

# Dietary patterns and frailty: a systematic review and meta-analysis

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**Context:** Assessing the relationship between single nutrients and frailty fails to take into consideration the interactions between nutrients. An increasing number of investigations in recent years have evaluated the association between dietary patterns and frailty. **Objective:** This systematic review and meta-analysis was conducted to summarize the association between dietary patterns and frailty. **Data Sources:** PubMed, Scopus, and Google Scholar were searched for epidemiological studies published up to April 2018 that assessed the association between dietary patterns and frailty. **Study Selection:** Cohort or cross-sectional studies that examined dietary patterns via an a priori or an a posteriori method in relation to risk of frailty without considering any specific age range were included. Studies were excluded if they examined single nutrients, single foods, or single food groups. **Data Extraction:** Pooled effect sizes of eligible studies and their corresponding 95% CIs were estimated using random-effects models. When publication bias was present, trim and fill analysis was conducted to adjust the pooled effect. **Results:** A total of 13 studies with 15 effect sizes were identified. Results from 9 cohort and cross-sectional studies were included in the meta-analysis. Higher adherence to a healthy dietary pattern was associated with lower odds of frailty (odds ratio = 0.69; 95%CI, 0.57–0.84;  $P < 0.0001$ ;  $I^2 = 92.1\%$ ;  $P$  for heterogeneity  $< 0.0001$ ). **Conclusions:** The findings suggest that a diet high in fruit, vegetables, and whole grains may be associated with reduced risk of frailty. Nevertheless, additional longitudinal studies are needed to confirm the association of dietary patterns with frailty.

## INTRODUCTION

Frailty is a state of poor homeostatic mechanisms in response to stressors as a result of multiple, age-related dysfunctions across physiological systems.<sup>1</sup> Frailty negatively affects quality of life as well as health outcomes such as frequency of falls, hospitalization, cognitive function, fracture, activities of daily living, and mortality in older people.<sup>1–3</sup> A systematic review and

meta-analysis demonstrated that the risk of incident or worsening disability and the combined risk of disability measured by activities of daily living and instrumental activities of daily living were approximately 2-fold higher in frail elderly people than in nonfrail elderly people.<sup>2</sup> Another meta-analysis reported lower mean scores of a physical and mental component summary when the association between frailty and quality-of-life in frail and prefrail older people was compared with

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that in nonfrail older people.<sup>3</sup> In addition, in a 7-year follow-up study, frail individuals had a 63% greater chance of mortality compared with nonfrail participants.<sup>1</sup> Frailty is defined as the presence of at least 3 components of the following physical abnormalities: (1) unintentional weight loss, (2) self-reported exhaustion, (3) weakness (in grip strength), (4) slow walking speed, (5) and low physical activity.<sup>4,5</sup> In view of both the increased life expectancy and the public health burden of aging and frailty,<sup>6,7</sup> new approaches to prevent frailty or delay its progression are needed.

Despite ongoing research to explore effective ways of improving both health status and productive longevity of older adults, there are large gaps in several areas. Certain modifiable environmental factors such as lifestyle, physical activity level, and diet can affect the degenerative aging process.<sup>8</sup> Moreover, they may affect the mechanisms of aging simultaneously and interrelatedly.

An emerging body of evidence supports the potential role of diet in the prevention of frailty. Most studies in this context have focused on single nutrients or foods, revealing that healthy dietary components such as whole grains, low-fat dairy products, and fruit and vegetables are associated with lower risk of frailty.<sup>9–13</sup> However, nutrients and foods consumed in combination often have interactions that can affect health outcomes.<sup>14</sup> Therefore, recent studies have shifted toward investigating dietary patterns rather than single nutrients. For instance, a recent meta-analysis revealed that better adherence to the Mediterranean diet was associated with lower incident frailty risk in the elderly.<sup>15</sup> Dietary patterns are derived by 2 approaches: (1) an a priori approach, which scores an individual's adherence to the recommended dietary guidelines or predefined dietary pattern, and (2) an a posteriori approach, which uses statistical exploratory methods to identify dietary patterns on the basis of the individual's dietary intake.<sup>16,17</sup>

Recent investigations have evaluated the association between dietary patterns and the incidence of frailty. To provide an overview of the role of diet in the risk of frailty, a systematic review of the current literature and a meta-analysis of observational studies were conducted to summarize the association between dietary patterns and risk of frailty.

## METHODS

This systematic review and meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.<sup>18</sup>

**Table 1 PICOS criteria for inclusion and exclusion of studies**

Parameter	Criteria
Population	Human adults
Intervention/exposure	Highest adherence to a healthy/Western dietary pattern
Comparator	Lowest adherence to a healthy/Western dietary pattern
Outcome	Incidence of frailty phenotype
Setting or study design	Observational studies (cohort and cross-sectional)

## Search strategy

Exclusion and inclusion criteria were defined on the basis of the PICOS framework (Table 1). The PubMed, Scopus, and Google Scholar databases were searched for relevant research articles published up to January 2018, using the following keywords: “frail elderly” or “frailty” or “frail older people” AND “dietary pattern\*” or “eating pattern\*” or “food\* pattern\*” or “dietary habit\*” or “diet” or “dietary.” The reference lists of relevant articles or narrative reviews were hand searched. The search was updated until April 2018 using PubMed's email alert service. No limitation was placed on the publication date or the language of articles.

## Study selection

The titles and abstracts of all articles retrieved in the initial search were screened by 2 authors independently (N.R.P.F. and F.H.). After inclusion and exclusion criteria were applied, the full texts of eligible articles were retrieved for further evaluation.

Studies were excluded for the following reasons: (1) they were not original research (published, eg, as letters to the editor, review articles, or editorials), (2) they examined single nutrients, single foods, or single food groups, (3) they did not report frailty as an outcome measure, (4) they lacked data on association measures (odds ratios [ORs] or hazard ratios), or (5) they were conducted in species other than *Homo sapiens*. Studies were included on the basis of the following: (1) they were original observational research (cohort or cross-sectional studies), (2) they examined dietary patterns via an a priori or an a posteriori method, (3) they reported risk of incident frailty as an outcome measure, (4) they reported the association of frailty with dietary patterns in a format that could be included in the analysis, and (5) they were conducted in adult humans without considering any specific age range. Any discrepancies about the screening and selection of studies or the extraction of data were resolved by discussion and consensus.

## Data extraction and quality assessment

Two authors abstracted all eligible studies independently. The following information was extracted from each article: first author, publication year and country, study population, sex and age range of participants, study design and duration of longitudinal studies, sample size, instruments used for dietary assessment, method used to identify dietary patterns, dietary patterns identified, factor loadings per pattern (if available), definition of frailty, adjusted confounders, main statistical findings (ORs or hazard ratios and the corresponding 95% CIs), and conclusion of study. When several adjusted models were provided in an article, the model that adjusted for the largest number of confounders was abstracted.

Since the identified dietary patterns varied across studies, 2 dietary patterns—healthy and unhealthy—were predefined according to the recommendations of different dietary guidelines.<sup>19,20</sup> The prudent/healthy diet was characterized mainly by high consumption or factor loading of fruit, vegetables, whole grains, and fish, while the Western/unhealthy diet was characterized mainly by high consumption or factor loading of meat, processed meat, refined grains, and high-sugar or high-fat snacks.<sup>21</sup> Since dietary patterns were labeled differently across different studies, the dietary patterns with the most similarities to the predefined diets (prudent/healthy and Western/unhealthy) were considered for meta-analysis, regardless of their original label. In studies that identified several healthy or unhealthy dietary patterns using a posteriori methods, a pattern was selected as the main pattern if it explained the largest variation in food groups and/or fulfilled the most criteria of a healthy or an unhealthy diet on the basis of highest factor loadings.

Study quality was assessed using the Newcastle-Ottawa scale for quality assessment.<sup>22</sup> This scale consists of 3 main domains (selection of participants, comparability of participants, and assessment of outcome/exposure) and 8 questions in total. The maximum total score that each cohort study could receive by this scale is 9 stars (2 stars for comparability). In the version adapted for cross-sectional studies, there are 7 questions, and the maximum total possible score is 10. In the present meta-analysis, studies were classified as having high methodological quality when they received 7 or more stars.<sup>23</sup> All studies, regardless of their quality score, were included in the current systematic review.

## Statistical analysis

The original research studies categorized dietary patterns in different ways such as tertiles, quintiles, or objective scores. To combine the results and run a meta-

analysis, the risk of frailty was evaluated in the highest vs the lowest categories of dietary patterns. If risk ratios or hazard ratios were reported in the original article instead of ORs, they were considered the same as ORs when the prevalence of frailty in the study population was  $\leq 20\%$ . If frailty was considered a continuous variable and was reported as a regression coefficient in the original article, then standardized coefficients and their corresponding 95% CIs were converted to ORs and standard errors, as described by da Costa et al.<sup>24</sup> A fixed-effect model was used to estimate the pooled effect when the heterogeneity was low ( $< 25\%$ ).<sup>25</sup> Heterogeneity was evaluated using the  $I^2$  statistic.<sup>25</sup> Subgroup analyses were run to explore the sources of heterogeneity on the basis of the following covariates: study design (cohort/cross-sectional), geographical region of the study (Mediterranean countries/non-Mediterranean countries), sex, methods used to determine dietary pattern (a priori/a posteriori), age group of participants (elderly [ $> 65$  years] versus middle-aged and elderly [ $> 45$  years]), and adjustment/nonadjustment for daily energy intake. Publication bias was evaluated by using a funnel plot and Egger regression test. When bias was present, trim and fill analysis was conducted to detect the contribution of the bias to the overall effect. Sensitivity analysis was performed to explore the relative effect of each study on the pooled estimate by omitting 1 study at a time.  $P$  values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata software (Version 11; StataCorp, College Station, TX).

## RESULTS

### Search results

The screening process of studies is shown in [Figure 1](#). The search strategy retrieved 985 citations (excluding duplicates,  $n = 661$ ). Of these publications, 626 were excluded on the basis of the title and abstract and 21 after the full text was reviewed. Nine cohort studies<sup>26–34</sup> and 4 cross-sectional studies<sup>35–38</sup> with a total of 15 effect sizes (2 additional effect sizes from cohort studies<sup>29,32</sup>) published between 2012 and 2018 were included in the systematic review (effect size = 15) and meta-analysis (effect size = 11) ([Table 2](#)<sup>26–38</sup>).

### Description of studies

Eight studies were conducted in Europe,<sup>27–30,33,34,36,38</sup> 2 in the United States,<sup>25,31</sup> 1 in China,<sup>31</sup> 1 in Taiwan,<sup>37</sup> and 1 in Australia.<sup>35</sup> The sample size of the studies ranged from 560 to 4421 in cohort studies and from 192 to 5922 in cross-sectional studies. All the included

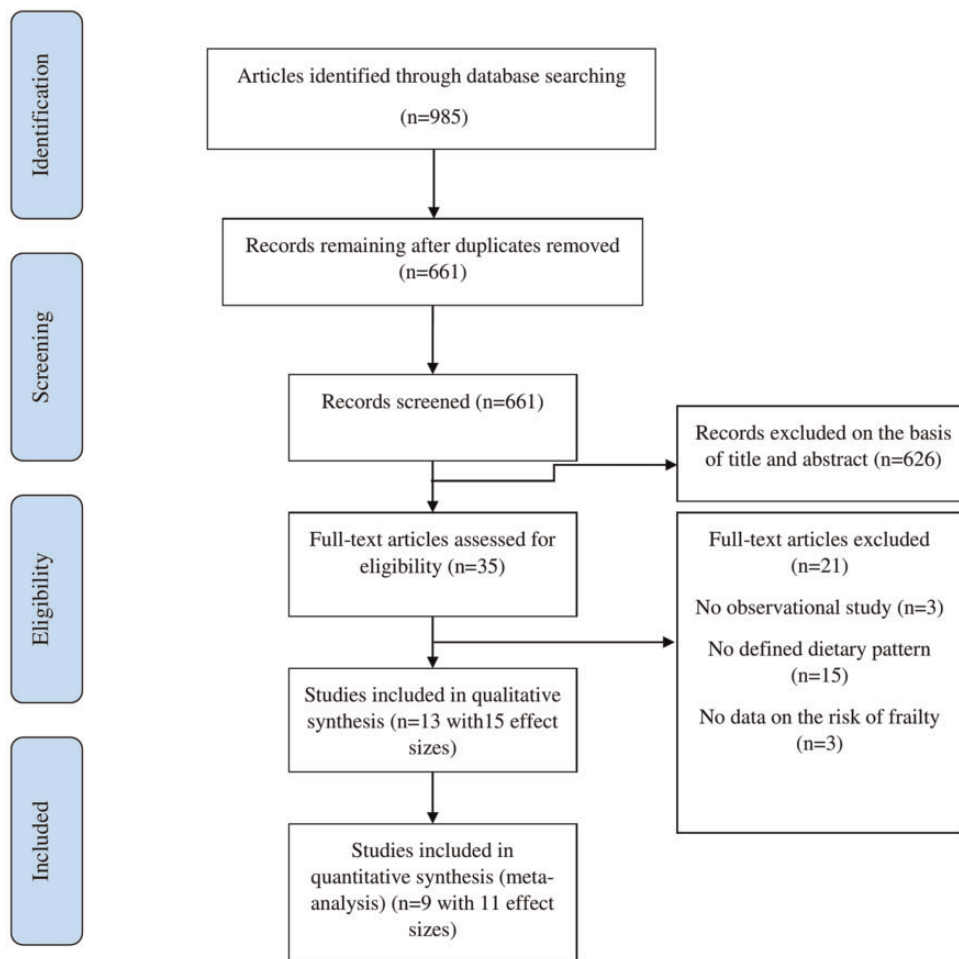


Figure 1 Flow diagram of the literature search process.

studies evaluated the risk of frailty as the endpoint. Participants were aged 45 years and over. Two studies were limited to male participants<sup>32,35</sup> and the remaining studies evaluated both sexes. The majority of studies assessed dietary intakes using a validated food frequency questionnaire ( $n = 9$ ),<sup>26,27,29,31,32,34,36–38</sup> while 1 study used both a food frequency questionnaire and a 24-hour recall<sup>28</sup> and 3 studies used dietary history.<sup>30,33,35</sup> Dietary patterns were defined using the a priori method in 8 studies,<sup>26,27,32–36,38</sup> the a posteriori method in 3 studies,<sup>28,30,37</sup> and both methods in 2 studies.<sup>29,31</sup> Frailty was assessed by means of a variety of instruments. Most studies used the frailty phenotype according to Fried et al<sup>4</sup> ( $n = 9$ ).<sup>27,28,30,32–35,37,38</sup> Two studies used physically oriented definitions,<sup>29,31</sup> 1 study used an index designed to predict falls, disability, and fractures,<sup>26</sup> and another study used an index of various health domains (eg, disabilities, mental health and cognitive function, and chronic diseases).<sup>36</sup> Confounding effects of age, sex, education, and comorbid conditions (including diabetes, hypertension, history of cardiovascular and cerebrovascular diseases, and others listed in the

Charlson Comorbidity Index) were controlled in most studies, but not all.<sup>28,35</sup> Overall, quality scores were high ( $\geq 7$ ) in all of the studies assessed.

## META-ANALYSIS

Results from the meta-analysis of the healthy diet are shown in Figure 2. Individuals with a higher adherence to the healthy diet were less likely to be affected by frailty (OR = 0.69; 95%CI, 0.57–0.84;  $P < 0.0001$ ). There was significant heterogeneity between studies ( $I^2 = 92.1\%$ ;  $P < 0.0001$ ). When studies were stratified by study design (cohort/cross-sectional), sex, tools used to assess dietary intake, and adjustment/nonadjustment for daily energy intake, the results in the subgroups remained consistent with the overall estimate, and heterogeneity had not disappeared (Table 3). However, subgroup analysis based on the methods used to define frailty (phenotype vs index) (Table 3), methods used to determine dietary pattern (a priori/a posteriori) (Figure 2), geographical region of the study (Mediterranean countries/non-Mediterranean countries) (Figure 3), and age group of participants

**Table 2 Characteristics of observational studies examining the association between dietary patterns and frailty**

Reference	Country or region	Study design	Study participants	Follow-up period	Method of dietary assessment/validation	Method used to define frailty (score)	Dietary patterns identified or dietary score used	Method used to define frailty	Adjustment for confounders	Main findings (effect and 95%CI)
Veronese et al (2018) <sup>26</sup>	North America	Cohort	Osteoarthritis initiative (n = 4421; mean age 61.2 y; range 45–79 y; 1857 M and 2564 F; cases: n = 362)	8 y	Validated, interview-based FFQ	MDS (0–55)	High intakes of cereals, potatoes, fruits, vegetables, legumes, and fish; low intakes of meat, poultry, and full-fat dairy products	SOF index. Based on 3 items: unintentional weight loss, the inability to rise from a chair, and poor energy	Age, sex, BMI, physical activity, race, smoking habit, educational level, yearly income, Charlson comorbidity index, daily energy intake	Highest vs lowest adherence: HR = 0.71; 95%CI, 0.50–0.99
Rahi et al (2018) <sup>27</sup>	France	Cohort	Population-based French Three-City Bordeaux cohort (n = 560; age > 75 y; 354 F; cases: n = 79)	2 y	Interview-based FFQ	MDS (0–9)	High intakes of fruits, vegetables, legumes, cereals, fish, seafood, and olive oil; low intakes of meat and dairy products	Slightly modified Fried frailty criteria. Based on 5 items: unintentional weight loss, exhaustion, slowness, weakness, physical activity	Age, sex, education, marital status, presence of diabetes, hypertension, history of cardio- and cerebrovascular diseases, BMI, taking $\geq 5$ drugs/d, cognitive status, and CES-D	Highest vs lowest adherence: OR = 0.32; 95%CI, 0.14–0.72
Pilleron et al (2016) <sup>28</sup>	France	Cohort	Community-dwelling elderly French adults (Bordeaux sample of the Three-City Study; 3C Bordeaux cohort) (n = 972; age > 73 y; 636 F; cases: n = 299)	12 y	Validated, interview-based FFQ and 24-h dietary recall	5 sex-specific dietary clusters characterized by hybrid clustering method	Small eaters: lower intakes of all food groups and lower daily energy intake Healthy pattern: higher fish intake in men and higher fruit and vegetable intake in women Biscuits and snacking pattern: higher intake of snacks, biscuits, and cakes, and a slightly higher energy intake Charcuterie, meat, and alcohol pattern in men; and charcuterie, starchy foods, and alcohol pattern in women Pasta in men, and pizza and sandwiches in women	Fried frailty criteria. Based on 5 items: unintentional weight loss, exhaustion, low energy expenditure, slowness, and weakness	Marital level, educational level, income, multi-morbidity, BMI, depressive symptomatology, and score on MMSE	Men: Small eaters vs healthy eaters: HR = 1.46; 95%CI, 0.77–2.78 Biscuits and snacking vs healthy pattern: HR = 1.35; 95%CI, 0.43–4.24 Charcuterie, meat, and alcohol vs healthy pattern: HR = 0.73; 95%CI, 0.28–1.91 Pasta vs healthy pattern: HR = 2.21; 95%CI, 1.11–4.40 Women: Small eaters vs healthy pattern: HR = 1.30; 95%CI, 0.91–1.86 Biscuits and snacking vs healthy pattern: HR = 1.81; 95%CI, 1.17–2.81 Charcuterie, starchy foods, and alcohol vs healthy pattern: HR = 1.28; 95%CI, 0.85–1.92 Pizza and sandwiches vs healthy pattern: HR = 1.45; 95%CI, 0.75–2.80

(continued)

**Table 2 Continued**

Reference	Country or region	Study design	Study participants	Follow-up period	Method of dietary assessment/validation	Method used to define dietary patterns (score)	Dietary patterns identified or dietary score used	Method used to define frailty	Adjustment for confounders	Main findings (effect and 95%CI)
de Haas et al (2018) <sup>29</sup>	The Netherlands	Cross-sectional and cohort	Population-based Rotterdam Study (n = 2632 in cross-sectional analysis and n = 2253 in cohort analysis; 1099 M; age > 45 y)	4 y	Validated 389-item self-administered semiquantitative FFQ	(1) A priori-defined index for diet quality (modified Dutch Healthy Diet index) (0–80) and (2) A posteriori-defined dietary patterns using principal component analysis	Dutch Health Diet index: high intakes of vegetables, fruit and fish juice, fish and fish oil, and fiber; low intakes of saturated fatty acids, <i>trans</i> fatty acids, alcohol, sodium, and acidic drinks and foods; high physical activity Traditional: high intakes of savory snacks, legumes, eggs, fried potatoes, alcohol, processed meat, and soup Carnivore: high intakes of red meat and poultry; low intake of meat replacements Health Conscious: high intakes of whole grains, vegetables, fruit, and nuts	Slightly adapted version of the frailty index designed for the Rotterdam Study. Based on 38 health-related variables covering several health domains: functional status (n = 13), health conditions (n = 6), cognition (n = 6), diseases (n = 6), nutritional status (n = 3), and mood (n = 4)	Age, sex, smoking, educational level, income, physical activity, supplement use, and total energy intake	Cross-sectional association: A priori pattern: $\beta = -0.07$ ; 95%CI, $-0.10$ to $-0.03$ A posteriori patterns: Traditional: $\beta = 0.01$ ; 95%CI, $-0.03$ to $0.05$ Carnivore: $\beta = 0.05$ ; 95%CI, $0.01$ – $0.07$ Health conscious: $\beta = 0.03$ ; 95%CI, $-0.01$ to $0.07$ Cohort association: A priori pattern: $\beta = -0.07$ ; 95%CI, $-0.10$ to $-0.04$ A posteriori patterns: Traditional: $\beta = -0.07$ ; 95%CI, $-0.11$ to $-0.04$ Carnivore: $\beta = 0.04$ ; 95%CI, $-0.01$ to $0.07$ Health conscious: $\beta = 0.01$ ; 95%CI, $-0.03$ to $0.04$
Leon-Munoz et al (2015) <sup>30</sup>	Spain	Cohort	Seniors-ENRICA cohort, noninstitutionalized individuals (n = 1872; age $\geq 60$ y; 51.5% F; cases: n = 96)	3.5 y	Validated self-reported diet history	Factor analysis	Healthy: high intakes of olive oil and vegetables Westernized: high intakes of refined bread, whole dairy products, and red and processed meat; low consumption of fruit and vegetables	Fried frailty criteria. Based on 5 items: unintentional weight loss, exhaustion, physical activity, slowness, and weakness	Number of frailty components at baseline, sex, age, educational level, occupation, tobacco, BMI, energy intake (kcal/d), cardiovascular disease, diabetes mellitus, cancer, asthma or chronic bronchitis, osteomuscular disease, depression requiring treatment, number of drug treatments, and score on MMSE	Highest vs lowest tertile: Healthy: OR = 0.40; 95%CI, 0.20–0.81 Westernized: OR = 1.61; 95%CI, 0.85–3.03

(continued)

**Table 2 Continued**

Reference	Country or region	Study design	Study participants	Follow-up period	Method of dietary assessment/validation	Method used to define dietary patterns (score)	Dietary patterns identified or dietary score used	Method used to define frailty	Adjustment for confounders	Main findings (effect and 95%CI)
Chan et al (2015) <sup>31</sup>	China	Cohort	Chinese community-dwelling men and women (n = 2724; age ≥ 65 y; 50.3% F; cases: n = 31)	4 y	Validated interview-based semiquantitative FFQ	A priori and a posteriori dietary patterns identified by factor analysis; ORs per 10-unit increase in diet quality score	A priori: DQI-I: an index of variety, adequacy, moderation, and overall balance (0–94), with higher score indicating better diet quality MDS (0–9) A posteriori: vegetables-fruit: high intakes of tomatoes, dark green and leafy vegetables, cruciferous vegetables, starchy vegetables, other vegetables, fruits, soy, legumes, and mushrooms and fungi Snacks, drinks, milk products: high intakes of condiments, coffee, fast foods, nuts, French fries and potato chips, milk and milk products, whole grains, sweets and desserts, and beverages Meat-fish: high intakes of dim sum, red and processed meats, fish and seafood, poultry, and wine	Morley frailty scale. Based on 5 items: fatigue, resistance, ambulation, having more than 5 diseases, and unintentional weight loss	Age, sex, BMI, energy intake, Physical Activity Scale for the Elderly, educational level, smoking status, alcohol use, Geriatric Depression Scale category, cognitive screening instrument for dementia category, living alone, and marital status at baseline	DQI-I: OR=0.69; 95%CI, 0.47–1.02 MDS: OR=1.06; 95%CI, 0.83–1.36 Vegetables-fruits: OR=0.76; 95%CI, 0.48–1.21 Snacks-drinks-milk and milk products: OR=0.78; 95%CI, 0.48–1.28 Meat-fish: OR=0.95; 95%CI, 0.63–1.41
Shikany et al (2014) <sup>32</sup>	USA	Cross-sectional and cohort	Osteoporotic Fractures in Men Study (n = 5922 for cross-sectional and 2423 for cohort; age > 65 y; cases at baseline: n = 496; cases for cohort: n = 25)	4.6 y	Validated self-reported Block 98 semiquantitative FFQ	A priori, DQI-R	DQI-R: percent energy intake from fat; percent energy intake from saturated fat; dietary cholesterol; fruit servings; vegetable servings; grain servings; calcium intake; iron intake; dietary diversity; and dietary moderation; scored from 0 (lowest quality) to 100 (highest quality)	Fried frailty criteria. Based on 5 items: appendicular lean mass (rather than weight loss), poor energy, weakness, slowness, low physical activity	Age, race, clinical center where participants were recruited, education, marital status, smoking, health status, medical conditions, BMI, and energy intake	Cross-sectional analysis: Highest vs lowest quintile: OR=0.44; 95%CI, 0.30–0.63 Cohort analysis: Highest vs lowest quintile: OR=0.67; 95%CI, 0.37–0.1.22

(continued)

**Table 2 Continued**

Reference	Country or region	Study design	Study participants	Follow-up period	Method of dietary assessment/validation	Method used to define dietary patterns (score)	Dietary patterns identified or dietary score used	Method used to define frailty	Adjustment for confounders	Main findings (effect and 95%CI)
León-Muñoz et al (2014) <sup>33</sup>	Spain	Cohort	Seniors-ENRICA (Estudio de Nutrición y Riesgo Cardiovascular) cohort of community-dwelling men and women (n = 1815; age > 60 y; cases: n = 137)	3.5 y	Validated, self-reported, computerized diet history that included 880 foods in the preceding year	MEDAS score (0–14) and MDS (0–9)	MEDAS: consists of 12 items, with targets for food consumption, and another 2 items, with targets for food-intake habits characteristic of the Mediterranean diet in Spain MDS: high intakes of vegetables, legumes, fruits and nuts, grains, and fish; low intakes of red meat, poultry, and dairy products	Fried frailty criteria. Based on 5 items: unintentional weight loss, exhaustion, low physical activity, slowness, and weakness	Sex, age, educational level, tobacco use, BMI, energy intake (kcal/d), cardiovascular disease, diabetes mellitus, cancer, asthma or chronic bronchitis, osteomuscular disease, depression requiring treatment, and number of drug treatments	Highest vs lowest MEDAS score: OR=0.65; 95%CI, 0.40–1.04 MDS: OR=0.48; 95%CI, 0.30–0.77
Talegawkar et al (2012) <sup>34</sup>	Italy	Cohort	Invecchiare in Chianti study of community-living persons (n = 690; 51.7% F; age ≥ 65 y)	6 y	Validated self-reported FFQ	MDS (0–9)	High intakes of vegetables, legumes, fruits, cereal, and fish; high ratio of monounsaturated to saturated fats; low intakes of meat and dairy products	Fried frailty criteria. Based on 4 items: exhaustion, slowness, weakness, and low physical activity	Age, sex, energy intake (kcal/d), status of frailty (or its components) at previous examinations, BMI, education (y), MMSE score, current smoker (yes/no), and presence of chronic diseases (yes/no)	Highest vs lowest tertile: OR=0.30; 95%CI, 0.14–0.66
Ribeiro et al (2017) <sup>35</sup>	Australia	Cross-sectional	CHAMP study of community-dwelling men (n = 794; age > 74 y; cases: n = 65)	–	Validated interview-based dietary history questionnaire that covered usual intake over the past 3 mo	DGI+2013 (food-based dietary index developed to investigate adults' adherence to the Australian Dietary Guidelines (0–130)	High intakes of fruit, vegetables, legumes, beans, grain foods (mostly whole grains and/or high-fiber cereal varieties), meats and poultry, fish, eggs, tofu, nuts, seeds, milk, yogurt, cheese, and water; low or moderate intakes of alcohol, sugar, unsaturated oils, spreads, fats, salt, and foods high in saturated fatty acids	Fried frailty criteria. Based on 5 items: unintentional weight loss, exhaustion, low physical activity, slowness, and weakness (with the same criteria and cutoff points)	Education and income	Estimate for total score of DGI-2013 ( $r^2 = -0.048$ ), 95%CI, -0.073 to -0.023

(continued)



**Table 2 Continued**

Reference	Country or region	Study design	Study participants	Follow-up period	Method of dietary assessment/validation	Method used to define dietary patterns (score)	Dietary patterns identified or dietary score used	Method used to define frailty	Adjustment for confounders	Main findings (effect and 95%CI)
Ntanasi et al (2018) <sup>36</sup>	Greece	Cross-sectional	HELIAID (a population-based, multidisciplinary study) (n = 1740; 59% F; age 65–99 y; cases: n = 325)	–	Validated interview-based 69-item semiquantitative FFQ	MDS (0–55)	High intakes of cereals, potatoes, fruits, vegetables, legumes, and fish; low intakes of meat, poultry, and full-fat dairy products	Rockwood frailty index. Based on 61 age-related deficits; including diseases, syndromes, functionality in activities of daily living, cognitive decline, mood disorders, and performance on physical activities	Sex, age group, educational level, dementia and depression diagnosis, number of comorbidities, and number of concomitant medications	Highest vs lowest tertile: OR = 0.702; 95%CI, 0.510–0.948. As a continuous variable: OR = 0.959; 95%CI, 0.931–0.987
Lo et al (2017) <sup>37</sup>	Taiwan	Cross-sectional	Nutrition and Health Survey in Taiwan (n = 923; 52.8% M; age > 65 y; cases: n = 50)	–	Validated interview-based 79-item FFQ	A posteriori method, reduced rank regression	High intakes of fruits, nuts and seeds, tea, vegetables, whole grains, shellfish, milk, and fish	Modified Fried frailty criteria. Based on 5 items: unintentional weight loss, exhaustion, low physical activity, slowness, and weakness	Age, sex, sampling strata, current smoker status, current alcohol status, BMI, number of drug treatments, and score on MMSE	Highest vs lowest tertile: OR = 0.12; 95%CI, 0.02–0.76
Bollwein et al (2013) <sup>38</sup>	Germany	Cross-sectional	German part of EPIC study; community-dwelling older volunteers (n = 192; 64.6% F; age > 75 y; cases: n = 29)	–	Validated interview-based FFQ	Alternate MDS (0–9)	High intakes of vegetables, legumes, fruits, unrefined cereals, and nuts; high MUFA:SFA ratio; moderate intakes of alcohol and fish; low intake of red and processed meat intake of milk and milk products not included in score	Fried frailty criteria. Based on 5 items: unintentional weight loss, exhaustion, low physical activity, slowness, and weakness	Age, sex, energy intake, comorbidity, and educational level	Highest vs lowest category: OR = 0.19; 95%CI, 0.05–0.82

*Abbreviations:* CES-D, Center for Epidemiologic Studies Depression Scale; CHAMP, Concord Health and Ageing in Men Project; DGI-1, Dietary Quality Index-International; DQI-R, Diet Quality Index-Revised; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; HELIAID, Hellenic Longitudinal Investigation of Aging and Diet; HR, hazard ratio; M, male; MDS, Mediterranean Diet Score; MEDAS, Mediterranean Diet Adherence Screener; MMSE, Mini-Mental State Examination; OR, odds ratio; SOF, Study of Osteoporotic Fracture.

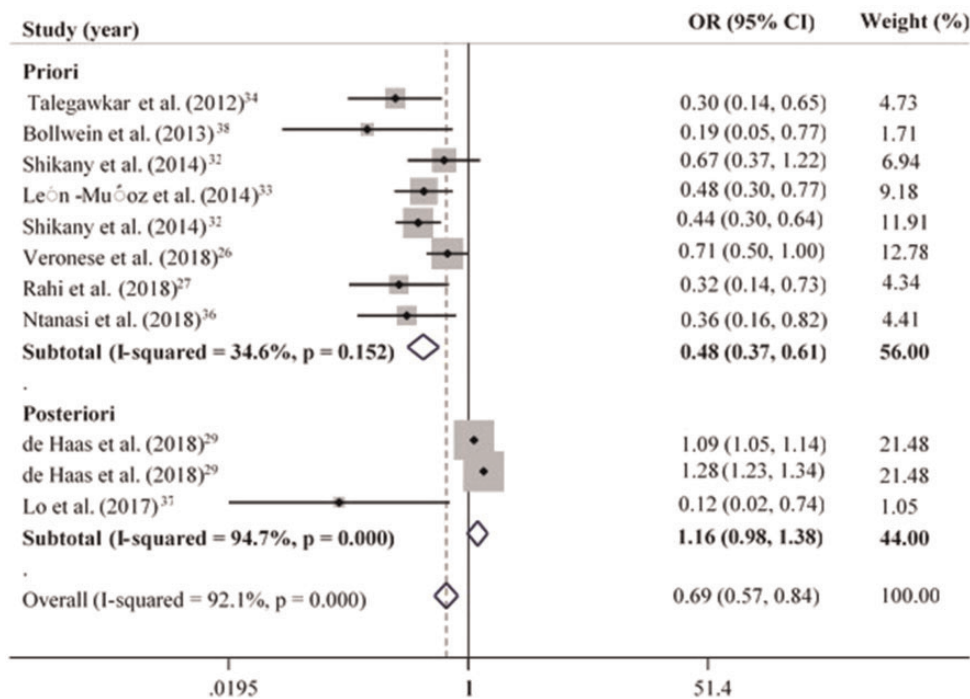


Figure 2 Subgroup analysis, based on the method used to define dietary pattern, to quantify the association between healthy dietary patterns and frailty.

Table 3 Subgroup analysis for the association of healthy dietary patterns with frailty

	Effect size	$I^2$	Odds ratio	95%CI	$P_{\text{between}}$
Study design					< 0.0001
Cohort	6	87.1	0.58	0.37–0.91	
Cross-sectional	5	92.6	0.42	0.18–0.98	
Sex					< 0.0001
Male and female	9	91.7	0.78	0.64–0.95	
Male	2	27.4	0.51	0.34–0.75	
Dietary tool					< 0.0001
FFQ	10	92.0	0.73	0.60–0.89	
Diet history	1		0.48	0.30–0.77	
Energy adjustment					< 0.0001
Adjusted	8	93.2	0.78	0.64–0.94	
Nonadjusted	3	0.0	0.31	0.18–0.54	
Frailty definition					< 0.0001
Phenotype	8	43.8	0.46	0.35–0.62	
Index	3	95.0	1.13	0.95–1.34	

Abbreviation: FFQ, food frequency questionnaire.

(elderly vs middle-aged and elderly) (Figure 4) demonstrated significant subgroup effects on the risk of frailty. In the subgroup analysis based on the definition of frailty, no significant association was found between the healthy diet and risk of frailty in studies using the index to define frailty, while in studies using the phenotype, there was a significant reduction in the risk of frailty.

Higher adherence to the healthy diet was associated with decreased risk of frailty in 3 subgroups: (1) studies conducted in Mediterranean countries (OR=0.39,

95%CI, 0.28–0.55;  $P < 0.0001$ ), (2) studies that used an a priori method to identify dietary patterns (OR=0.48, 95%CI, 0.37–0.61;  $P < 0.0001$ ), and (3) studies that were conducted only among the elderly (OR=0.40, 95%CI, 0.30–0.54;  $P < 0.0001$ ). The heterogeneity level decreased considerably in these subgroups (Mediterranean countries:  $I^2 = 0.0\%$ ;  $P = 0.701$ ; in the studies with the a priori method:  $I^2 = 34.6\%$ ;  $P = 0.152$ ; and in the elderly subgroup:  $I^2 = 10.7\%$ ;  $P = 0.348$ ). There was an asymmetry in the funnel plot, and the Egger test ( $P = 0.002$ ) revealed a possible publication bias. Consistently, on the basis of the trim and fill algorithm, the adjusted value showed an inverse association between the healthy dietary pattern and risk of frailty (OR = 0.694; 95%CI, 0.573–0.840). Comparing the adjusted value (0.694) with the original estimate (0.69) indicates a small contribution of the study effect to the original results. Findings from the sensitivity analysis indicated that excluding an individual study would not change the significance of the findings.

## Narrative review

Data from 9 studies were included in the meta-analysis.<sup>26,27,29,32–34,36–38</sup> Three cohort studies<sup>27,33,34</sup> and 1 cross-sectional study<sup>38</sup> evaluated adherence to the Mediterranean diet using the method proposed by Trichopoulou et al,<sup>39</sup> while 1 cohort study<sup>26</sup> and 1 cross-sectional study<sup>36</sup> used the method proposed by

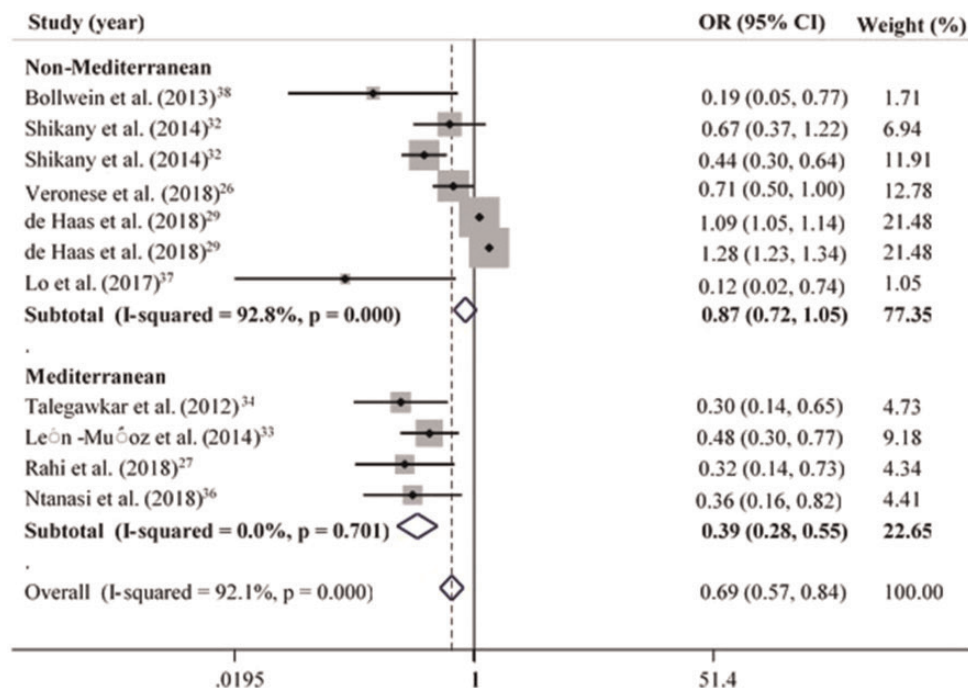


Figure 3 Subgroup analysis, based on the geographical region of the study, to quantify the association between healthy dietary patterns and frailty.

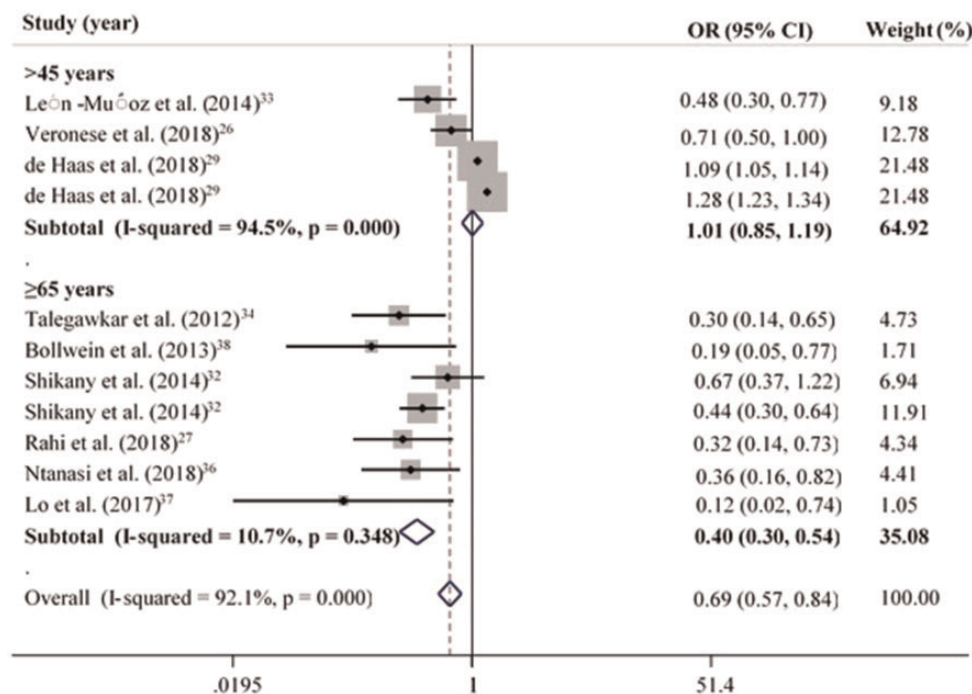


Figure 4 Subgroup analysis, based on the age group of participants, to quantify the association between healthy dietary patterns and frailty.

Panagiotakos et al.<sup>40</sup> All these studies revealed an inverse association between adherence to the Mediterranean diet and frailty risk. de Haas et al.<sup>29</sup>

assessed the cross-sectional and longitudinal associations of dietary patterns derived from both a priori and a posteriori methods. In the studies that investigated

diets derived by a priori methods, they found that greater adherence to the Dutch Healthy Diet index (Table 2) was slightly inversely correlated with the risk of frailty in both cross-sectional and cohort analyses. Using the principle component analysis, they identified 3 dietary patterns: traditional, carnivore, and health conscious (Table 2). In the cross-sectional analysis, they found a positive correlation between the carnivore pattern and frailty and no significant correlation between the 2 other patterns and frailty. In the cohort analysis, the traditional pattern was inversely correlated with frailty, while the other 2 patterns were not significantly related to frailty risk.<sup>29</sup> Another cohort study evaluated the risk of frailty across the quintiles of adherence to the Diet Quality Index Revised (Table 2) using both cross-sectional and cohort data.<sup>32</sup> The cross-sectional analysis showed that individuals in the highest quintile had a lower risk for frailty compared with those in the lowest quintile, although the cohort analysis showed no significant association. In another cross-sectional analysis, conducted in Taiwanese participants, Lo et al<sup>37</sup> used reduced rank regression and identified a dietary pattern rich in fruit, nuts and seeds, tea, vegetables, whole grains, shellfish, milk, and fish that was inversely related to frailty risk in a dose-response manner.

Data from 4 studies could not be used in the meta-analysis because the dietary patterns identified in these studies were not in accordance with the definitions of a healthy dietary pattern<sup>30,35</sup> used for the current meta-analysis or because the studies reported data in a format that could not be pooled and analyzed with other estimates.<sup>28,31</sup> Therefore, these studies are summarized here in a narrative review. One study in Chinese participants assessed the risk of incident frailty per 10-unit increase in the Mediterranean diet score and showed no significant association (multivariate adjusted OR = 1.06; 95%CI, 0.83–1.36).<sup>31</sup> Other studies used different definitions of a healthy diet. A Spanish study found no significant association between frailty risk and a healthy diet rich in vegetables and olive oil.<sup>30</sup> This study was the only study that assessed the relationship of a Western dietary pattern with incident frailty. The authors observed that the Western dietary pattern—high in refined grains, high-fat dairy products, and red and processed meats and low in fruit and vegetables—was not related to the risk of frailty after 3.5 years of follow-up.<sup>30</sup> Another study defined a healthy dietary pattern as high consumption of fish in men and high consumption of fruit and vegetables in women,<sup>28</sup> which was not in accordance with the definition of a healthy diet in the current meta-analysis. The authors found that greater adherence to the “pasta” pattern in men and the “biscuits and snacking” pattern in women was associated with higher risk of frailty when compared with the

“healthy” pattern.<sup>28</sup> However, the “meat and alcohol,” “charcuterie and starchy foods,” and “pizza and sandwiches” patterns were not associated with frailty.<sup>28</sup> A cross-sectional study assessed the association between adherence to the Australian Dietary Guidelines 2013 and frailty in Australians.<sup>35</sup> Some dietary components in these guidelines were not congruent with the healthy diet as defined in the current meta-analysis (ie, meat and dairy products). The authors found an inverse association between adherence to the Australian Dietary Guidelines and frailty risk after adjustment for educational status and income.<sup>35</sup>

## DISCUSSION

This systematic review and meta-analysis evaluated the association of dietary patterns with the risk of frailty in cohort and cross-sectional studies. The findings demonstrated an inverse association between the healthy dietary pattern and the risk of frailty, with substantial heterogeneity between studies. Subgroup analysis revealed that this association depends on the geographical region of the study, the methods used to define frailty and identify dietary patterns, and the age group of participants.

The healthy diet is based on high consumption of fruit, vegetables, and whole grains as well as low intakes of high-fat dairy products, red and processed meat, and refined grains.<sup>19,20</sup> In general, this meta-analysis revealed an inverse association between adherence to a healthy diet and risk of frailty, although the results were heterogeneous. Various potential mechanisms underlying the health benefits of a healthy diet have been reported in previous literature. The anti-inflammatory properties and the antioxidants that characterize a healthy diet may delay the development of frailty.<sup>41</sup> This hypothesis has been confirmed in several prospective studies in which antioxidant consumption was linked to lower incidence of frailty,<sup>42–44</sup> while a proinflammatory diet was associated with increased risk of frailty.<sup>45</sup> Moreover, there is evidence that a healthy dietary pattern is linked to a lower risk of various chronic diseases, including cardiovascular disease, diabetes,<sup>46</sup> insulin resistance and metabolic syndrome,<sup>47</sup> depression,<sup>48</sup> and impaired cognitive function,<sup>49</sup> whereas the Western dietary pattern has been directly linked to these diseases.<sup>47,48,50,51</sup> Since diabetes mellitus, metabolic syndrome, insulin resistance,<sup>52,53</sup> endothelial dysfunction,<sup>54</sup> and depression and poor cognitive function<sup>55</sup> are known as some relevant risk factors for frailty, it is probable that a healthy diet decreases the risk of frailty by improving protein pathways involved in these metabolic abnormalities.<sup>50,56,57</sup>

Although comorbidity can influence physical conditions and frailty risk, the current analysis was performed by using the estimates adjusted for the largest numbers of confounders. In most studies included in this meta-analysis, the confounding effects of certain comorbid conditions have been controlled. Therefore, this may suggest that a favorable association between the healthy dietary pattern and frailty is independent from the effects of a healthy diet on health conditions. Some studies, but not all,<sup>30</sup> showed that healthy diets may be associated with lower odds of sarcopenia,<sup>58,59</sup> unintentional weight loss, slow walking speed, and low physical activity.<sup>38</sup> Conversely, the Western dietary pattern has been directly related to all components of frailty, particularly unintended weight loss and low walking speed.<sup>29</sup>

The subgroup analysis revealed that the method used to identify dietary patterns was a potential source of heterogeneity. The nonsignificant association in studies with a posteriori methods might be attributable to the lower mean age of the study participants, as the mean age in the study of de Haas et al<sup>29</sup> was 57 years, and it is less likely that middle-aged people experience frailty. In addition, a posteriori methods are subjective techniques; therefore, different procedures at almost every step (eg, classifying food items into food groups and determining the number and characteristics of derived patterns) may lead to variations in dietary patterns across studies.<sup>14,60</sup> Moreover, dietary patterns derived from a posteriori methods may have some shared components despite being predominantly different in composition and, as a consequence, may not be easily comparable. However, to minimize the risk of bias, the most common dietary patterns and the matching factor loadings for common foods across studies were selected, a method used in another other meta-analysis that investigated dietary patterns.<sup>21</sup>

The subgroup analysis indicated that geographical region was related to the association between diet and risk of frailty. Although heterogeneity disappeared in the Mediterranean countries after the subgroup analysis, it remained highly significant in the other countries. It might be explained by the use of both a priori and a posteriori methods in the “other countries” subgroup, which was found to be a potential source of heterogeneity per se, while all studies in the “Mediterranean countries” subgroup assessed the Mediterranean diet by the a priori method. In addition, food availability as well as culturally related dietary habits may affect consumption of certain foods. For example, fresh vegetables and fruits are much more available and more reasonably priced in Mediterranean countries than in non-Mediterranean countries.<sup>61</sup> In addition, some factors related to culture and ethnicity, such as cooking

methods and food grouping, may affect the associations. For example, the traditional and popular foods of the Mediterranean countries are largely healthy foods. As a result, Mediterranean populations typically have greater intakes of nutritious foods.<sup>61</sup>

The age of participants was also found to be another potential source of heterogeneity. The results showed an inverse significant association between adherence to the healthy diet and risk of frailty in studies that were conducted among the elderly ( $\geq 65$  years), while no significant association was found in studies with middle-aged and elderly participants ( $> 45$  years). This might be explained by the cumulative effect of age-related decline in various physiological systems. Indeed, aging is associated with a gradual decline in several physiological systems, which in turn increases vulnerability to sudden changes in health status (eg, falls, delirium, and disability), even following a relatively minor stressor event.<sup>1</sup> Considering the role of inflammation and loss of muscle strength and power in the elderly, both inflamm-aging<sup>62</sup> and reduced physical activity levels in older adults<sup>63</sup> may provide further explanation for this finding. Moreover, older people usually have anorexia of aging, which is defined as age-related reduction in appetite and food intake. This might be caused by a combination of factors that may be physiological (eg, poor smelling and tasting capabilities and delayed gastric emptying), pathophysiological (eg, cognitive dysfunction and poor oral health status), or social (eg, isolation, living alone, poverty) in nature.<sup>64</sup> In the setting of inadequate protein and energy intake, even the healthiest diet will lead to sarcopenia and frailty.<sup>65</sup> Therefore, to maximize the benefits of a healthy dietary pattern, it would be worthwhile to screen the elderly for appetite loss and to treat those at risk.

Unexplained heterogeneity between studies in some subgroups might be attributable to the socioeconomic status of the study populations. Several studies reported that people with higher levels of education and income were less likely to experience frailty.<sup>29,31,32,36,38</sup> Furthermore, food price and overall unaffordability of a healthy diet are pivotal barriers to healthy eating for people with lower incomes.<sup>66</sup> Existing evidence indicates that people with lower socioeconomic status consume lower-quality diets and are more vulnerable to increasing food prices.<sup>67</sup> However, in the present meta-analysis, there was not enough information available to assess associations according to the socioeconomic status of study populations.

The present meta-analysis has several limitations, the main one being the small number of studies included. Future prospective cohort studies are warranted to examine the link between dietary patterns and incident frailty. A second limitation is some interstudy

inconsistency in reference points and interval units caused by the method of reporting dietary intake in observational nutritional epidemiological studies; therefore, only information of the highest category of dietary pattern or dietary score was extracted and included in the meta-analysis. Although the interval collapsing method (in which information of all categories is extracted and used in analysis) might be advantageous over the highest vs lowest method, its results would not differ from those of the highest vs lowest method in terms of directionality and significance.<sup>68</sup> A third limitation is that the studies included in this meta-analysis assessed dietary intake using different tools that have their own measurement errors; therefore, a combination of measurement error and misclassification of participants may have dramatically affected the results. A fourth limitation, possibly, is the inclusion of the a posteriori-identified dietary patterns, since there may have been considerable differences in dietary patterns between countries. In addition, factor loadings of individual foods varied between different populations, which may have led to misclassification of dietary patterns. Nevertheless, both healthy and unhealthy food items were consistently considered between included studies to reduce misclassification bias. The fifth limitation is the lack of a cutoff level to quantitatively determine adherence to a healthy dietary pattern. In addition, all food items in this analysis were assessed together within a dietary pattern, and therefore it is not possible to qualitatively determine the specific role of each individual food item in relation to frailty risk. A sixth limitation is that the observational nature of the studies included in this meta-analysis may have prevented the confounding effect of residual and unknown confounders from being ruled out, even after adjustments for known and speculated confounders. This may be important because dietary patterns may be indicators of a lifestyle in general. However, the statistical analysis was conducted on fully adjusted models, which were controlled for various common confounders, to minimize the effects of confounders. A seventh limitation is that some studies included in the current meta-analysis were cross-sectional studies, which do not allow causality to be determined. However, in the subgroup analysis, the results of the cohort studies, which investigate a causal relationship,<sup>69</sup> were found to be remarkably similar to the results of the cross-sectional studies, thereby indicating the robustness of the findings of the meta-analysis. Finally, the significant publication bias in this meta-analysis is another limitation; however, even after the trim and fill analysis was conducted, the results did not change considerably.

This study also has its strengths. To the best of knowledge, this is the first meta-analysis summarizing

the association of dietary patterns with frailty in cohort and cross-sectional studies. The findings are in line with the results of an earlier meta-analysis that demonstrated an inverse association between adherence to the Mediterranean diet and the incidence of frailty in prospective studies.<sup>15</sup> Nevertheless, in the current study, other dietary patterns derived from both a posteriori and a priori methods, rather than the Mediterranean diet, were examined in relation to frailty risk. The results showed that the region in which a study was conducted and the method used to define dietary patterns are both potential sources of heterogeneity.

## CONCLUSION

In summary, a healthy diet has a strong potential to reduce the risk of frailty in older adults. At this time, prospective studies are limited in number, and thus there is a need for more clinical trials and population-based prospective cohort studies to examine the causality between a healthy diet and frailty and to determine which components of a healthy diet contribute to the prevention of frailty.

## Supporting Information

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

*Table S1* PRISMA 2009 checklist

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The authors alone are responsible for the content and writing of this review.

*Author contributions.* F.H. conceived the review and analyzed the data. F.H. and N.R.P.F. contributed to the literature search and data extraction. All authors contributed to the drafting and review of the manuscript and approved the final draft for submission.

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## REFERENCES

1. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet*. 2013;381:752–762.
2. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. *Disabil Rehabil*. 2017;39:1897–1908.
3. Kojima G, Iliffe S, Jivraj S, et al. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. *J Epidemiol Community Health*. 2016;70:716–721.

4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156.
5. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14:392–397.
6. Buckinx F, Rolland Y, Reginger JY, et al. Burden of frailty in the elderly population: perspectives for a public health challenge. *Arch Public Health*. 2015;73:19. doi:10.1186/s13690-015-0068-x
7. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. *Lancet*. 2015;385:549–562.
8. Södergren M. Lifestyle predictors of healthy ageing in men. *Maturitas*. 2013;75:113–117.
9. García-Esquinas E, Rahi B, Peres K, et al. Consumption of fruit and vegetables and risk of frailty: a dose–response analysis of 3 prospective cohorts of community-dwelling older adults. *Am J Clin Nutr*. 2016;104:132–142.
10. Ribeiro SM, Morley JE, Malmstrom TK, et al. Fruit and vegetable intake and physical activity as predictors of disability risk factors in African-American middle-aged individuals. *J Nutr Health Aging*. 2016;20:891–896.
11. Lana A, Rodríguez-Artalejo F, Lopez-García E. Dairy consumption and risk of frailty in older adults: a prospective cohort study. *J Am Geriatr Soc*. 2015;63:1852–1860.
12. Kobayashi S, Asakura K, Suga H, et al. Inverse association between dietary habits with high total antioxidant capacity and prevalence of frailty among elderly Japanese women: a multicenter cross-sectional study. *J Nutr Health Aging*. 2014;18:827–839.
13. Jacobs DR Jr, Hohe C, Mursu J, et al. Whole grain intake, incident hip fracture and presumed frailty in the Iowa Women's Health Study. *Br J Nutr*. 2010;104:1537–1543.
14. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol*. 2002;13:3–9.
15. Kojima G, Avgerinou C, Iliffe S, et al. Adherence to Mediterranean diet reduces incident frailty risk: systematic review and meta-analysis. *J Am Geriatr Soc*. 2018;66:783–788.
16. Schulze MB, Hoffmann K. Methodological approaches to study dietary patterns in relation to risk of coronary heart disease and stroke. *Br J Nutr*. 2006;95:860–869.
17. Schulze MB, Hu FB. Dietary patterns and risk of hypertension, type 2 diabetes mellitus, and coronary heart disease. *Curr Atheroscler Rep*. 2002;4:462–467.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006–1012.
19. US Department of Health and Human Services and US Department of Agriculture. *Dietary Guidelines for Americans 2015–2020*. 8th ed. <http://health.gov/dietaryguidelines/2015/guidelines/>. Published December 2015. Accessed October 2, 2018.
20. National Health and Medical Research Council. *Australian Dietary Guidelines*. <https://www.nhmrc.gov.au/guidelines-publications/n55>. Published February 2013. Accessed October 2, 2018.
21. Lai JS, Hiles S, Bisquera A, et al. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *Am J Clin Nutr*. 2014;99:181–197.
22. Wells GA, Shea D, O'Connell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Published 2016. Accessed March 30, 2018.
23. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.
24. da Costa BR, Rutjes AW, Johnston BC, et al. Methods to convert continuous outcomes into odds ratios of treatment response and numbers needed to treat: meta-epidemiological study. *Int J Epidemiol*. 2012;41:1445–1459.
25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
26. Veronese N, Stubbs B, Noale M, et al. Adherence to a Mediterranean diet is associated with lower incidence of frailty: a longitudinal cohort study. *Clin Nutr*. 2018;37:1492–1497.
27. Rahi B, Ajana S, Tabue-Teguio M, et al. High adherence to a Mediterranean diet and lower risk of frailty among French older adults community-dwellers: results from the Three-City-Bordeaux Study. *Clin Nutr*. 2018;37:1293–1298.
28. Pilleron S, Ajana S, Jutand MA, et al. Dietary patterns and 12-year risk of frailty: results from the Three-City Bordeaux Study. *J Am Med Dir Assoc*. 2017;18:169–175.
29. de Haas SCM, de Jonge EAL, Voortman T, et al. Dietary patterns and changes in frailty status: the Rotterdam study. *Eur J Nutr*. 2018;57:2365–2375.
30. León-Muñoz LM, García-Esquinas E, López-García E, et al. Major dietary patterns and risk of frailty in older adults: a prospective cohort study. *BMC Med* 2015;13:11. doi:10.1186/s12916-014-0255-6
31. Chan R, Leung J, Woo J. Dietary patterns and risk of frailty in Chinese community-dwelling older people in Hong Kong: a prospective cohort study. *Nutrients* 2015;7:7070–7084.
32. Shikany JM, Barrett-Connor E, Ensrud KE, et al. Macronutrients, diet quality, and frailty in older men. *J Gerontol A Biol Sci Med Sci*. 2014;69:695–701.
33. León-Muñoz LM, Guallar-Castillón P, López-García E, et al. Mediterranean diet and risk of frailty in community-dwelling older adults. *J Am Med Dir Assoc* 2014;15:899–903.
34. Talegawkar SA, Bandinelli S, Bandeen-Roche K, et al. A higher adherence to a Mediterranean-style diet is inversely associated with the development of frailty in community-dwelling elderly men and women. *J Nutr*. 2012;142:2161–2166.
35. Ribeiro RV, Hirani V, Senior AM, et al. Diet quality and its implications on the cardio-metabolic, physical and general health of older men: the Concord Health and Ageing in Men Project (CHAMP). *Br J Nutr*. 2017;118:130–143.
36. Ntanasi E, Yannakoulia M, Kosmidis MH, et al. Adherence to Mediterranean diet and frailty. *J Am Med Dir Assoc*. 2018;19:315–322.e2.
37. Lo YL, Hsieh YT, Hsu LL, et al. Dietary pattern associated with frailty: results from nutrition and health survey in Taiwan. *J Am Geriatr Soc*. 2017;65:2009–2015.
38. Bollwein J, Diekmann R, Kaiser MJ, et al. Dietary quality is related to frailty in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2013;68:483–489.
39. Trichopoulou A, Costacou T, Bamia C, et al. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*. 2003;348:2599–2608.
40. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. *Nutr Metab Cardiovasc Dis*. 2006;16:559–568.
41. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev*. 2016;31:1–8.
42. Sandoval-Insausti H, Pérez-Tasigchana RF, Lopez-García E, et al. Macronutrients intake and incident frailty in older adults: a prospective cohort study. *J Gerontol A Biol Sci Med Sci*. 2016;71:1329–1334.
43. Michelon E, Blaum C, Semba RD, et al. Vitamin and carotenoid status in older women: associations with the frailty syndrome. *J Gerontol A Biol Sci Med Sci*. 2006;61:600–607.
44. Semba RD, Bartali B, Zhou J, et al. Low serum micronutrient concentrations predict frailty among older women living in the community. *J Gerontol A Biol Sci Med Sci*. 2006;61:594–599.
45. Shivappa N, Stubbs B, Hebert JR, et al. The relationship between the dietary inflammatory index and incident frailty: a longitudinal cohort study. *J Am Med Dir Assoc*. 2018;19:77–82.
46. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr*. 2012;142:1009–1018.
47. Rodríguez-Monforte M, Sánchez E, Barrio F, et al. Metabolic syndrome and dietary patterns: a systematic review and meta-analysis of observational studies. *Eur J Nutr*. 2017;56:925–947.
48. Li Y, Lv M-R, Wei Y-J, et al. Dietary patterns and depression risk: a meta-analysis. *Psychiatry Res*. 2017;253:373–382.
49. Solfrizzi V, Custodero C, Lozupone M, et al. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. *J Alzheimers Dis*. 2017;59:815–849.
50. McEvoy CT, Cardwell CR, Woodside JV, et al. A posteriori dietary patterns are related to risk of type 2 diabetes: findings from a systematic review and meta-analysis. *J Acad Nutr Diet*. 2014;114:1759–1775.e4.
51. Ashby-Mitchell K, Peeters A, Anstey KJ. Role of dietary pattern analysis in determining cognitive status in elderly Australian adults. *Nutrients* 2015;7:1052–1067.
52. Pérez-Tasigchana RF, León-Muñoz LM, Lopez-García E, et al. Metabolic syndrome and insulin resistance are associated with frailty in older adults: a prospective cohort study. *Age Ageing*. 2017;46:807–812.
53. Sinclair A, Dunning T, Rodríguez-Mañas L. Diabetes in older people: new insights and remaining challenges. *Lancet Diabetes Endocrinol*. 2015;3:275–285.
54. Mansur HN, Lovisi JC, Colugnati FA, et al. Association of frailty with endothelial dysfunction and its possible impact on negative outcomes in Brazilian predialysis patients with chronic kidney disease. *BMC Nephrol* 2015;16:157. doi:10.1186/s12882-015-0150-1
55. Ding YY, Kuha J, Murphy M. Pathways from physical frailty to activity limitation in older people: identifying moderators and mediators in the English Longitudinal Study of Ageing. *Exp Gerontol*. 2017;98:169–176.
56. Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis*. 2014;24:929–939.
57. Corsino L, Sotres-Alvarez D, Butera NM, et al. Association of the DASH dietary pattern with insulin resistance and diabetes in US Hispanic/Latino adults: results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *BMJ Open Diab Res Care*. 2017;5:e000402.
58. Hashemi R, Motlagh AD, Heshmat R, et al. Diet and its relationship to sarcopenia in community dwelling Iranian elderly: a cross sectional study. *Nutrition* 2015;31:97–104.
59. Isanejad M, Sirola J, Mursu J, et al. Association of the Baltic Sea and Mediterranean diets with indices of sarcopenia in elderly women, OSPRE-FPS study. *Eur J Nutr* 2018;57:1435–1448.

60. Martínez ME, Marshall JR, Sechrest L. Invited commentary: factor analysis and the search for objectivity. *Am J Epidemiol*. 1998;148:17–19.
61. Zbeida M, Goldsmith R, Shimony T, et al. Mediterranean diet and functional indicators among older adults in non-Mediterranean and Mediterranean countries. *J Nutr Health Aging*. 2014;18:411–418.
62. Cevenini E, Monti D, Franceschi C. Inflamm-ageing. *Curr Opin Clin Nutr Metab Care*. 2013;16:14–20.
63. Taylor D. Physical activity is medicine for older adults. *Postgrad Med J*. 2014;90:26–32.
64. Wysokiński A, Sobów T, Kłoszewska I, et al. Mechanisms of the anorexia of aging—a review. *Age (Dordr)*. 2015;37:9821. doi:10.1007/s11357-015-9821-x
65. Vanitallie TB. Frailty in the elderly: contributions of sarcopenia and visceral protein depletion. *Metabolism* 2003;52:22–26.
66. Zorbas C, Palermo C, Chung A, et al. Factors perceived to influence healthy eating: a systematic review and meta-ethnographic synthesis of the literature. *Nutr Rev* 2018;76:861–874.
67. Lee A, Mhurchu CN, Sacks G, et al. Monitoring the price and affordability of foods and diets globally. *Obes Rev*. 2013;14(suppl 1):82–95.
68. Bae JM. Comparison of methods of extracting information for meta-analysis of observational studies in nutritional epidemiology. *Epidemiol Health*. 2016;38:e2016003.
69. De Rango P. Prospective cohort studies. *Eur J Vasc Endovasc Surg*. 2016;51:151.