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ADHERENCE TO A MEDITERRANEAN DIET IS ASSOCIATED WITH LOWER INCIDENCE OF FRAILTY: A LONGITUDINAL COHORT STUDY

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ABSTRACT

Backround & aims: There is a paucity of data investigating the relationship between the mediterranean and frailty, with no data among North American people. We aimed to investigate if adherence to a Mediterranean diet is associated with a lower incidence of frailty in a large cohort of North American people.

Methods: This study included subjects at higher risk or having knee osteoarthritis. Adherence to the Mediterranean diet was evaluated using a validated Mediterranean diet score (aMED) as proposed by Panagiotakos and classified into five categories. Frailty was defined using the Study of Osteoporotic Fracture (SOF) index as the presence of ≥2 out of: (i) weight loss ≥5% between baseline and the subsequent follow-up visit; (ii) inability to do five chair stands; (iii) low energy level.

Results: During the 8 years follow-up, of the 4,421 participants initially included (mean age: 61.2 years, % of females=58.0), the incidence of frailty was approximately half in those with a higher adherence to the Mediterranean diet (8 for 1,000 person years) vs. those with a lower adherence (15 for 1,000 persons-years). After adjusting for 10 potential confounders (age, sex, race, body mass index, education, smoking habits, yearly income, physical activity level, Charlson co-morbidity index and daily energy intake), participants with the highest aMED scores were found to have a significant reduction in incident frailty (hazard ratio=0.71; 95% CIs: 0.50-0.99, p=0.047) with respect to those in a lower category. Regarding individual components of the Mediterranean diet, low consumption of poultry was found to be associated with higher risk of frailty.

Conclusions: A higher adherence to a Mediterranean diet was associated with a lower incidence of frailty over an 8-year follow-up period, even after adjusting for potential confounders.

Key words : frailty; Mediterranean diet; Osteoarthritis Initiative, older people

INTRODUCTION

Defined as "a state of increased vulnerability to stressors resulting from a decrease in physiologic reserves in multiple organ systems causing limited capacity to maintain homeostasis",[1] frailty is a common condition in older people. It has been associated with an increased risk of several deleterious outcomes in that population, including disability, hospitalization and institutionalization.[2] Recent studies have also suggested that frailty could be considered an independent risk factor for cardiovascular[3,4] and metabolic[5] diseases that could further hasten the typical transition from frailty to disability.

Although the risk factors for frailty are numerous, diet could play its own relevant role in its development. Some observational studies have suggested that a deficiency of single nutrients, such as carotenoids, vitamins D, E, and C, folates, proteins, and whole grains [6–12] might play a putative role in the development of frailty. But as the deficiency of some nutrients is often associated with the paucity of others, assessment of whole dietary patterns seems more appropriate for epidemiological purposes.[13] Interestingly, a higher consumption of fruits and vegetables was associated with a reduced risk of frailty in a large cohort of older European subjects.[14] The Mediterranean diet is one of the most important dietary patterns that has been investigated in view of its beneficial effects on several diseases. The term 'Mediterranean diet,' which describes traditional dietary habits of peoples from Mediterranean countries, is frequently depicted as a food pyramid[15]. For epidemiological purposes, adherence to the Mediterranean diet is usually evaluated using standardized questionnaires that take into consideration foods that are commonly eaten by Mediterranean populations. The Mediterranean-style diet is an established healthy-eating behavior that has consistently been shown to have beneficial effects on quality of life[16] and on musculoskeletal[17], cardiovascular[18], metabolic[19], and cognitive[20,21] diseases.

Until now, to the best of our knowledge, only four studies have investigated the effect of the Mediterranean diet on incident frailty.[22–25] While all of these advanced the field and suggested that the Mediterranean diet may play a role in delaying the onset of frailty, three were nevertheless limited because of their short follow-up period [22,23,25] (less than 4 years). No study has, moreover, investigated the possible role of higher adherence to Mediterranean diet on frailty in a North American population a population in which the higher presence of some medical conditions (such as obesity)[26] that predicts frailty, could alter the association between Mediterranean diet and frailty.

Given the potential benefits of the Mediterranean diet on several diseases and the absence of data on North American subjects, the current study aimed to investigate whether adherence to a Mediterranean diet is associated with a lower incidence of frailty in a large cohort of North Americans participating in the Osteoarthritis Initiative. We hypothesized that higher adherence to the Mediterranean diet is associated with a lower incidence of frailty.

METHODS

Data source and subjects

Data were gathered from the Osteoarthritis Initiative (OAI) [27], available for public access at http://www.oai.ucsf.edu/. The specific datasets utilized for this research were registered during the baseline and screening evaluations (V00) and each database reporting data on frailty until 96 months from baseline (V10). Patients at high risk or having knee OA were recruited at four clinical centers in the USA (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006.

All the participants provided written informed consent. The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco.

Adherence to Mediterranean diet (exposure)

Participants' diet patterns were analyzed using the Block Brief 2000 food frequency (FFQ) questionnaire during the baseline appointment.[28] The validated tool, containing a food list of 70 items, was designed to assess the individual's food and beverage consumption over the past year. Frequency of food consumption of the items included was reported at nine levels of intake from "never" to "every day". There were also seven dietary behavior questions on food preparation methods and fat intake, one question on fiber intake, and 13 questions on vitamin and mineral intakes.

Adherence to a Mediterranean diet was evaluated using the Mediterranean diet score (aMED) proposed by Panagiotakos et al.[29] The score was calculated based on a food frequency questionnaire completed during the baseline OAI visit. The aMED takes into consideration foods commonly consumed by individuals living in Mediterranean area. Participants were asked to rate their consumption of each single food item using a score ranging from 0 (less adherence) to 5 (better

adherence); the total possible score ranges from 0 to 55, with higher values indicating higher adherence to a Mediterranean diet. Cereals (e.g. bread, pasta, rice), potatoes, fruits, vegetables, legumes (e.g. peas, beans), fish were categorized on the basis of servings/month and specifically as: 0=never; 1=1 to 4 servings for month; 2=5 to 8; 3=9 to 12; 4=13 to 18; 5= more than 18 servings/month. As no distinction was made with reference to whole vs. refined cereals, all types of grains were considered under the same heading. Consumption of red meat, poultry, and full fat dairy products (e.g. milk cheese, yogurt) were categorized as: 0=more than 18 servings/month; 1=13 to 17 servings/month; 2=9 to 12; 3=5 to 8; 4=1 to 4; 5= never). Consumption of olive oil was categorized as the times it was used in a week's time and specifically as: 0=never; 1=rare; 2 ≤1/weekly; 3= 2 times/weekly; 4=3 to 6; 5=daily. Alcoholic beverages were categorized as: 0≥700 ml/day or 0; 1=600 to 699 ml/day; 2=500 to 599 ml/day; 3=400 to 499 ml/day; 4=300 to 399 ml/day; 5=< 300 ml/day.

We arbitrary divided the population into 5 categories depending on their total scores as follows: aMED score <24 = Q1, 25-27 = Q2, 28-30 = Q3, 31-32 = Q4 and > 32 =Q5.

Outcome

The study's outcome of interest was incident frailty. In agreement with the Study of Osteoporotic Fracture (SOF) index[30,31] frailty was defined as the presence of at least ≥2 out of three of the following criteria: (i) weight loss ≥5% taking place between baseline and the follow-up examinations (at the baseline examination a body mass index, BMI, of less than 20 Kg/m^2, a common cut-off for identifying underweight people the elderly[32,33], was used, since no information regarding weight changes were recorded). Weight and height were measured at baseline and during follow-up examinations by a trained nurse; (ii) the inability to rise from a chair five times without arm support (hereafter referred to as inability to carry out chair stands); and (iii) poor energy based

on the SF12 questionnaire response of “little at a time” or “none at a time” to the question “in the past 4 weeks, did you have a lot of energy?”

The assessment of the outcome was made at the baseline and during the V01 (12 months), V03 (24 months), V05 (36 months), V06 (48 months), V08 (72 months) until the V10 (96 months).

Covariates

We identified 10 potential self-reported confounders including BMI; physical activity evaluated using the Physical Activity Scale for the Elderly (PASE);[34] race; smoking habit, educational level and yearly income (< or ≥ $50,000 and missing data) to assess the relationship between aMED and incident frailty.

Validated general health measures of self-reported comorbidities were assessed using the modified Charlson comorbidity score[35]. The medical morbidities that were assessed using that score regarded diseases/disorders that were common in North Americans such as fractures, heart attack and failure, stroke, chronic obstructive pulmonary disease, diabetes and cancer. [36]

Statistical analyses

Normal distributions of quantitative variables were tested using the Kolmogorov-Smirnov test. Data are reported as means±standard deviations (SD) for continuous measures, and frequency and percentages for all discrete variables. Levene’s test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch’s ANOVA was used. P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical ones.

Cox’s regression analysis was used to explore the association between aMED at baseline and incident frailty. Deaths were censored and in a sensitivity analysis removed from the main analysis.

Factors significantly different across aMED categories (considering a p-value<0.10) or significantly associated with incident frailty at univariate analysis (p-value<0.05) were included. Multi-collinearity among covariates was assessed using the variance inflation factor (VIF), with a score of 2 leading to the exclusion of a variable, but no parameter was excluded for this reason. The basic model was not adjusted for any confounders. The fully adjusted model included: age (as a continuous variable); sex; race (white vs. others); BMI (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as $\geq$ or < $50,000 and missing data); Charlson comorbidity index; use of analgesic drugs (yes vs. no) and total energy intake (as a continuous variable). Cox's regression analysis data were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

We also ran the same analyses taking each single component of the Mediterranean diet as an outcome and classifying adherence as a low score (a score of 0, 1, or 2) or a high one (4-5). Adjusted HRs and 95% CI were in the end calculated to estimate the strength of the associations between aMED and incident frailty.

To test the robustness of our analyses, sensitivity analyses were conducted evaluating the interaction between aMED and selected factor (e.g. age below or more than 60 years, gender, race, education, smoking habits, yearly income and presence/absence of diseases at baseline) in predicting incident frailty, but no moderator emerged as significant.

All the analyses were performed using the SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value <0.05.

RESULTS

Sample selection

The OAI dataset includes a total of 4,796 North American participants. At baseline, 229 participants were excluded because data about their aMED adherence was missing or because they had implausible caloric intake (<500 or >5000 Kcal/day). Seventeen, who were already frail at baseline, were excluded and 129 were lost during the follow-up, leaving 4,421 participants whose data were included in the analyses. The excluded participants did not differ in terms of mean age and percentage of females compared to those included in this research.

Descriptive characteristics

Of the 4,421 participants, 1,857 were males and 2,564 females. Mean age was 61.2 years (±9.2 years; range: 45-79). Mean aMED score was 28.1 points (±5.1 points; range: 5-44).

Table 1 outlines the participants' characteristics classified into aMED categories. Those in the highest group (reflecting higher adherence to Mediterranean diet) were older (p for trend<0.0001), more likely to be female (p for trend<0.0001), white (p for trend<0.0001), with a higher educational level (p for trend<0.0001) with respect to those in the other categories. They also had lower BMI values (p for trend<0.0001) and a lower prevalence of diabetes (p for trend<0.0001) than other participants (**Table 1**).

Finally, those in the highest group, reported a significant lower presence of poor energy compared with the other participants (p for trend<0.0001) (**Table 1**).

212 **Table 1. Characteristics of the participants classified according to their adherence to a Mediterranean diet pattern.**

	Q1 (n=1063) aMED<24	Q2 (n=884) aMED 25-27	Q3 (n=996) aMED 28-30	Q4 (n=597) aMED 31-32	Q5 (n=881) aMED > 32	P value for trend[a]
Energy intake (Kcal/day)	1407.1 (606.5)	1391.4 (557.7)	1437.8 (593.4)	1414.3 (541.7)	1417.7 (519.1)	0.31
Age (years)	58.9 (8.6)	61.1 (9.0)	61.6 (9.3)	62.7 (9.2)	63.0 (9.1)	<0.0001
PASE (points)	159.1 (84.1)	161.8 (79.9)	166.3 (83.9)	152.3 (77.6)	162.3 (82.0)	0.88
Females (n, %)	542 (51.0)	525 (59.4)	599 (60.1)	351 (58.8)	547 (62.1)	<0.0001
White race (n, %)	751 (70.7)	694 (78.5)	818 (82.2)	519 (86.9)	771 (87.6)	<0.0001
Smoking (previous/current) (n, %)	485 (45.9)	412 (46.8)	456 (46.1)	293 (49.2)	431 (49.2)	0.10
Graduate degree (n, %)	243 (22.9)	261 (29.6)	297 (29.8)	211 (35.3)	334 (37.9)	<0.0001
Yearly income (≥ $50,000)	560 (52.7)	518 (58.6)	596 (59.8)	376 (63.0)	567 (64.4)	<0.0001
Medical conditions						
BMI (Kg/m^2)	29.8 (4.9)	29.2 (4.7)	28.4 (4.7)	28.1 (4.6)	27.4 (4.6)	<0.0001
Fractures (n, %)	166 (15.7)	166 (18.8)	165 (16.6)	124 (20.9)	165 (18.8)	0.12
Heart attack (n, %)	29 (2.8)	17 (2.0)	13 (1.3)	4 (0.7)	24 (2.8)	0.43

	Q1 (n=1063) aMED<24	Q2 (n=884) aMED 25-27	Q3 (n=996) aMED 28-30	Q4 (n=597) aMED 31-32	Q5 (n=881) aMED > 32	P value for trend[a]
Heart failure (n, %)	27 (2.6)	21 (2.4)	15 (1.5)	6 (1.0)	17 (1.9)	0.09
Stroke (n, %)	33 (3.1)	35 (4.0)	23 (2.3)	14 (2.4)	27 (3.1)	0.41
COPD (n, %)	27 (2.6)	19 (2.2)	23 (2.3)	9 (1.5)	18 (2.1)	0.30
Diabetes (n, %)	99 (9.6)	81 (9.3)	72 (7.3)	36 (6.1)	42 (4.8)	<0.0001
Cancer (n, %)	45 (4.2)	34 (3.8)	62 (6.2)	26 (4.4)	48 (5.5)	0.15
Frailty items at baseline						
Weight loss (n, %)	19 (1.8)	15 (1.7)	22 (2.2)	12 (2.0)	31 (3.5)	0.07
Inability to rise from a chair five times (n, %)	6 (0.6)	7 (0.8)	9 (0.9)	4 (0.7)	6 (0.7)	0.83
Poor energy (n, %)	160 (15.1)	110 (12.5)	100 (10.0)	53 (8.9)	67 (7.6)	<0.0001

213

214 **Notes:** The data are presented as means (with standard deviations) for continuous variables and number (with percentage).

215 [a] P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for

216 categorical ones.

Abbreviations: aMED: adherence to Mediterranean diet score; PASE: Physical Activity Scale for the Elderly; BMI: body mass index; COPD: chronic obstructive pulmonary disease.

Adherence to Mediterranean diet and incident frailty

During the 8 year follow-up, 362 (=8.2% of the baseline population) developed frailty for a global incidence rate of 13 (95%CI: 8-18)/1,000 persons-year.

Table 2 illustrates the association between aMED and frailty in the participants studied. The incidence of frailty was approximately half in those with higher aMED scores with respect to those with lower ones Q5: 8 (95%CI: 2-14) vs. Q1: 15, 95%CI: 8-22 for 1,000 persons-year, p<0.0001). Using Cox's regression analysis adjusting for 10 potential confounders, and taking those with the lowest adherence to Mediterranean diet as a reference (=Q1), the participants with the highest adherence to the Mediterranean diet had a significantly reduced probability of incident frailty of 29% (HR=0.71; 95% CI: 0.50-0.99, p=0.047; **Table 2**). However, the p for trend was not significant (p=0.24). Excluding 223 participants dead during the follow-up period attenuated our findings (adjusted HR for the highest quintile= 0.77; 95%CI: 0.54-1.10; p=0.11).

Of note, no moderator emerged as important in this association since the for interaction between aMED and age (more or below 60 years) was p=0.17, for gender p=0.29 and for presence of frailty criteria at baseline=0.17.

Table 2. Association between adherence to Mediterranean diet and incidence of frailty.

	Cumulative incidence (%)	Incidence (95% CI)	Unadjusted HR (95%CI)	P value	Fully-adjusted[a] HR (95%CI)	P value
Q1 (aMED<24)	105/1063 (=9.9%)	15 (8-22)	1 [reference]		1 [reference]	
Q2 (aMED 25-27)	65/884 (=7.4%)	11 (4-18)	0.73 (0.54-1.00)	0.046	0.77 (0.56-1.05)	0.10
Q3 (aMED 28-30)	86/996 (=8.6%)	13 (6-20)	0.83 (0.63-1.11)	0.21	0.92 (0.68-1.23)	0.56
Q4 (aMED 31-32)	50/597 (=8.4%)	11 (3-19)	0.80 (0.57-1.12)	0.20	0.92 (0.65-1.30)	0.62
Q5 (aMED>32)	56/881 (=6.4%)	8 (2-14)	0.62 (0.45-0.85)	0.004	0.71 (0.50-0.99)	0.047

Notes:

All the data are presented as hazard ratios (HRs) with their 95% confidence intervals.

[a]Fully-adjusted model included as covariates: age (as continuous); sex; race (whites vs. others); body mass index (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as ≥ or < 50,000$ and missing data); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index; daily energy intake (in Kcal/die).

Abbreviations: CI: confidence intervals; HR: hazard ratio.

243 **Table 3** shows Cox's regression analyses of the single components of the Mediterranean diet. After adjusting for potential confounders, no
244 component was associated with a significantly lower incidence of frailty; lower consumption of poultry was associated with a higher risk of incident
245 frailty (HR=1.34, 95%CI: 1.07-1.67, p=0.0009).

246 **Table 3. Singular components of Mediterranean diet and incidence of frailty.**

	Number of events/number of participants (=cumulative incidence, %) [higher adherence; 4-5 points]	Number of events/number of participants (=cumulative incidence, %) [higher adherence; 0-3 points]	Unadjusted HR (95%CI)	P value	Fully-adjusted[a] HR (95%CI)	P value
Cereals	31/351 (8.8)	331/4070 (8.1)	0.89 (0.62-1.29)	0.55	0.80 (0.55-1.18)	0.26
Potatoes	311/3947 (7.9)	50/471 (10.6)	1.35 (1.00-1.82)	0.05	1.08 (0.79-1.48)	0.64
Fruits	107/1208 (8.9)	255/3212 (7.9)	0.87 (0.70-1.10)	0.24	0.86 (0.68-1.09)	0.20
Vegetables	24/186 (12.9)	337/4233 (8.0)	0.59 (0.38-0.89)	0.01	0.70 (0.45-1.08)	0.11
Legumes	290/3532 (8.2)	71/887 (8.0)	0.99 (0.77-1.29)	0.97	0.87 (0.66-1.14)	0.31
Fish	336/4020 (8.4)	25/375 (6.7)	0.82 (0.55-1.24)	0.35	0.77 (0.51-1.16)	0.21
Meat	320/3828 (8.4)	42/593 (7.1)	0.85 (0.62-1.17)	0.32	0.88 (0.63-1.23)	0.45

	Number of events/number of participants (=cumulative incidence, %) [higher adherence; 4-5 points]	Number of events/number of participants (=cumulative incidence, %) [higher adherence; 0-3 points]	Unadjusted HR (95%CI)	P value	Fully-adjusted[a] HR (95%CI)	P value
Poultry	187/2483 (7.5)	174/1912 (9.1)	1.21 (0.99-1.49)	0.07	**1.34 (1.07-1.67)**	**0.009**
Dairy	348/4196 (8.3)	14/224 (6.3)	0.81 (0.47-1.38)	0.44	0.64 (0.37-1.11)	0.12
Alcohol	224/2378 (9.4)	134/2027 (6.6)	0.68 (0.55-0.84)	<0.0001	0.85 (0.68-1.06)	0.15
Olive oil	311/3809 (8.2)	50/572 (8.7)	1.07 (0.79-1.44)	0.67	1.17 (0.86-1.58)	0.31

Notes:

All the data are presented as hazard ratios (HRs) with their 95% confidence intervals.

In all the analyses, we considered higher adherence to a component (as 4 or 5 points) vs. lower (0 to 3; reference).

[a]Fully-adjusted model included as covariates: age (as continuous); sex; race (whites vs. others); body mass index (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as ≥ or < 50,000$ and missing data); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index; daily energy intake (in Kcal/die).

Abbreviations: CI: confidence intervals; HR: hazard ratio.

DISCUSSION

Our analysis of the OAI multi-center, longitudinal, prospective study of knee osteoarthritis in people living in North America uncovered that those who more closely followed a Mediterranean diet had a significantly lower incidence of frailty. After adjusting for 10 potential confounders, those with the highest aMED score had a significantly lower incidence of frailty by 29%. However, the significant association between Mediterranean diet and frailty disappears after excluding dead people, indicating that the Mediterranean diet is probably able to prevent severe forms of frailty and when considering the p for trends, suggesting that the association between aMED score and frailty is not necessarily linear.

Individuals reporting a higher adherence to a Mediterranean diet had significantly lower BMI values, a lower prevalence of diabetes and a higher education level with respect to the other participants. These factors could play a role in the lower incidence of frailty in individuals strictly following a Mediterranean diet. However, it should be noted that obese people tend to report significant lower calorie intake than those really introduced[37] and this may introduce a bias in our findings. There was also a significantly higher presence of two important risk factors for frailty in these participants, namely being female and older. This discrepancy, however, further confirmed a significant and independent association between higher adherence to this dietary pattern and lower incidence of frailty.

Several studies have examined the association between the intake of nutrients, and in particular protein intake,[38,39] and the prevalence or incidence of frailty. A study including 1,345 older French participants reported that higher intake of proteins (and not of energy) was associated with a lower prevalence of frailty, also after taking in account several potential confounders.[12] A large study focusing on 24,417 women showed that increased protein intake is protective against the incidence of frailty.[7] Other studies have reported, instead, that increased protein intake, particularly of an

281 animal origin, increases mortality rate[40,41] or could be associated to an increased rate of oxidative
282 stress in the intracellular compartment.[42,43] Our study found conflicting results regarding the intake
283 of animal proteins and incidence of frailty, since higher consumption of meat was not associated
284 with the risk of frailty, although lower consumption of poultry did. Again, previous literature
285 reported a clear association between higher proteins intake (independently from the source) and
286 lower presence of frailty[12], suggesting that proteins are important in the prevention of frailty. The
287 mechanism underlying this finding is unclear, but it is possible that poultry's nutritional
288 characteristics (in particular its lower fat content compared to red meat) could play a role. Further
289 research is needed to answer these questions.
290
291 Study results suggest that a Mediterranean diet is indeed associated with lower incidence of frailty,
292 independently from potential confounders. The fact that a higher adherence to a Mediterranean diet
293 was found to be linked to a decrease in inflammation[44] could mean that inflammation plays a role
294 in the development of frailty[45] and that the anti-inflammatory properties linked to the
295 phytochemicals present in foods contained in the diet are able to modify this association.[46] This
296 hypothesis has been confirmed by other studies showing that higher use of antioxidant nutrients
297 leads to lower incidence of frailty.[6,8,9] In addition, several studies have demonstrated that a higher
298 adherence to Mediterranean diet improves some protein pathways that are involved in the
299 development of frailty, such as insulin resistance[47] and endothelial dysfunction.[48] Finally, a
300 Mediterranean diet may reduce the risk of several chronic diseases, such as cardiovascular diseases,
301 which may also lead to frailty.
302
303 Although other studies investigating the effect of higher adherence to Mediterranean diet on the
304 development of frailty produced significant results,[22–24] it is important to remember that they were
305 carried out in continents other than North America, where quite different dietary patterns are
306 utilized. The generalizability of these findings regarding North Americans people is thus

questionable. Furthermore, only one study had a long follow-up (six years) as the time window for frailty to develop.[24] The association between the Mediterranean diet and frailty uncovered by our data was thus confirmed by data linked to a large sample and with a long follow-up. Study results thus clearly indicate that this diet pattern is an important measure to prevent frailty and the conditions consequent to it, such as disability. Another important point is that these studies used the criteria suggested by Fried et al.[49] for defining frailty modified compared to the original version and other tools for assessing the adherence to Mediterranean diet, such as that suggested by Trichopoulou et al. in the EPIC study.[50] However, how these different definitions could affect the results of our and these studies is hard to determine.

The study does have some limitations, the main one being that we used a slightly different definition of frailty at baseline with respect to the one used at the follow-up as far as weight loss was concerned. Using that definition, only 17 participants were considered frail at baseline. Unfortunately, no data regarding weight changes were available before the enrollment in the OAI. Another concern regarding weight loss is that the reasons of this were not investigated and it is possible that some participants lost weight intentionally over the 8-year follow-up for improving the symptoms related to OA. Moreover, participants of the OAI are at high risk of OA at baseline and this could introduce another bias in our results. We were, moreover, unable to assess the influence of bio-humoral markers (e.g. inflammation, insulin-resistance) on the association between Mediterranean diet and frailty. In addition, the medical conditions were simply self-reported and not adjudicated by trained physicians. Fourth, we used a slightly modified version of the well-known Mediterranean diet adherence score[29]. Finally, as we did not consider changes in dietary habits between baseline and the follow-up, this too could have introduced another bias.

In conclusion, our data analysis indicated that a higher adherence to a Mediterranean diet is associated with lower incidence of frailty, even after adjusting for several important confounders.

As far as single components were concerned, less consumption of poultry was associated with higher risk of frailty; this could suggest that animal origin proteins should be included in an optimum Mediterranean diet. Future interventional studies are warranted to confirm our findings.

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