Adherence to Mediterranean Diet Reduces Incident Frailty Risk: Systematic Review and Meta-Analysis

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OBJECTIVES: To conduct a systematic review of the literature on prospective cohort studies examining associations between adherence to a Mediterranean diet and incident frailty and to perform a meta-analysis to synthesize the pooled risk estimates.

DESIGN: Systematic review and meta-analysis.

SETTING: Embase, MEDLINE, CINAHL, PsycINFO, and Cochrane Library were systematically searched on September 14, 2017. We reviewed references of included studies and relevant review papers and performed forward citation tracking for additional studies. Corresponding authors were contacted for additional data necessary for a meta-analysis.

PARTICIPANTS: Community-dwelling older adults (mean age ≥60).

MEASUREMENTS: Incident frailty risk according to adherence to a Mediterranean diet.

RESULTS: Two reviewers independently screened the title, abstract, and full text to ascertain the eligibility of 125 studies that the systematic search of the literature identified, and four studies were included (5,789 older people with mean follow-up of 3.9 years). Two reviewers extracted data from the studies independently. All four studies provided adjusted odds ratios (ORs) of incident frailty risk according to three Mediterranean diet score (MDS) groups (0–3, 4–5, and 6–9). Greater adherence to a Mediterranean diet was associated with significantly lower incident frailty risk (pooled OR = 0.62, 95% CI = 0.47–0.82, $P = .001$ for MDS 4–5; pooled OR = 0.44, 95% CI = 0.31–0.64, $P < .001$ for MDS 6–9) than poorer adherence (MDS 0–3). Neither significant heterogeneity ($I^2 = 0–16\%$, $P = .30$) nor evidence of publication bias was observed.

CONCLUSION: Greater adherence to a Mediterranean diet is associated with significantly lower risk of incident frailty in community-dwelling older people. Future studies should confirm these findings and evaluate whether adherence to a Mediterranean diet can reduce the risk of frailty, including in non-Mediterranean populations. **J Am Geriatr Soc 66:783–788, 2018.**

Key words: frailty; Mediterranean diet; systematic review; meta-analysis

Frailty is a geriatric syndrome common in older people, and its prevalence is considered to increase with population aging.[1] Although consensus has not been reached on a criterion standard definition, frailty is generally defined as a state of greater vulnerability due to age-related accumulation of deficits and low physiological reserves across multiple systems.[1] Frailty predicts numerous negative health outcomes in older people, including falls,[2] fractures,[3] hospitalization,[4] nursing home placement,[5] disability,[6] dementia,[7] and premature death,[8] and is associated with poorer quality of life.[9]

Nutrition is considered to play a crucial role in the complex pathogenesis of frailty.[10] Nutrition provides energy and essential nutrients and helps the human body to function properly and maintain homeostasis. The nutrients found in observational and intervention studies to show promising results in relation to frailty are protein and some selected micronutrients, such as carotenoids and vitamins.[11,12] Although evidence on individual nutrients or food items is important, when the food is consumed, various micro- and macronutrients interact with each other, and may cause synergistic effects. Therefore, instead of focusing on a single dietary component, it may be more reasonable to describe the overall consumption of a diet as a dietary pattern.[13]

The Mediterranean diet is based on food patterns typical of Greece and southern Italy in the 1960s. This dietary pattern, which is traditionally presented as a food pyramid,[14] consists of abundant plant foods (fruit, vegetable, cereals, potatoes, beans, nuts and seeds), olive oil as the principal source of fat, dairy products, fish and poultry consumed in low to moderate amounts, 0 to 4

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eggs per week, red meat consumed in low amounts, and wine consumed in low to moderate amounts, normally with meals. This diet is low in saturated fat and has been associated with multiple health benefits, including lower incidence of cardiovascular disease, neurodegenerative diseases, diabetes, and overall cancer, as well as longer survival.[15–17] Only a few studies have examined associations between the Mediterranean diet and frailty risk, and the results have been mixed and inconclusive.[11,13] Furthermore, to our knowledge, no meta-analysis has been performed. The objectives of the current study were thus to conduct a systematic review of the literature on prospective cohort studies examining associations between adherence to a Mediterranean diet and incident frailty and to perform a meta-analysis to synthesize the pooled risk estimates.

METHODS

Data Source and Search Strategy

A systematic search of the literature was conducted on September 14, 2017, based on a protocol generated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews.[18] The 5 databases used were Embase, MEDLINE, CINAHL Plus, PsycINFO, and Cochrane Library (Table S1). We searched for studies published in 2000 or later, because the most commonly used frailty phenotype criteria were first published in 2001.[19] The search terms used were a combination of Medical Subject Heading (MeSH) and text terms, including "Mediterranean diet" (MeSH) OR "Mediterranean*" AND "Frailty Syndrome" (MeSH) OR "frail*." We used explosion functions where available and did not restrict the search by language. We reviewed references of included studies and relevant review papers and performed forward citation tracking using Google Scholar for additional studies. We also contacted corresponding authors for additional data necessary for a meta-analysis.

Study Selection

Two reviewers (GK, CA) independently screened titles, abstracts, and full texts to ascertain the eligibility of the studies identified in the literature search. Disagreements were resolved by discussion. Studies were included if they involved community-dwelling older people with a mean age of 60 and older; assessed adherence to a Mediterranean diet using a tool such as the Mediterranean Diet Score (MDS)[17]; prospectively examined risk of developing frailty, defined using an original or modified version of validated criteria designed to define frailty, according to adherence to a Mediterranean diet at baseline; and provided odds ratios (ORs), hazard ratios (HRs), or risk ratios (RRs) to quantify risk or sufficient information to calculate these risk estimates.

Studies were excluded if they defined frailty according to a single factor (e.g., being certified for long-term care insurance) or an individual component of frailty criteria (e.g., slow walking speed); used selected cohorts with specific diseases or conditions; or were review papers, randomized controlled trials, conference abstracts, comments, or editorials.

Methodological Quality Assessment

We used the 9-item Newcastle-Ottawa Scale for cohort studies to assess methodological quality of eligible studies.[20] A study was considered to have adequate methodological quality when the study met 5 criteria or more out of 9.

Data Extraction

Two reviewers (GK, CA) independently extracted the following data from the included studies: first author, publication year, cohort name if any, location, sample size, proportion of female participants, mean age, age range, tool used to measure adherence to a Mediterranean diet, frailty criteria, and follow-up period. We also extracted risk estimates along with 95% confidence intervals (CIs) of the final models and covariates used for adjustment.

Statistical Analysis

A meta-analysis was attempted when there were 3 or more studies providing the same type of effect measures of frailty risk and adherence to a Mediterranean diet was based on the same tool. Adjusted effect measures were preferred to unadjusted ones when a study reported both. The presence and degree of heterogeneity were assessed using the chi-square test and I^2 statistic, respectively, and I^2 values of 25%, 50%, and 75% were considered to be low, moderate, and high degrees of heterogeneity, respectively.[21] A fixed-effects model was used if heterogeneity was absent, and a random-effects model was used if heterogeneity was present, to calculate a pooled risk estimate using the generic inverse variance method. Publication bias was assessed using visual inspection of funnel plots. If significant heterogeneity was observed, sensitivity analysis, subgroup analysis, and random-effects metaregression analysis would be performed to further explore the cause of the heterogeneity. Review Manager 5, version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark) was used for all analyses, and the level of significance was set at $P < .05$.

RESULTS

Selection Process and Study Characteristics

Figure 1 presents the PRISMA flowchart of the study selection process. Of a total of 125 studies identified, 4 were included (5,789 older people with a mean follow-up of 3.9 years), all of which met 7 or more of the 9 items of the Newcastle-Ottawa scale (mean 8.0, range 7–9, Table S2). Characteristics of the 4 included studies are summarized in Table 1. All 4 studies used the MDS, which is a tool used to measure adherence to the traditional Mediterranean diet based on the salient characteristic of this diet; scores range from 0 to 9, with a higher score indicative of greater adherence.[17] Three studies[22–24] used modified versions of the Cardiovascular Health Study

frailty criteria, which is one of the most widely used measures to define physical frailty based on 5 criteria (unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, low physical activity).[19] One study[25] used the FRAIL scale, which can measure frailty according to the answers to 5 simple questions about fatigue, resistance, ambulation, illnesses, and loss of weight.[26] Two studies divided their cohort into 3 groups (MDS 0–3, 4–5, 6–9),[23,24] and 1 study used sex-stratified tertiles.[22] Two studies used the MDS as a continuous variable.[24,25] All 4 studies included in this review provided ORs of incident frailty risks and used the MDS to measure adherence to a Mediterranean diet,[22–25] so ORs according to the MDS were chosen for the meta-analysis. One of the 4 studies showed results using the Mediterranean Diet Adherence Screener as well.[22] All ORs were adjusted for multiple confounders, which included age, sex, education, marital status, body mass index, smoking, alcohol, living status, energy intake, medication, physical activity, and comorbidities (Table 1).

Adherence to a Mediterranean Diet and Risk of Incident Frailty

ORs of incident frailty risk according to 3 MDS groups (0–3, 4–5, 6–9) were available from 4 studies[22–25] and used for a fixed-effects meta-analysis because no significant heterogeneity ($I^2 = 0\%$, $P = .84$; $I^2 = 16\%$, $P = .31$, respectively) was observed. The forest plots are shown in Figure 2. Greater adherence to a Mediterranean diet was associated with significantly lower incident frailty risks than low adherence (MDS 0–3) (4 studies: pooled OR = 0.62, 95% CI = 0.47–0.82, $P = .001$ for MDS 4–5; pooled OR = 0.44, 95% CI = 0.31–0.64, $P < .001$ for MDS 6–9). No obvious asymmetry was observed in the funnel plots for either analysis. We repeated meta-analyses using a random-effects model (4 studies: pooled OR = 0.62, 95% CI = 0.47–0.82, $P = .001$ for MDS 4–5; pooled OR = 0.44, 95% CI = 0.29–0.66, $P < .001$ for MDS 6–9) and excluding the Chinese study[25] (3 studies: pooled OR = 0.60, 95% CI = 0.44–0.82, $P = .001$ for MDS 4–5; pooled OR = 0.40, 95% CI = 0.27–0.65, $P < .001$ for MDS 6–9). These made little difference in our findings. Subgroup analysis and metaregression analysis were not performed because of the low degree of heterogeneity and the small number of included studies.

DISCUSSION

This systematic review and meta-analysis identified 4 studies that included a total of 5,789 community-dwelling older people followed for a mean 3.9 years and found that greater adherence to a Mediterranean diet was significantly associated with lower risk of incident frailty.

Adherence to a Mediterranean diet was measured using the MDS[17] in all the included studies. The MDS is based on intake of food items specific to the traditional Mediterranean dietary pattern: high intake of fruits,

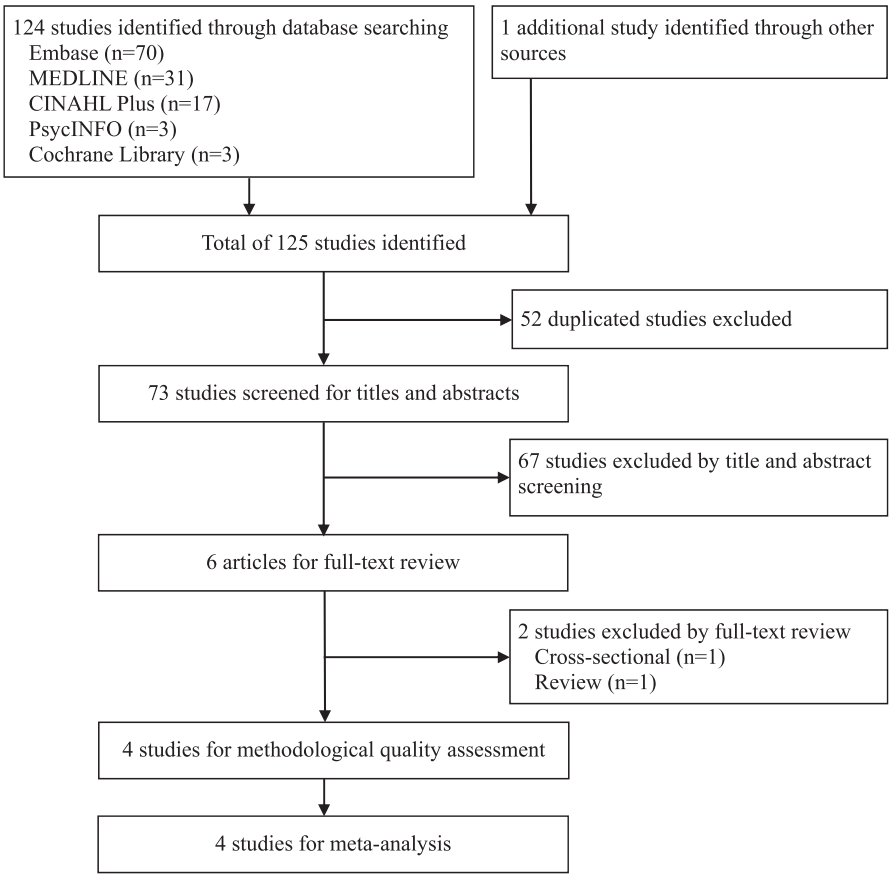

Figure 1. Flow chart of systematic literature review.

Table 1. Summary of Included Studies on Mediterranean Diet and Incident Frailty

Author, Year, Study	Location	Sample Size, n	Female, %	Age, Mean (Range)	Mediterranean Diet Measurement	Frailty Criteria	Follow-Up, Years	Newcastle-Ottawa Scale Score (Range 0–9)
Rahi, 2017, Three-City Study	France	560	63.2	81.7 (≥75)	MDS	mCHS	2	9
Chan, 2015	China	2,724	50.3	71.8 (≥65)	MDS	FRAIL Scale	4	8
Leon-Munoz, 2014, Study on Nutrition and Cardiovascular Risk Factors in Spain	Spain	1,815	—	(≥60)	MDS; Mediterranean Diet Adherence Screener	mCHS	3.5	8
Talegawkar, 2012, Invecchiare in Chianti	Italy	690	51.7	73.0 (≥60)	MDS	mCHS	6	7

MDS = Mediterranean Diet Score; mCHS = Modified Cardiovascular Health Study frailty criteria.

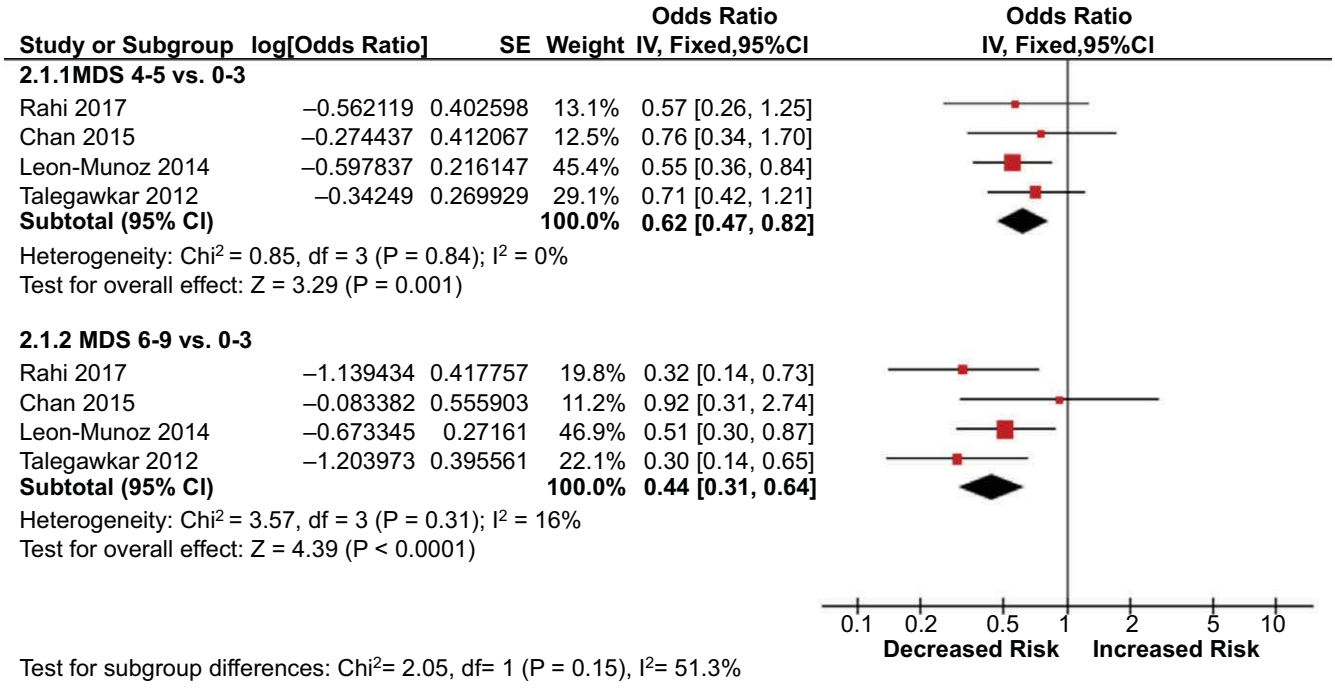

Figure 2. Forest plots of incident frailty risk according to Mediterranean diet score (4–5 vs 0–3; 6–9 vs 0–3).

vegetables, legumes, nuts, cereals, fish, and olive oil (coupled with low intake of saturated fats); low intake of meat and dairy products; and regular but moderate intake of alcohol, mostly wine.[17] The beneficial effects of a Mediterranean dietary pattern on frailty that we observed is consistent with findings from a cross-sectional study of 923 older Taiwanese adults that explored 79 food items to find the dietary pattern most protective against frailty using reduced rank regression analysis.[27] In the dietary pattern identified as best for explaining frailty status, fresh fruits, nuts and seeds, vegetables, whole grains, fish, and breakfast cereals were among the top food items demonstrating protective effects against frailty (factor loading value = −0.48, −0.39, −0.33, −0.27, −0.20, and −0.17, respectively).[27] Olive oil and wine were not included, perhaps because this non-Mediterranean population did not commonly consume them.

In addition to the Mediterranean diet, other dietary patterns have been investigated and found to be associated with future frailty risks. A "prudent" dietary pattern characterized by high consumption of olive oil, vegetables, potatoes, legumes, blue fish, pasta, and meat was identified using principal component analysis and was shown to be associated with lower risk of incident frailty over 3.5 years of follow-up in 1,872 older Spanish adults.[28] Another study used the Three-City Study Bordeaux cohort of 972 older adults and showed that a "healthy" cluster defined according to a hybrid clustering method, which is associated with high intake of fish in men and fruits and vegetables in women, was associated with lower risk of developing frailty during a follow-up of 12 years.[29] A study from the Netherlands found that high adherence to a "traditional" dietary pattern, characterized by a high intake of savory snacks, legumes, eggs, fried potatoes, alcohol, processed meat, and soup, was also associated with less frailty defined according to the Frailty Index 4 years later.[30] This effect was observed despite this dietary pattern including foods such as fried potatoes and

processed meat, which are associated with higher incidence of cardiovascular disease. Three studies examined associations between quality of diet using the Dietary Quality Index (based on dietary variety; adequacy of vegetables, fruits, grains, fiber, protein, iron, calcium, and vitamin C; moderation of total fat, saturated fat, cholesterol, sodium, and empty calorie foods; and overall balance of macronutrient ratio and fatty acid ratio)[25,31] and the Dutch Healthy Diet index (based on vegetables, fruits, fiber, fish and fish oil, saturated fatty acid, trans-fatty acids, sodium, and alcohol)[30] and subsequent frailty risks and found that higher dietary quality was consistently associated with lower future frailty risks. These findings are at least partially in line with ours in that some dietary components are in common with a Mediterranean diet, such as olive oil, vegetables, fruits, legumes, and fish.

This study's strengths include its robust methodology, including a comprehensive and reproducible search strategy following PRISMA guidelines.[18] Two authors independently reviewed the search results and extracted the data. In addition, methodological quality, heterogeneity, and publication bias were assessed. We were able to include all 4 of the studies in the meta-analysis by obtaining additional data from the authors of the original articles.[22,25] All 4 studies had adequate methodological quality, and there was low degree of heterogeneity in their findings. Furthermore, all the effect measures combined in the meta-analysis were fully adjusted for multiple confounders, including age, sex and education, which should contribute to the robustness of our synthesized results. Nevertheless, the current study is not without limitations. Only a small number (n = 4) of studies were identified, probably because frailty research in relation to diet has only recently emerged. Further studies are warranted to elucidate associations between the Mediterranean diet and frailty, in particular in non-Mediterranean countries. In addition, further information on which components of the Mediterranean diet are associated with frailty (e.g. fruit and vegetable, red wine) and which components of frailty are most affected (e.g. measure of muscle strength, exhaustion or weight loss) would give further insight. Adherence to a Mediterranean diet was measured using the MDS in all the studies included. Although the MDS may be a good indicator of adherence to a Mediterranean diet in Mediterranean populations, its relevance to non-Mediterranean populations is contested.[32] Some of the MDS components were based on actual food consumption with cut-points specific to the study population (e.g., median value of the intake), rather than based on the intake recommended in a traditional Mediterranean diet.[17] Therefore the findings based on the MDS may not reflect true adherence to a Mediterranean diet,[33] especially in non-Mediterranean populations.[25] Lastly, there may be potentially unmeasured confounding because not all studies adjusted for factors related to a healthier lifestyle in general, such as smoking, alcohol, and physical activity.

There are several potential mechanisms underlying the association between greater adherence to a Mediterranean diet and lower risk of frailty. One possibility is the high intake of foods rich in antioxidants. Fruits and vegetables are rich in carotenoids and vitamins, and red wine contains abundant polyphenols. Oxidative stress is a risk factor for frailty,[34] and fruits and vegetables rich in antioxidants may decrease the risk of frailty by counteracting oxidative status. Inflammation is another possible explanation. Frail individuals have higher levels of inflammatory markers, and inflammation is considered to be closely associated with frailty.[35] A Mediterranean diet is associated with low levels of inflammatory markers[36] and may reduce frailty risk through this mechanism. Adherence to a Mediterranean diet has been associated with better cognitive function, lower rates of cognitive decline, and lower risks of Alzheimer's disease and dementia.[37,38] Moreover, the Mediterranean diet has been associated with lower incidence of cardiovascular disease[39] and certain types of cancers, such as colorectal cancer.[40] All of the above may contribute to the accumulation of fewer health deficits over time, resulting in a lower incidence of frailty.

CONCLUSION

This systematic review and meta-analysis shows the first pooled evidence that greater adherence to a Mediterranean diet is associated with significantly lower risk of incident frailty in community-dwelling older people. Related topics warranting future research include a focus on which components or combination of foods contributes to the decrease in frailty. We now also need studies to confirm these findings and determine whether increasing adherence to a Mediterranean diet can reduce the risk of frailty, including in non-Mediterranean populations.

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Conflict of Interest: The authors have no conflicts.

Author Contributions: Kojima, Iliffe and Walters: Study concept and design. Kojima and Avgerinou: Acquisition of data. Kojima, Avgerinou, Iliffe and Walters: Analysis and interpretation of data. Kojima: Drafting the article. Avgerinou, Iliffe and Walters: Critical revision of manuscript for important intellectual content. Kojima, Avgerinou, Iliffe and Walters: Final approval of version to be published.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Search strategy.

Table S2. Methodological quality assessment using the Newcastle-Ottawa Quality Assessment Scale for cohort studies.

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