeletal muscle mass plus strength or physical performance	
Study design	Any design	RCTs[d] and prospective cohort studies
Minimum duration of follow-up or timing of outcome assessment	Any follow-up period	$\geq$ 6 months for fracture incidence, BMD, BMC, sarcopenia incidence, and skeletal muscle mass plus strength or physical performance; $\geq$ 1 month for bone turnover markers

Abbreviations: BMC, bone mineral content; BMD, bone mineral density; MD, Mediterranean diet; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; RCTs, randomized controlled trials; SFAs, saturated fatty acids.
[a]*High consumption* defined as intake greater than or equal to the sex-specific median of the study population, or greater than or equal to a specified minimum number of servings.
[b]*Low consumption* or *consumption discouraged* defined as intake less than or equal to the sex-specific median of the study population, or less than or equal to a specified maximum number of servings.
[c]It can be unclear which food categories have been assessed in an a posteriori approach, which hinders comparability across studies.
[d]RCTs were eligible whether randomization was done at the individual or the group level. Crossover RCTs were eligible if data from the first period of the crossover could be used; data from the second period were not eligible because of the risk of carryover of eating patterns from the first period.

(outcome terms) (see Appendix S1 in the Supporting Information online). No language or date restrictions were applied. Potentially eligible records identified subsequent to that date via, eg, automated email notifications, were assessed for eligibility up until April 15, 2016. Bibliographies of eligible studies and of related systematic reviews were searched for additional potentially eligible studies.

Eligibility criteria

Studies were eligible for inclusion in the evidence map and systematic review if published in full or, in the case of shorter reports, such as conference abstracts, if methods and results were reported. Non-English-language studies were eligible, provided acceptable translations into English language could be obtained. The criteria by which studies were selected for inclusion in the evidence map differed from those used for the more focused systematic review in terms of the following: type of Mediterranean diet intervention or exposure, timing of outcome measures, and type of study design (Table 1). Randomized controlled trials, the optimum design to investigate the health effects of an intervention,[41] and prospective observational cohort studies were considered sufficiently robust to include in the systematic review. Other designs, such as cross-sectional studies, in which exposures and outcomes are measured at the same, single time point, were not eligible for the systematic review but have been included in

the broader evidence map. The inclusion criteria for types of outcomes (Table 1), applicable to both the evidence map and the systematic review, were supplemented with a list of possible outcome measures to further aid reviewers in the study selection process (see Appendix S2 in the Supporting Information online). As there is little evidence to inform the time frame required for a dietary pattern to bring about modification of the parameters, the minimum eligible follow-up times for each outcome—for the systematic review studies only (Table 1)—were determined by the study team, informed by the literature where available.[15,46]

Study selection

Following de-duplication of references, 2 reviewers independently screened titles and abstracts. Potentially relevant full-text reports were retrieved and assessed independently by 2 reviewers using a prepiloted checklist to determine eligibility for the evidence map and, if eligible, whether the reports also met the more stringent criteria for inclusion in the systematic review. Disagreements were discussed and a third reviewer consulted if further clarification was required to reach consensus on eligibility.

Data extraction

Using a prepiloted form, data on study design and purpose, dates, setting, types of participants, Mediterranean diet intervention and comparator diet(s) (interventional studies), assessment of dietary intake and exposure to a Mediterranean diet, and musculoskeletal outcomes were extracted for all studies. For studies meeting the more stringent systematic review criteria, results pertaining to the musculoskeletal outcomes (hazard ratios [HRs] or odds ratios [ORs] with corresponding 95%CI and *P* values), from the most-adjusted multivariable model, together with the potential confounding variables that had been entered into the model were tabulated, grouped by outcome.

Data extraction was undertaken by 1 reviewer and checked by a second reviewer for studies included in the evidence map and was performed by 2 reviewers independently for the systematic review studies. Discrepancies on extracted data, discussed with other reviewers in the team, were resolved by consensus. Corresponding authors were contacted to provide clarification on results, where required.

Assessment of risk of bias (systematic review studies)

Studies eligible for the systematic review (all prospective cohort studies) were assessed by 2 reviewers independently using the standard domains in the appropriate Newcastle-Ottawa quality assessment scale (NOS),[47] revised to include review specific guidance (see Appendix S3 in the Supporting Information online). No attempt was made to conceal from the assessors the identity of the study authors or the journal of publication. The quality of evidence pertaining to each outcome in included studies was scored as high (NOS scores 7–9), moderate to good (5 or 6), or poor (<5). Study findings were interpreted in the context of study quality.

Data synthesis

Higher vs lower Mediterranean diet exposures were compared for each musculoskeletal outcome, and these data were synthesized narratively, subgrouped by age and sex where possible. For the evidence map, study characteristics, but not results, were tabulated and synthesized narratively, grouped by outcome.

RESULTS

Following removal of duplicate records, 1738 titles and abstracts were screened. Of these, 238 full-text articles were assessed for eligibility, yielding 18 studies that investigated the relationship between Mediterranean diet and 1 or more of the predefined musculoskeletal outcomes (Figure 1). To aid clarity in the reporting of findings, the 3 studies that fulfilled the tighter systematic review criteria were separated from the other 15 studies in the evidence map. From here on, the 2 sets of studies are referred to as systematic review studies and evidence map studies. Figure 2 represents the totality of evidence identified in the systematic review and evidence map studies for each outcome, by study design.

Systematic review studies

Three prospective cohort studies, 2 reporting on fracture incidence[48,49] and 1 on sarcopenia incidence,[50] were included in the systematic review (Table 2[48–50]). The quality of evidence ratings was moderate to good in the fracture incidence studies (NOS scores 6[48] and 5[49]) and high in the sarcopenia study (NOS score 7)[50] (Table 3[48–50]).

Fracture incidence. First incident fracture was assessed at the hip in 2 European studies[48,49] and, in 1 of these studies,[49] at the wrist and vertebra as well. Benetou et al.[48] report on 188 765 participants (74% female; mean age [± SD] 48.6 ± 10.8 years) from 10 centers in 8 European countries. Fracture data were obtained from self-reports (7 centers), record linkage (2 centers),

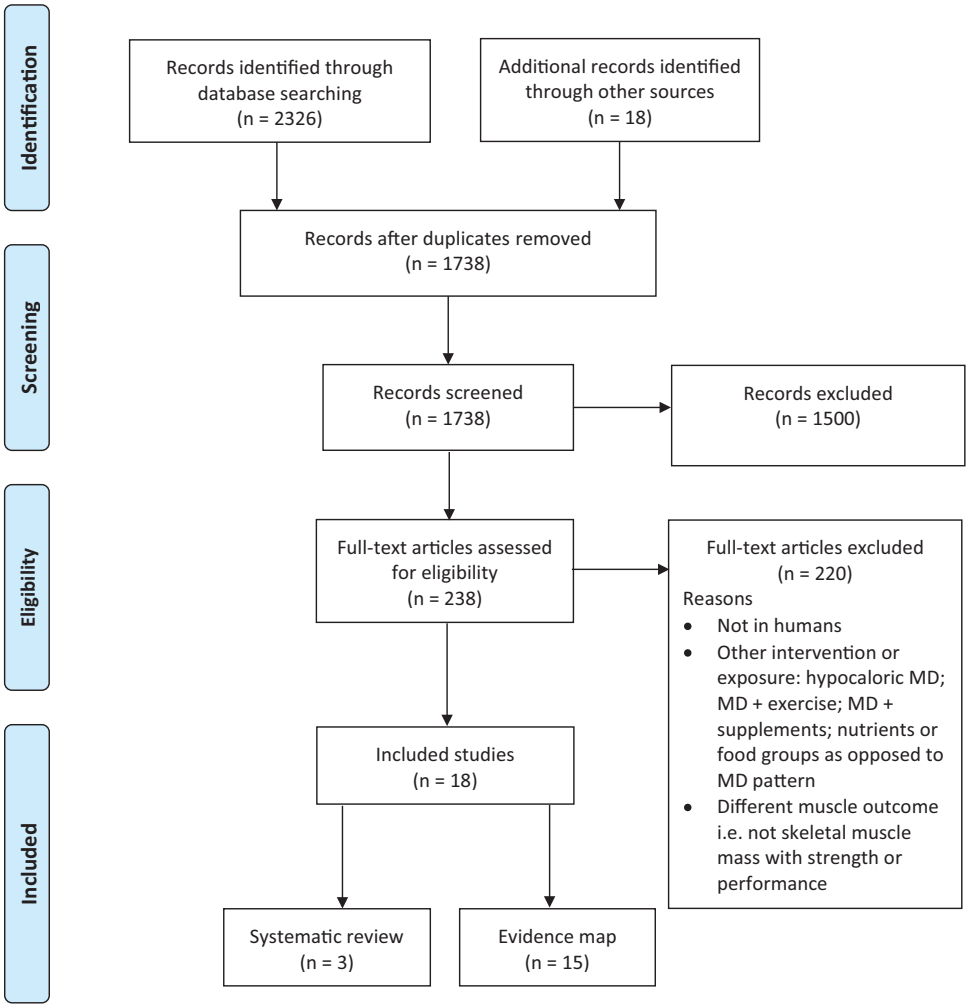


Figure 1 **Flow diagram of the literature search process.** *Abbreviation*: MD, Mediterranean diet.

or x-ray–verified registers (1 center). Feart et al.[49] report on self-reported fracture incidence in 1482 participants (63% female; mean age [range] 75.9 [67.7–94.9] years) from Bordeaux (Table 2).

Dietary intake in both studies was assessed at baseline only. The pan-European study[48] used self-administered (7 centers) or interviewer-administered (2 centers) food frequency questionnaires (FFQs) or diet history questionnaires (1 center) that were quantitative, semiquantitative, or nonquantitative[51] to estimate habitual dietary intake over the previous 12 months. In addition, 24-hour dietary recall data from interviews in a random sample of 10%–15% of participants per center were used to calibrate data to a common reference scale across participating countries: sex- and center-specific differences in mean estimated intake value between FFQs (which differed across countries) and the referent 24-hour recall were calculated and added to the FFQ values. These calibrated dietary data were used in the analysis. Feart et al.[49] used interview-administered FFQs (not semiquantitative, time period not specified) and 24-hour dietary recall for all participants. Both studies used the Mediterranean diet index created by Trichopoulou et al.[52] (referred to hereafter as the "Mediterranean diet score") to assess dietary adherence, but the index was modified for lipid intake in 1 study.[48]

Hip fracture. In the study by Benetou et al.,[48] the proportion of individuals experiencing first incident fracture at the hip during the 9-year study period was 0.4% (802 of 188 765 participants), almost 10-fold lower than that reported by Feart et al.[49] over an 8-year period (3.9%, 57 of 1482 participants). Benetou et al.[48] report an HR of 0.93 (95%CI, 0.89–0.98; *P* value not reported), indicating a 7% decrease in risk of incident hip fracture per unit increase of the Mediterranean diet score in the monitored time period of 9 years (the 7% reduced risk of hip fracture is assumed to apply to each 1-unit increment across the entire 0- to 9-point adherence index). There was evidence of a significant interaction by sex, with the inverse association between hip fracture and Mediterranean diet adherence being proportionately

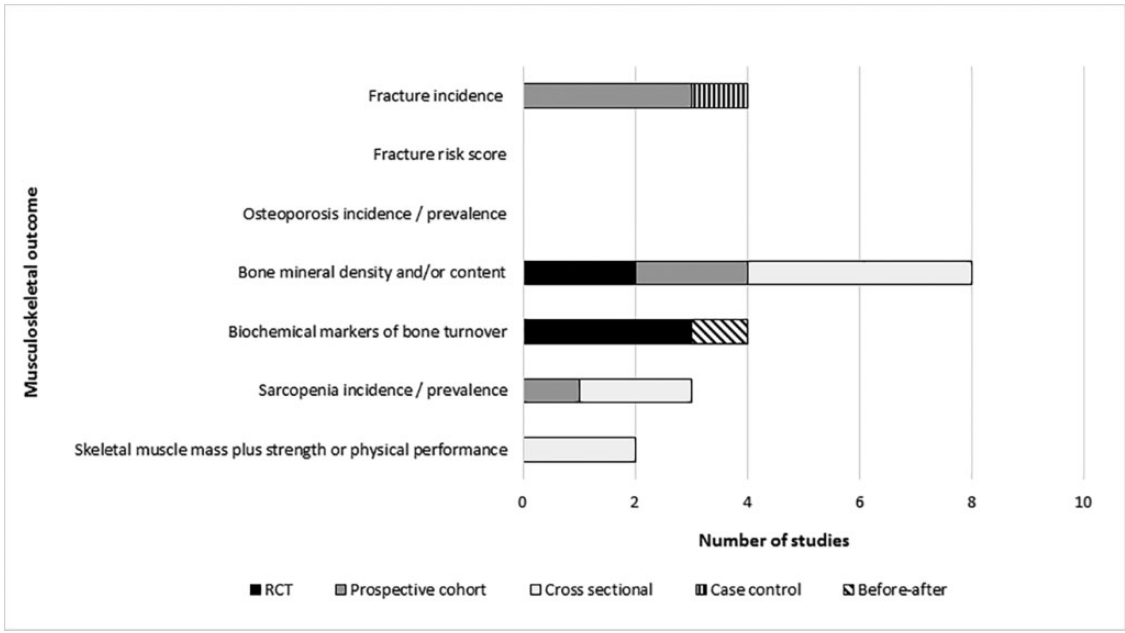


Figure 2 **Volume (no. of studies) and nature (study designs) of evidence identified in the systematic review and evidence map, grouped by outcome: 18 studies in total, some of which reported more than 1 outcome**. *Abbreviation*: RCT, randomized controlled trial.

stronger in men (men, HR = 0.90, 95%CI 0.80–1.01; women, HR = 0.97, 95%CI 0.91–1.02; $P = 0.004$ for interaction), but not by age group (< 60 years, HR = 0.96, 95%CI 0.89–1.03; ≥ 60 years, HR = 0.92, 95%CI 0.86–0.99; $P = 0.884$ for interaction). A post hoc analysis of data from 84 522 participants aged 50 years and older, excluding premenopausal women, also yielded a reduced risk of hip fracture with better Mediterranean diet adherence (HR = 0.91, 95%CI 0.86–0.96; grouped by sex: men, HR = 0.87, 95%CI 0.76–0.99; women, HR = 0.95, 95%CI 0.89–1.01; *P* values not reported). In contrast, Feart et al.[49] found that first incident hip fracture during the monitored time period of 8 years was a nonsignificant 1.18 times more likely with a 1-unit increase in the Mediterranean diet score (HR = 1.18, 95%CI 0.99–1.39; $P = 0.06$). Results have been confirmed by the lead author to be first incident fractures.

In both studies, these associations were assessed using Cox regression, adjusting for potential confounders, and the results given here are for the most-adjusted models. Figure 3 shows the extent to which the results from the 2 studies are diametrically opposed. Statistical synthesis of the results was not done because it may have yielded a misleading pooled result, even if a random-effects model to incorporate the heterogeneity had been used.[41]

Fracture at other sites. Reported in 1 study,[49] first incident fracture at the hip, wrist, or vertebra during the follow-up period (8 years) was a nonsignificant 1.10 times more likely with a 1-unit increase in the Mediterranean diet adherence score (HR = 1.10, 95%CI, 0.99–1.21; $P = 0.08$) (Figure 3). No association was found between a 1-unit increase in the Mediterranean diet adherence score and first incident fracture at the vertebra (HR = 1.06, 95%CI 0.87–1.29; $P = 0.55$) or wrist (HR = 1.06, 95%CI 0.94–1.26; $P = 0.25$). The observed difference in mean baseline Mediterranean diet adherence score (± SD) in participants experiencing first incident fracture at any site (n = 155) during the study period vs those experiencing no fracture (n = 1327) was 4.64 units (± 1.72) vs 4.25 units (± 1.67), $P = 0.04$. As before, results are for the most-adjusted models.

Benetou et al.[48] report that some study centers collected data on fractures at anatomical sites other than the hip, but the data were not presented in the publications reviewed.

Sarcopenia incidence. The study investigating sarcopenia incidence[50] in 2898 Chinese adults aged 65 years and older living in Hong Kong, 50% of whom were women, found no association between a 1-unit increase in Mediterranean diet adherence (assessed using the Mediterranean diet score[52]) and presence of sarcopenia in the 1449 men (most-adjusted OR = 0.98, 95%CI 0.86–1.10; $P = 0.68$) or the 1449 women (most-adjusted OR = 0.96, 95%CI 0.83–1.11; $P = 0.602$) studied over 4 years (Table 2). Sarcopenia was defined according to the Asian Working Group for Sarcopenia algorithm,[22]

Table 2 **Studies included in the systematic review**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake	Assessment of Mediterranean diet adherence[a]	Adjusted variables	Duration of follow-up	No. (%) experiencing event during study period	HR incidence (95%CI) per 1-unit increment in MD adherence score[b], *P* value
Bone outcomes										
Benetou et al. (2013)[48]	Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, UK	Prosp cohort	N = 188 765 (74.2)	Adults; mean age ± SD, 48.6 ± 10.8 y; cohort from EPIC study; inclusion criteria varied by center; excluded if key data were incomplete or if ratio of estimated energy requirements to energy intake was in top or bottom 1% of study cohort	Baseline FFQ pertaining to previous 12 mo (by interview, 2 centers; self-administered, 7 centers) or DHQ (1 center); 24-h dietary recall interviews in 5%–12% of participants (all centers)	↑ Fruit and nuts, ↑ vegetables, ↑ legumes, ↑ cereals and cereal products, ↑ fish and shellfish, ↑ MUFAs + PUFAs:SFAs ratio, ↑ ethanol intake (M: 10–50 g/d; F: 5–25 g/d); ↓ meat and meat products, ↓ dairy	Age, sex, BMI, smoking, CVD, cancer, history of DM, fracture, other health-related variables, menopause (pre/post), height, PA, total energy intake, education	Median 9 y	1st incident fracture at hip: 802 (0.43)	1st incident fracture at hip: 0.93 (0.89–0.98), *P* = N/R
Feart et al. (2013)[49]	France	Prosp cohort	N = 1482 (62.9)	Community-dwelling older adults; mean age 75.9 (range, 67.7–94.9) y; cohort from 3C Study who completed a diet survey in 2001–2002 (baseline for this study); no exclusion criteria reported	Baseline FFQ (time period N/R) and 24-h dietary recall, both by interview	↑ Fruit, ↑ vegetables, ↑ legumes, ↑ cereals (eg, bread, pasta, rice, whole/refined grains), ↑ fish and seafood, ↑ MUFAs:SFAs ratio, ↑ alcohol intake (M: 10–20 g/d; F: 1.4–5.7 g/d; corresponds to 2nd quartile distribution of total intake for study population); ↓ meat, ↓ dairy (including yogurt, milk, cheese)	Age, sex, BMI, osteoporosis, calcium and/or vitamin D supplement, PA, total energy intake, education	Median 8 y	1st incident fracture: at hip, 57 (3.9); at wrist, 73 (4.9); at vertebra, 43 (2.9); at any of above, 155 (10.5)	1st incident fracture: at hip, 1.18 (0.99–1.39), *P* = 0.06; at wrist, 1.09 (0.94–1.26), *P* = 0.25; at vertebra, 1.06 (0.87–1.29), *P* = 0.55; at any of above, 1.10 (0.99–1.21), *P* = 0.08

(continued)

Table 2 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake	Assessment of Mediterranean diet adherence[a]	Adjusted variables	Duration of follow-up	No. (%) experiencing event during study period	HR incidence (95%CI) per 1-unit increment in MD adherence score[b], *P* value
Muscle outcomes Chan et al. (2016)[50]	Hong Kong	Prosp cohort (see Table 5 for other data)	N = 2948 (50.8)	Community-dwelling adults; aged ≥ 65 y (mean age N/R for prosp cohort); able to walk or take public transport to study site; excluded if key data were incomplete or if energy intake was extreme (not defined)	Baseline FFQ pertaining to previous 12 mo by interview (frequency, usual portion sizes determined using pictures)	↑ Fruit and nuts, ↑ vegetables, ↑ legumes, ↑ cereals and cereal products, ↑ fish and shellfish, ↑ MUFAs:SFAs ratio, ↑ ethanol intake (M: 10–50 g/d; F: 5–25 g/d); ↓ meat and poultry, ↓ dairy	Age, sex, BMI, smoking, alcohol use, chronic diseases (no.), dementia, depression, PA, total energy intake, education, marital status/living alone	Mean 3.9 ± 0.1 y	Sarcopenia: All, 264 (9.0) M: 160 (11.0) F: 104 (6.9)	Sarcopenia: M: 0.98 (0.86–1.10), *P* = 0.678 F: 0.96 (0.83–1.11), *P* = 0.602

Abbreviations and symbols: BMI, body mass index; CVD, cardiovascular disease; DHQ, diet history questionnaire; DM, diabetes mellitus; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; M, male; MD, Mediterranean diet; MUFAs, monounsaturated fatty acids; N/R, not reported; PA, physical activity; prosp, prospective; PUFAs, polyunsaturated fatty acids; SD, standard deviation; SFAs, saturated fatty acids; 3C Study, Three-City Study (prospective cohort study of vascular risk factors for dementia and cognitive impairment); ↑, higher intakes of foods treated as positive, assigned score of 1 if intake was above sex-specific study median (and 0 if below); ↓, higher intakes of foods treated as negative, assigned score of 1 if intake was below sex-specific study median (and 0 if above).

[a]Mediterranean diet score of Trichopoulou et al. (2003)[52];Scale of 0–9; 9 = maximal adherence to MD.

[b]Most-adjusted model.

Table 3 **Quality of evidence of systematic review studies assessed using the Newcastle-Ottawa score (adapted)**

Reference	Selection criteria				Comparability (confounding) criteria	Outcome criteria			Total points awarded (0–9)
	Selection of exposed cohort (1 point max)	Selection of nonexposed cohort (1 point max)	Ascertainment of exposure (1 point max)	Assessment outcome not present at start of study (1 point max)	Comparability of cohorts (2 points max)	Adequacy of outcome assessment (1 point max)	Duration follow-up (1 point max)	Adequacy of cohort follow-up (1 point max)	
Benetou et al. (2013)[48]	0	1	1	1	2	0	1	0	6
Feart et al. (2013)[49]	0	1	1	1	1	0	1	0	5
Chan et al. (2016)[50]	0	1	1	1	2	1	1	0	7

with cutoff values as follows: (1) appendicular skeletal muscle mass index (appendicular skeletal muscle mass ÷ height^2) $< 7.0\,kg/m^2$ (men) or $< 5.4\,kg/m^2$ (women), assessed using dual-energy x-ray absorptiometry scan of 4 limbs, with the sum of lean mass measured at "cut lines" according to the anatomical landmarks of Heymsfield et al.,[53] plus either (2) hand grip strength $< 26\,kg$ (men) or $< 18\,kg$ (women), assessed by dynamometer using average value of 2 measurements, or (3) gait speed over 6 meters at usual walking speed $< 0.8\,m/s$ (men and women), assessed using the average value of 2 measurements.

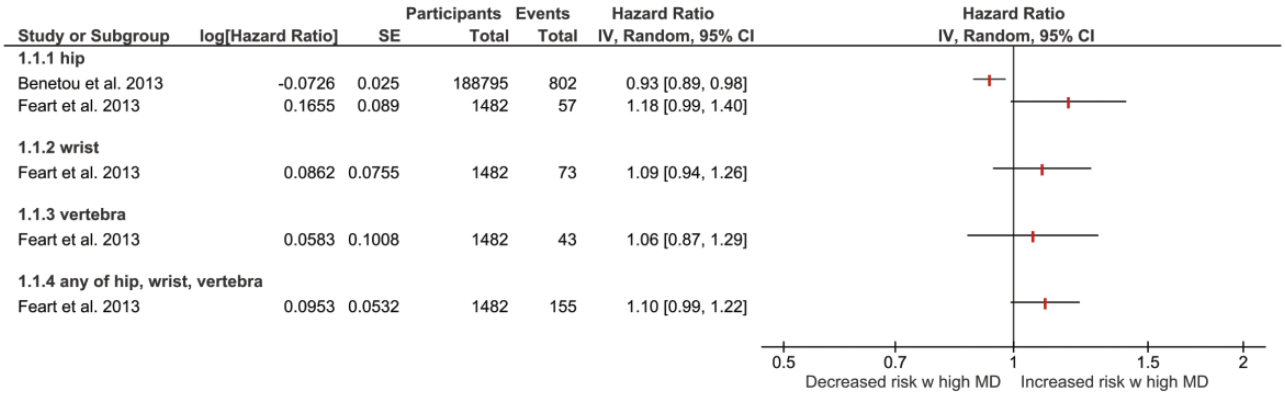
In common with the fracture studies, dietary intake was assessed at baseline only, using an FFQ (interviewer-administered, semiquantitative) to capture habitual food intake over the previous 12 months and the Mediterranean diet score[52] to assess Mediterranean diet adherence.

Evidence map studies

The evidence map comprises 15 studies that investigated the association between a Mediterranean diet and musculoskeletal outcomes but failed to meet the systematic review eligibility criteria for the following reasons: the type of Mediterranean diet described (3 RCTs,[54–56] 2 prospective cohort studies,[57,58]); the study design (5 cross-sectional studies,[50,59–62] 1 before–after study,[63] 1 case–control study[64]); or both (3 cross-sectional studies[65–67]). Eleven studies were from Europe[54–56,58–63,65–67] and 1 each from the United States,[57] Iran,[66] Hong Kong,[50] and China.[64] Eleven studies have been reported since 2012,[50,55–59,61,62,64,66,67] 1 of which is ongoing,[56] reflecting the growing attention to the effect of diet on musculoskeletal health. Details of the interventional studies included in the evidence map are outlined in Table 4[54–56,63,] and those of the observational studies in Table 5.[50,57–62,64–67]

Dietary intake data were collected at baseline in all 15 studies and at follow-up time point(s) in 4 of the 6 prospective studies.[54–56,63] Approaches to collecting data varied. Eight of the 10 studies that reported using either diet history questionnaires or FFQs to assess habitual food intake stated the time periods that participants were asked to recall, comprising 7 days (1 study),[62] 3 months (1 study),[57] or 12 months (6 studies).[50,54,55,58,61,64] Self-reported food diaries, where used, captured dietary intake over 3 days,[60,65] 7 days,[56] or the entire intervention period of 28 days.[63] One study did not report the approach used to collect dietary intake.[67]

Ten studies described using a priori indices to examine the extent to which collected dietary data adhered to prespecified quotas in food categories deemed by the index developers to be integral to a



Key:
Horizontal lines represent the confidence intervals (CI) around the hazard ratios (HR) by fracture site for each study. A HR (CI) that falls entirely to the left of the 1.0 value (vertical line) indicates a significant association between decreased risk of fracture incidence and higher adherence to a MD. Where the 95% CI touches or crosses the line, any association is not significant.

Figure 3 **Forest plot of most-adjusted hazard ratios for first fracture incidence associated with a 1-unit increment in MD adherence score (on a scale of 0–9, 9 indicating greatest adherence to MD), by fracture site.** *Abbreviations*: IV, inverse variance; MD, Mediterranean diet; SE, standard error; w, with.

Mediterranean diet. The Mediterranean diet score[52] was used in 4 studies,[50,59,61,62] the Alternate Mediterranean diet index[68–71] in 2 studies,[57,64] the Mediterranean diet quality index[72] in 2 studies,[58,67] and the indices of Martínez-González et al.[73] and Panagiotakos et al.[74,75] in 1 study each.[54,60] There are differences between these indices in types, groupings, and/or scoring of food categories. The ongoing NU-AGE RCT[56] is developing a diet index. In 1 study, the Mediterranean dietary pattern of study participants was derived a posteriori by collecting and analyzing dietary data and applying principal component analysis to ascertain the dietary patterns, 1 of which was then labeled a Mediterranean diet.[66]

Two of the 4 interventional studies drew participants from the PREDIMED (Prevención con Dieta Mediterránea) RCT,[54,55] and so the dietary interventions, details of which were extracted from the PREDIMED protocol,[76] were the same for both of these sets of participants, comprising group and individual, personalized, motivational advice on a Mediterranean diet plus 1 of the following: virgin olive oil (group 1), nuts (group 2) (oil and nuts supplied), or advice on a low-fat diet (group 3). In the NU-AGE RCT,[56] participants were randomized to receive either individually tailored advice on a Mediterranean diet, along with some of the food items required by the diet and vitamin D supplementation (interventional arm), or general dietary advice alone (control arm). In the before–after study,[63] the Mediterranean diet intervention again differed, being based on recommendations of the Spanish government for dietary intake for adolescents and on the main characteristics of a Mediterranean diet.[77] Participants were provided with lunch and dinner for the duration of the trial and were advised on what to eat for all other meals and snacks. Full details are given in Table 4.

Eleven of the 15 studies investigated bone-related outcomes[54–58,60–65] and 4 investigated the stipulated muscle outcomes,[50,59,66,67] 2 of which reported on sarcopenia prevalence.[50,66]

Fracture incidence/risk (2 studies). In a case–control study,[64] 726 cases (aged 55–80 years) with hip fracture were age and sex matched with controls, and adherence to a Mediterranean diet over the previous 12 months was assessed using the Mediterranean diet score adherence index.[52] The Women's Health Initiative prospective cohort study[57] followed 90 014 postmenopausal women, aged 50–79 years, for a median of 15.9 years to assess hip fracture incidence. Mediterranean diet adherence was assessed at baseline using the alternate Mediterranean diet index (an index that does not consider dairy products).

Bone mineral density and bone mineral content (8 studies). Bone mineral density was investigated in 2 RCTs,[54,56] 2 prospective cohort studies,[57,58] and 4 cross-sectional studies,[60–62,65] 2 of which also investigated bone mineral content.[60,62] Assessment was by dual-energy x-ray absorptiometry scan in 6 of the 8 studies, although there was variation in the body areas scanned. Three studies scanned single sites, namely the L2–L4 region of the lumbar spine,[60] the distal radius of the non-dominant arm,[58] and the calcaneus,[61] and 3 studies scanned multiple sites, namely the femoral neck and the L2–L4 region of the lumbar spine,[62] the femoral neck and the total body[57] and the femur, the total body, and the spine.[56] Other methods used were ultrasound of the calcaneus[54] and peripheral quantitative computed

Table 4 **Interventional studies (randomized controlled trials, before–after study) included in the evidence map**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Dietary intervention and comparator diet	Assessment of dietary intake, and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
Bone outcomes									
Bulló et al. (2009)[54]	Spain	RCT	N = 202 (49) 3 groups: n = 73 n = 70 n = 59	Community-dwelling adults; mean age ± SD, 68 ± 6.2 y[a]; at risk of CVD; enrolled in PREDIMED trial	Intervention [groups (1) MD + virgin olive oil, and (2) MD + nuts]: group training plus 3 monthly individual motivation interviews, personalized advice on MD (fruit, vegetables ≥ 2 s/d; legumes, nuts or seeds, fish/seafood ≥ 3 s/wk; sofrito ≥ 2 s/wk; abundant olive oil; cured/fatty cheeses, chocolate [dark], cured ham and/or red meat ≤ 1 s/wk; white meat instead of red/processed meat; wine 1 glass/d if usually taken; ad libitum consumption of eggs, low-fat cheese, wholegrain cereals, fat from oily fish/plants; avoidance of cream, butter, margarine, cold meat, sugared beverages, pastries, commercially baked products, potato chips), meals to be taken at table over a period of at least 20 min, supplied with either virgin olive oil ≥ 50 mL/d or nuts 30 g/d, according to group	FFQ pertaining to previous 12 mo, at baseline and 1 y (type, frequency, portion size) MD adherence assessed using extended version of index of Martínez-González et al. (2004)[73]; food components and scoring approach N/R	1 y	Bone density/quality (BMD, broadband ultrasound attenuation, speed of sound, assessed twice by ultrasound of calcaneae); bone turnover markers in 24-h urine (DPD:Cr ratio, Ca:Cr excretion) and in fasting blood or serum samples (Ca, PTH, ALP isoenzymes, 25-OH vitamin D, OPG)	Type of MD (guidelines informing dieticians' advice did not address cereals; allowed ad libitum but not actively encouraged, as per MD inclusion criteria)

(continued)

Table 4 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Dietary intervention and comparator diet	Assessment of dietary intake, and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
					Comparator diet [group (3)]: advice to follow a low-fat diet of AHA, unclear if 1-time advice or group training plus 3 monthly individual motivation interviews (PREDIMED protocol amended year 4 of trial)				
Fernández-Real et al. (2012)[55]	Spain	RCT	N = 127 (0) 3 groups: n = 42 n = 51 n = 34	Community-dwelling men; mean age ± SD, 67.9 ± 6.3 y[a]; at risk of CVD; enrolled in PREDIMED trial	Intervention [groups (1) MD + virgin olive oil, and (2) MD + nuts] and comparator diet (group 3): as above for study by Bulló et al.[54]	FFQ previous 12 mo at baseline and annually (type, frequency, portion size) MD adherence assessment N/R	1 y and 2 y	Bone turnover markers in blood or serum samples (total and uncarboxylated osteocalcin, CTX, P1PNP, Ca, phosphate)	Type of MD (same as above, for study by Bulló et al.[54])
Santoro et al. (2014)[56]	France, Italy, the Netherlands, Poland, UK	RCT	Aim to recruit: N = 1250	Adults; aged 65–79 y (mean age N/R); enrolled in the NU-AGE trial; free of disease with < 2 y prognosis; competent to make decisions; living independently	Intervention: 9 sessions of motivational interviews in 12 mo plus additional mail/email contact, personalized MD advice derived from dietary guidelines for the elderly from the participating countries (whole grains 4–6 s/d; vegetables ≥ 3 s/d [100 g/s]; fruits [fresh, frozen, dried, juice] ≥ 2 s/d; legumes 200 g 1×/wk; potatoes 3 s/d [50 g/s] or whole-grain pasta or rice 2–4 s/wk [80 g/s, raw]; dairy 500 mL/d, includes 30 g cheese	Self-completed preformatted diary over 7 d, at baseline and at 1 y (recipes, food type, preparation, portion sizes using household measures) MD adherence assessment N/R; NU-AGE index being developed as part of this study	1 y	Bone density/quality (BMD, assessed by DXA scan of total body, femur, and spine); bone turnover markers in blood or serum samples (25-hydroxy vitamin D, Ca, PTH)	Type of MD (intervention group received vitamin D supplement, while control group did not)

(continued)

Table 4 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Dietary intervention and comparator diet	Assessment of dietary intake, and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
					[lean, low salt]; eggs 2–4×/wk; meat or poultry [lean, not fried] 4 s/wk [125 g/s]; fish [preferably oily] and seafood 2 s/wk [125 g/s]; nuts [unsalted, mixed] 2 s/wk [20 g/s]; fat $\leq$ 50 g/d [oil 20 g/d, margarine 30 g/d]; alcohol, if consumed, $\leq$ 2 g/d [M], $\leq$ 1 g/d [F]; other fluid $\geq$ 1.5 L/d; salt $\leq$ 5 g/d; sweets and sweet drinks, limit intake); daily vitamin D supplement, some MD foods provided by researchers Comparator diet: leaflet with general national dietary guidelines				
Seiquer et al. (2008)[63]	Spain	Before–after	N = 20 (0)	Male adolescents; mean age ± SD[b], 12.9 ± 1.14 y; medium–high socioeconomic status and education level; healthy	3 d of usual (basal) diet, then 28-d intervention diet: individualized 7-d menu based on recommended nutritional intakes for Spanish adolescents and an MD informed by Serra-Majem et al.[77] (pasta, rice, cereals 4.5 s/d, dairy products 3 s/d, fruits 2 s/d, vegetables 1.7 s/d, meat and eggs 1.5 s/d, fish 0.5 s/	Daily record sheets of consumed and uneaten (weighed) foods during intervention period MD adherence assessment N/R	28 d	Bone turnover markers in 24-h urine (DPD, Cr, and Ca:Cr, Na:Cr, Ca:Na, P:Cr ratios) or in blood or serum samples (Ca, PTH, ALP)	Study design (not RCT or prospective cohort study)

(continued)

Table 4 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Dietary intervention and comparator diet	Assessment of dietary intake, and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
					d, legumes 0.4 s/d, olive oil as the main dietary fat); mineral/vitamin supplements and fortified foods prohibited; restaurant and take-out foods prohibited; lunch and dinner provided; breakfasts and snacks prepared at home to guidelines				

Abbreviations: AHA, American Heart Association; ALP, alkaline phosphatase; BMD, bone mineral density; Ca, calcium; Cr, creatinine; CTX, human cross-linked C-telopeptide of type 1 collagen; CVD, cardiovascular disease; DPD, deoxypiridinoline; DXA, dual-energy x-ray absorptiometry; F, female; FFQ, food frequency questionnaire; g/s, grams/serving; M, male; MD, Mediterranean diet; Na, sodium; N/R, not reported; OPG, osteoprotegerin; P, phosphorus; P1PNP, procollagen I N-terminal propeptide; PREDIMED, Prevención con Dieta Mediterránea (RCT investigating effects of Mediterranean diet on cardiovascular mortality; PTH, parathyroid hormone; RCT, randomized controlled trial; s/d or s/wk, servings/day or servings/week; SD, standard deviation; u/s, ultrasound.

[a]Age data calculated for entire study population; original publication gives breakdown by groups, eg, by intervention group, age, sex, and/or quantiles.

[b]Assumed to be standard deviation (not reported if the figure given is the standard deviation or the standard error).

Table 5 **Observational studies (prospective cohort, case-control, cross-sectional) included in the evidence map**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
Bone outcomes								
Di Leo et al. (2000)[65]	Italy (published in Italian, translated by native-speaking Italian)	Cross-sectional	N = 30 (100%) n = 15 cases; n = 15, controls	Adults; mean age ± SD, 36 ± 4 y; cases ate vegetarian diet rich in soya and legumes; controls ate MD, low in legumes relative to the vegetarian diet, without soya, and were matched for age and body mass	Self-reported food diary for 3 d incorporating weekend day (type, quantity), plus summary of the week's food intake; MD adherence assessment N/R	N/A	Bone density/quality (cross-sectional area, trabecular area, cortical area, cortical thickness, strength strain index; assessed by pQCT at forearm)	Study design (not RCT or prosp cohort study); type of MD (details of MD adherence assessment/food categories N/R)
Haring et al. (2016)[57]	USA	Prosp cohort	N = 90 014 (100%) All assessed for fracture; n = 7961 (subset) assessed for BMD	Women, aged 50–79 y (mean ages in 3 age bands reported for full cohort, by MD adherence); enrolled in the WHI-OS; generally healthy; postmenopausal	FFQ previous 3 mo at baseline (frequency, portion size, food preparation practices, types of added fats); MD adherence using the aMED index created by Trichopoulou[52] and developed by Fung et al.[69] and others, scale 0–9 with 9 = maximal MD adherence, scoring ↑ fruit, ↑ vegetables, ↑ legumes, ↑ whole grains, ↑ nuts, ↑ fish, ↑ MUFAs:SFAs ratio, alcohol intake 5–15 g/d, red and processed meats	15.9 y (median) for fracture prevalence; 6 y for BMD	Fracture (incident hip fracture from medical records; total fractures excluding toes, fingers, sternum, clavicle from self-reported data); bone density/quality (BMD, assessed by DXA scan of femoral neck and total body)	Type of MD (aMed dietary adherence index does not address dairy intake)
Kontogianni et al. (2009)[60]	Greece	Cross-sectional	N = 196 (100%) n = 100 were premenopausal; n = 96 were	Females; mean age ± SD, 48 ± 12 y[a]; recruited	Self-reported food records over 3 consecutive days incorporating	N/A	Bone density/quality (BMD, total body BMC, assessed by DXA scan of L2–	Study design (not RCT or prosp cohort study)

(continued)

Table 5 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
			peri- or postmenopausal	via local magazine advert; healthy	weekend day (frequency, portion size using standard household measurements); MD adherence index of Panagiotakos et al.,[74,75] scale 0–5 for each food group with 55 = maximal MD adherence, scoring ↑ fruit, ↑ vegetables, ↑ legumes, ↑ nonrefined cereals, ↑ fish, ↑ olive oil, ↑ potatoes, ↑ alcohol intake > 0 to < 300 mL/d (36 g ethanol); ↓ meat products, ↓ poultry, ↓ full-fat dairy		L4 of lumbar spine)	
Monjardino et al. (2012)[58]	Portugal	Prosp cohort and cross-sectional	N = 1023 (54%), prosp cohort dataN = 1264 (53%), cross-sectional data	Teenagers; born in 1990, recruited to the EPITeen study at 13 y of age; recruited from public and private schools	FFQ previous 12 mo at baseline (frequency, but not portion size); MD adherence using KIDMED index of Sera-Majem et al.,[72] scale of 0–12 with 12 = maximal MD adherence, scoring+ 1 a fruit or fruit juice every day,+ 1 a 2nd fruit every day,+ 1 vegetables	4 y	Bone density/quality (BMD, assessed by DXA scan of forearm)	Type of MD (KIDMED dietary adherence index does not assess meat intake apart from fast food [hamburger] consumption)

(continued)

Table 5 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
					(fresh or cooked) 1/d,+ 1 vegetables (fresh or cooked) > 1/d,+ 1 cereals or grains (eg, bread) for breakfast,+ 1 a dairy product for breakfast,+ 1 yogurts (×2) and/or cheese (40 g) 1/d,+ 1 pasta or rice 5×/wk,+ 1 nuts ≥ 2–3×/wk,+ 1 fish ≥ 2–3×/wk, 1 likes and eats pulses > 1×/wk, 1 uses olive oil at home, −1 sweets and candies several times per day, −1 commercial baked breakfast (eg, pastries), −1 skips breakfast, −1 fast-food (hamburger) > 1×/wk			
Rivas et al. (2013)[61]	Spain	Cross-sectional	N = 200 (100%) n = 100 premenopausal; n = 100 postmenopausal	Women; mean age ± SD, 44.4 ± 11.7 y[a]; recruited from a larger study investigating the effect of aquatic activities on BMD; healthy	FFQ previous 12 mo, by interview (type, frequency, portion size in household measures); MD adherence using MDS index of Trichopoulou et al.,[52] scale of 0–9 with 9 = maximal MD adherence,	N/A	Bone density/quality (BMD, assessed by DXA scan of calcaneous)	Study design (not RCT or prosp cohort study)

(continued)

Table 5 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
					scoring ↑ fruit and nuts, ↑ vegetables, ↑ legumes, ↑ cereals and cereal products, ↑ fish and shellfish, ↑ MUFAs:SFAs ratio, ethanol intake 5–25 g/d, ↓ meat, ↓ dairy			
Whittle et al. (2012)[62]	Northern Ireland	Cross-sectional	N = 489 (49%)	Young adults; mean age ± SD, 22.6 ± 1.7 y[a]; participating in the 3rd contact of Young Hearts Project	Diet history previous 7 d, by interview (portion sizes estimated against photographs of known portions and commonly used household vessels); MD adherence using MDS index of Trichopoulou et al.,[52] scale of 0–9 with 9 = maximal MD adherence, scoring ↑ fruit and nuts, ↑ vegetables, ↑ legumes, ↑ cereals, ↑ fish, ↑ MUFAs:SFAs ratio, alcohol intake (M: 10–50 g/d; F: 5–25 g/d), ↓ meat and meat products, ↓ dairy	N/A	Bone density/quality (BMD, BMC, assessed by DXA scan L2–L4 of lumbar spine and femoral neck)	Study design (not RCT or prosp cohort study)

(continued)

Table 5 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
Zeng et al. (2014)[64]	China	Case–control	N = 1452 (76%) n = 726 cases; n = 726 controls	Adults; mean age ± SD, 70.9 ± 7.3 y[a]; cases hospitalized with hip fracture, diagnosed < 2 wk previously; controls without history of hip fracture, matched for age (± 3 y) and sex, from same city or hospital as cases	FFQ previous 12 mo, by interview (frequency, quantity); MD adherence assessed using aMED, referenced as created by Trichopoulou et al.[52] and developed by Fung et al.,[69] scale of 0–9 with 9 = maximal MD adherence, scoring ↑ fruit, ↑ vegetables, ↑ legumes, ↑ whole grains, ↑ nuts, ↑ fish, ↑ MUFAs:SFAs ratio, moderate alcohol intake; ↓ red and processed meats	N/A	Fracture risk (hip fracture confirmed by x-ray report in cases)	Study design (not RCT or prosp cohort study)
Muscle outcomes Chan et al. (2016)[50]	Hong Kong	Cross-sectional (see other data in Table 2)	n = 3957 (50%)	Community-dwelling older adults; mean age ± SD in those without sarcopenia, 72.2 ± 5.0 y, in those with sarcopenia, 76.2 ± 6.1 y; volunteers; able to attend study center	FFQ previous 12 mo by interview, at baseline (frequency, usual portion size determined using pictures); MD adherence assessed using MDS index of Trichopoulou et al.,[52] scale of 0–9 with 9 = maximal MD adherence, scoring ↑ fruit and nuts, ↑ vegetables,	N/A	Sarcopenia prevalence, using algorithm of AWGS, Chen et al.,[22] with the following cut-off values: ASM index (ASM/height^2 [kg/m^2]) < 7.0 (M), < 5.4 (F), assessed using DXA; plus hand grip strength < 26 kg (M), < 18 kg (F), assessed using dynamometer; and/or gait speed, 6-m	Study design (not RCT or prosp cohort study)

(continued)

Table 5 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
					↑ legumes, ↑ cereals and cereal products, ↑ fish and shellfish, ↑ MUFAs:SFAs ratio, ethanol intake (M: 10–50 g/d; F: 5–25 g/d), ↓ meat, poultry, ↓ dairy		walk < 0.8 m/s (M, F)	
Hashemi et al. (2015)[66]	Iran	Cross-sectional	N = 300 (50%)	Adults; mean age ± SD, 66.8 ± 7.72 y; living in Tehran; selected by cluster random sampling based on postcodes	FFQ (time period not specified), by interview (frequency, standard portion size); a posteriori classification of dietary pattern using principal component analysis, MD pattern had high factor loadings (> 0.4) in food groups such as olives and olive oil, low- and high-carotenoid vegetables, tomatoes, whole grains, nuts, fish, fresh and dried fruits, pickles	N/A	Sarcopenia prevalence, using algorithm of EWGSOP[17] with the following cutoff values: ASM index (ASM/height^2 [kg/m^2]) < 7.26 (M), < 5.45 (F), assessed using DXA; plus hand grip strength less than prespecified age/sex cutoff points, assessed using dynamometer; and/or gait speed, 4-m walk < 0.8 m/s	Study design (not RCT or prosp cohort study), type of MD (not defined a priori)
Kelaiditi et al. (2016)[59]	UK	Cross-sectional	n = 1914 subset 1 (100%) n = 949 subset 2 (100%) Subset 1 assessed for skeletal muscle mass and leg explosive power; subset 2	Women; mean age ± SD, 48.3 ±12.7 y in subset 1 and 59.1 ± 9.3 y in subset 2; from the Twins UK registry if data on FFQ, skeletal muscle mass and skeletal	FFQ (time period not specified); MD adherence assessed using MDS index of Trichopoulou et al.,[52] scale of 0–9 with 9 = maximal MD	N/A	Skeletal muscle mass (fat-free mass [kg], percent fat-free mass [fat-free mass (kg)/ weight (kg) × 100], fat-free mass index [fat-free mass	Study design (not RCT or prosp cohort study)

(continued)

Table 5 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
			assessed for skeletal muscle mass and grip strength	muscle strength or power were available	adherence, scoring ↑ fruit and nuts, ↑ vegetables, ↑ legumes, ↑ cereals, ↑ fish, ↑ MUFAs + PUFAs:SFAs ratio, ↑ alcohol intake (5–25 g/d), ↓ meat and meat products, ↓ dairy		(kg)/height (m^2), assessed by DXA scan]; skeletal muscle strength/power (isometric hand grip strength in dominant hand [kg] using dynamometer, arm muscle quality calculated as ratio of grip strength [kg] to mean arm lean mass [kg], leg explosive power [force and velocity of (principally) quadriceps muscle contraction] using Nottingham power rig)	
Rubio-Arias et al. (2015)[67]	Spain (translated from Spanish using web-based translation, verified by an individual who speaks Spanish as a second language)	Cross-sectional	N=12 (100%)	Young adult females; mean age ± SD[b], 20.3 ± 2.7 ± y; professional indoor football (soccer) players	Dietary intake assessment N/R; MD adherence using KIDMED index of Serra-Majem et al.,[72] scale 0–12 with 12 = maximal MD adherence, scoring +1 a fruit or fruit juice every day, +1 a 2nd fruit every day, +1 vegetables (fresh or cooked) 1/d, +1 vegetables (fresh or cooked) > 1/d, +1 cereals or	N/A	Skeletal muscle mass (total lean mass [kg] assessed by DXA); skeletal muscle strength/power assessed on 2 different days 7 d apart, preceded by standardized warm-up session (vertical jump tests × 2; counter movement and squat jumps using measurement platform; isokinetic strength of knee joint using	Study design (not RCT or prosp cohort study), type of MD (KIDMED dietary adherence index does not assess meat intake apart from fast food [hamburger] consumption)

(continued)

Table 5 **Continued**

Reference	Country	Study design	Sample size (% female)	Characteristics of participants	Assessment of dietary intake and of adherence to Mediterranean diet	Duration of follow-up	Types of outcomes and outcome measures	Reason for exclusion from systematic review
					grains (eg, bread) for breakfast, +1 a dairy product for breakfast, +1 yogurts (×2) and/or cheese (40 g) 1/d, +1 pasta or rice ≥ 5×/wk, +1 nuts ≥ 2–3×/wk, +1 fish ≥ 2–3×/wk, +1 likes, eats pulses > 1/wk, +1 uses olive oil at home, −1 sweets and candies several times per day, −1 commercial baked breakfast (eg, pastries), −1 skips breakfast, −1 fast food (hamburger) > 1×/wk		dynamometer; kicking ball speed using radar; sprint speed 3 × 30 m, separated by 5-min periods; repeated sprint ability 8 × 30-m sprints, separated by 25-s recovery periods, assessed using photo-finish equipment)	

Abbreviations and symbols: aMED, alternate Mediterranean diet score; ASM, appendicular skeletal mass; AWGS, Asian Working Group for Sarcopenia; BMC, bone mineral content; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; EPITeen, Epidemiological Health Investigation of Teenagers in Porto (prospective cohort study); EWGSOP, European Working Group on Sarcopenia in Older People; F, female; FFQ, food frequency questionnaire; M, male; MD, Mediterranean diet; MDS, Mediterranean diet score; MUFAs, monounsaturated fatty acids; N/A, not applicable; N/R, not reported; pQCT, peripheral quantitative computed tomography; prosp, prospective; PUFAs, polyunsaturated fatty acids; RCT, randomized controlled trial; SD, standard deviation; SFAs, saturated fatty acids; WHI-OS, Women's Health Initiative Observational Study (investigated morbidity and mortality in postmenopausal women); YH, Young Hearts (prospective cohort study examining CVD risk factors in adolescents in Northern Ireland); ↑, higher intakes of foods treated as positive, eg, assigned score of 1 if intake above sex-specific study median (and 0 if below); ↓, higher intakes of foods treated as negative, eg, assigned score of 1 if intake below sex-specific study median (and 0 if above).

[a]Age data calculated for entire study population; original publication gives breakdown by group, eg, by intervention group, age, sex, and/or quantiles.

[b]Assumed to be standard deviation (it is not stated whether the figure given is standard deviation or standard error).

tomography of the nondominant forearm.[65] In the longitudinal studies, bone mineral density was assessed at baseline and at 12 months,[54,56] 4 years,[58] or 6 years.[57]

Studies ranged in size from 30[65] to 7961[57] participants. Four studies investigated women only, either premenopausal (aged 29–42 years),[65] postmenopausal (aged 50–79 years),[57] or pre- and postmenopausal (mean age, 48 years[60] and 42.9 years[61]). In the 4 remaining studies in which both male and female participants were included in roughly equal proportions (46%–51%), studies comprised teenagers,[58] young adults (aged 20–25 years),[62] or older adults only (aged $>$ 55 years).[54,56] The Mediterranean diet adherence indices, where reported, were the Mediterranean diet score, used in 2 studies,[61,62] the alternate Mediterranean diet index in 1 study,[57] and the Mediterranean diet quality index in 1 study.[58] The interventional diets in the RCTs[54,56] are described in Table 4.

Markers of bone turnover (4 studies). Three RCTs[54–56] and a before–after study[63] assessed the effects of dietary intervention on markers of bone turnover. Bulló et al.[54] reported on urinary and serum markers of bone metabolism in a cohort of 238 men and women after 1 year in the PREDIMED RCT. Fernández-Real et al.[55] investigated serum concentrations of markers of bone formation and resorption at 1- and 2-year follow-up points in a cohort of 127 older men from the same PREDIMED RCT. Mediterranean diet adherence in both studies was assessed using an extended version of the index by Martínez-González et al.[73] The NU-AGE RCT[56] investigating a Mediterranean diet plus vitamin D supplementation included 3 serum markers of bone health (25-OH vitamin D, calcium, parathyroid hormone) in a planned sample size of 1250 community-dwelling healthy adults. In the before–after interventional study involving 20 male adolescents (aged 11–14 years),[63] serum and urinary markers of bone turnover were assessed at 1 month.[63] The Mediterranean diet adherence assessment index was not specified.

Muscle-related outcomes (4 studies). Four cross-sectional studies investigated skeletal muscle mass plus either skeletal muscle strength or physical performance.[50,59,66,67] In a study of 2863 women aged 18–79 years, skeletal muscle mass measures of fat-free mass, percentage of fat-free mass, and fat-free mass index were assessed using dual-energy x-ray absorptiometry, and muscle strength was assessed using either hand grip strength and arm muscle quality or leg explosive power.[59] The before–after interventional study involving 20 adolescent female footballers (soccer players) reports on the skeletal muscle mass measure of total lean mass assessed using dual-energy x-ray absorptiometry, muscle strength (isokinetic strength of knee joint), power (vertical jump test, kicking ball speed), and performance (3 $\times$ 30-m sprint and repeated sprint ability).[67] In the 2 remaining studies, both investigating adults older than 55 years, with sample sizes of 3957[50] and 300,[66] the muscle-related measures were used to determine the presence or absence of sarcopenia, and the association between Mediterranean diet and sarcopenia prevalence was reported. Both studies reported gait speed, hand grip strength assessed using a dynamometer, and values for appendicular skeletal muscle mass index assessed using dual-energy x-ray absorptiometry. However they used different operational definitions of sarcopenia that resulted in slightly different cutoff values to determine the presence or absence of sarcopenia. Mediterranean diet adherence in the 4 studies was assessed by the Mediterranean diet score (2 studies),[50,59] by the Mediterranean diet quality index (1 study),[67] or by determining a Mediterranean dietary pattern using an a posteriori approach.[66]

DISCUSSION

While national dietary guidelines such as the recently published *2015–2020 Dietary Guidelines for Americans*[78] recommend a Mediterranean diet, the data from this comprehensive systematic and mapping review in which 1738 unique records were screened for eligibility indicate that the implications of this diet for bone and musculoskeletal health are not understood. This work demonstrates an overall paucity of RCTs and prospective longitudinal studies investigating the association between the Mediterranean diet and outcomes indicative of bone or skeletal muscle health (relevant to sarcopenia) in adults and a lack of such studies in children and young people. Studies of any design investigating skeletal muscle outcomes relevant to sarcopenia are particularly sparse. This is in contrast to the more comprehensively investigated relationship between Mediterranean diet and other clinical conditions such as type 2 diabetes, stroke, and overall mortality.[39,79,80]

In the systematic review, only 3 studies, all prospective cohort studies in adults, investigated the association between a traditional Mediterranean diet (as defined) and the musculoskeletal outcomes of interest. The 2 studies reporting on the outcome of hip fracture incidence, both of which were assessed as yielding moderate- to good-quality evidence, produced opposing findings, the cause of which could not be examined statistically but is likely due, in part, to the between-study variability in participant characteristics and exposure assessment. The study that demonstrated a positive effect of the Mediterranean diet on hip fracture incidence (Benetou et al.[48]) included a substantially larger number

of participants from a more diverse range of countries within northern and southern Europe and comprised a younger population that incorporated pre- and perimenopausal women, unlike the study by Feart et al.[49] that recruited participants in southern France and included individuals aged 65 years and older. The study by Benetou et al.[48] did not report on total fractures or fractures at sites other than the hip. There were large differences in the size of populations included in the 2 studies, with the smaller study by Feart et al.[49] potentially having less power to detect associations with accuracy. There were also differences in the covariate factors included in the statistical models that could potentially contribute to heterogeneity in the results: whilst age, sex, body mass index, educational level, physical activity, and energy intake were adjusted for in both studies, smoking, menopause status, previous fracture and history of various, specified, chronic diseases were adjusted for only by Benetou et al.,[48] and osteoporosis status, osteoporosis medication, calcium, vitamin D use, and marital status were adjusted for only by Feart et al.[49]

Although no association was found between the Mediterranean diet and fracture incidence in the 1 study that investigated multiple anatomical sites[49] there was consistency in each of the point estimate hazard ratios towards increased fracture incidence with increased Mediterranean diet adherence. In that study the authors also found through secondary analysis that low (vs high) intake of dairy products was associated with an increased risk of incident fractures at any of the 3 sites together and, when examined separately, of wrist but not hip or vertebra fractures. In the larger pan-European study that investigated hip fracture[48] there was no relationship with dairy products alone.

There was potential for clinical heterogeneity between the studies in dietary intake assessment, with Benetou et al.[48] using 24-hour dietary data, assessed in a percentage of patients, to calibrate the FFQ dietary data to a common reference scale across participating countries. Also, importantly, in both studies, the cut-off point for assigning an adherence score of either 0 or 1 for each food category in the dietary adherence index (Mediterranean diet score) was ascertained from the sex-specific median of the study sample, and these medians are likely to have differed between studies given the participants were not from the same country. Median intakes of food categories can differ markedly across countries according to availability and cultural preferences as shown in the European Prospective Investigation into Cancer and Nutrition study, which found considerable differences across countries in consumption of food groups such as animal, processed and plant foods.[81] For this reason, results from studies that use such scoring methods when assessing dietary exposure are not immediately generalizable across populations with differing dietary habits. It was not possible in this systematic review to accurately compare mean daily intake of foods within each food category across the 2 studies in question, as data are presented in different formats (grams/day[48] vs servings/week[49]).

The finding of no association between sarcopenia incidence and adherence to Mediterranean diet in Chinese adults after 4 years of follow-up is considered robust for this specific study population,[50] but generalizability to other populations is cautioned: the opposing findings of the 2 hip fracture studies above illustrate that the findings of a single prospective cohort study investigating Mediterranean diet should be viewed with prudence. Dietary patterns are assumed to operate through the nutrients provided in the food within them, and therefore the variability in consumption of food groups, which occurs across (and within) countries, results in differences in the nutrients consumed. The resultant differences complicate the interpretation of the effects of the dietary patterns on health outcomes. Nevertheless, the investigation of dietary patterns and their influence on health outcomes is an established research approach that can complement the more specific investigation of individual nutrients or food groups.

The 15 studies included in the evidence map, although not eligible for this systematic review on the basis of the a priori defined criteria, provide important insights for the planning of future research. A range of musculoskeletal outcomes have been investigated in studies of varying design (Figure 2) that use different methods to ascertain dietary intake and/or adherence to the Mediterranean diet, or that use different interventional diets and methods of providing dietary advice. Between-study differences in the types of outcome measures are particularly obvious with regard to assessment of bone mineral density and skeletal muscle mass, strength, or physical performance, reflecting ongoing debates about how to characterize skeletal muscle health.

This review has a number of strengths in the scope of the subject as well as the methodology. Mapping the broader research evidence alongside the systematic review evidence has enabled a comprehensive overview of the diverse research undertaken on this topic. Studies that investigated skeletal muscle outcomes and sarcopenia (not only fracture and osteoporosis outcomes) were included in acknowledgment of the recently understood interactive nature of the bone and skeletal muscle systems. At the time of writing, this systematic review appears to be the first to include sarcopenia and its constituent components (loss of skeletal muscle mass and function) in association with the Mediterranean dietary pattern. It expands the work of a previously published

literature review investigating bone health[40] by extending the number of databases searched from 3 to 10; by including studies of any language, provided adequate English translations could be obtained (no studies were excluded on the basis of language); by using recognized Cochrane methodology; and by limiting admissible studies to those whose designs provide the strongest evidence, ie, RCTs and prospective cohort studies in which outcome measures were assessed at appropriate time points.

A further strength of this study is the a priori characterization of the Mediterranean diet, accomplished through careful examination of relevant dietary adherence indices at the start of this study. The potential for substantial between-study heterogeneity in exposure to a Mediterranean diet was somewhat reduced by requiring the interventional diets and/or diet adherence assessment indices to have addressed 8 prespecified food categories as a minimum. Nevertheless, heterogeneity on this factor was inevitable, given the numerous Mediterranean diet adherence assessment indices with differing scoring approaches. These issues related to characterization of dietary patterns are an important limitation of studies that intend to provide evidence about the role of diet on health outcomes, rendering the results difficult to interpret. A more consistent definition of the Mediterranean diet that describes not just the principles of the diet but gives an amount of consumption for the food groups composing the score, which can be used at an individual level, has been proposed.[39]

A drawback to the approach used to define the inclusion criteria for the systematic review was that 3 RCTs and 2 prospective cohort studies were excluded for the following reasons: the adherence assessment scores did not assess dairy or meat intake, the Mediterranean diet intervention did not specifically encourage the intake of cereals, and participants in the Mediterranean diet intervention arm, but not the control arm, received a vitamin D supplement. Nevertheless, the combined mapping and systematic review approach ensured that the characteristics of these 5 studies have been captured and tabulated.

CONCLUSION

While there is a notable body of research pertaining to the Mediterranean diet and health outcomes such as cardiovascular and metabolic disease, there is a paucity of evidence to understand the relationship between this diet and musculoskeletal outcomes in children, young people, and adults. Evidence relating to the association between fracture incidence at the hip in adults living in Europe and a Mediterranean diet rich in fruit, vegetables, legumes, cereals, and fish and low in meat, milk, and saturated fatty acids is contradictory, highlighting the complexities of interpreting data from studies in which a dietary pattern is the exposure of interest. The lack of agreement in the findings for hip fracture incidence emphasizes the need for further studies that can be assessed alongside the 1 study that found no association between Mediterranean diet adherence and fracture incidence at the wrist or vertebra. No association was found between the Mediterranean diet and sarcopenia in Chinese men and women, but the findings were from a single study, and aggregate support from additional studies is needed to understand this association in the context of other populations. At present, there is insufficient research evidence to inform policy decisions about the role of Mediterranean diet in fracture risk and/or skeletal muscle outcomes. That which is available is methodologically diverse in key aspects such as methods to assess the dietary pattern. Future research to answer these questions needs to use a consistent definition of the Mediterranean diet, robust methods for assessing exposure to dietary patterns that yield generalizable data, appropriate musculoskeletal outcomes, sufficiently long follow-up times to assess the outcomes, and prospective study designs.

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Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website:

Table S1 **PRISMA checklist**

Appendix S1 **Search strategy used in Ovid Medline database**

Appendix S2 **Details of inclusion criteria for outcome measures, applicable to both the evidence map and the systematic review**

Appendix S3 **Newcastle-Ottawa Scale to assess quality of a cohort study, tailored to meet the requirements of this systematic review**

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