Mediterranean diet and risk of frailty syndrome among women with type 2 diabetes

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ABSTRACT

Background: Previous research indicates that patients with type 2 diabetes are at higher risk of becoming frail. Emerging evidence also indicates that the Mediterranean diet may prevent frailty in the older population.

Objective: The aim of this study was to assess whether a Mediterranean-style diet pattern was associated with lower risk of frailty among older women with diabetes.

Design: This was a prospective cohort study in 8970 women aged ≥60 y with type 2 diabetes from the Nurses' Health Study. Adherence to the alternate Mediterranean diet (aMED) score was first measured in 1990 and repeated every 4 y until 2010. Frailty occurrence was ascertained up to 2012 and was defined as having ≥3 of the following 5 criteria from the fatigue, resistance, aerobic, illnesses, loss of weight (FRAIL) scale: Fatigue, low Resistance, low Aerobic capacity, having ≥5 Illnesses, and weight Loss of ≥5%. Those with frailty at baseline were excluded.

Results: During follow-up, we identified 569 incident cases of frailty. After adjustment for lifestyle factors and medication use, the HR (95% CI) of frailty was 1 for the lowest quartile of the aMED score, 0.88 (0.71, 1.10) for the second quartile, 0.69 (0.53, 0.88) for the third quartile, and 0.54 (0.42, 0.71) for the highest quartile (*P*-trend < 0.001). A 2-point (∼1 SD) increase in the aMED score was associated with a 28% (95% CI: 19%, 36%) reduced risk of frailty. The largest reduction in the risk was observed for a higher consumption of vegetables and fruit, as well as for alcohol intake.

Conclusion: A Mediterranean-style diet pattern was associated with reduced risk of frailty syndrome in older women with type 2 diabetes. *Am J Clin Nutr* 2018;107:763–771.

Keywords: Mediterranean diet, frailty, type 2 diabetes, Nurses' Health Study, women

INTRODUCTION

Frailty is a geriatric syndrome characterized by a state of increased vulnerability to stressors (e.g., urinary infection, a new drug treatment), which leads to an increased risk of falls, hospitalization, disability, institutionalization, or death, both among individuals from the general population and those with diabetes (1). Frailty is a common condition with an average prevalence in cohorts from different countries of ∼10% in the population over the age of 60 y and reaching 25% in those aged ≥80 y (2). Moreover, frailty shows an important social gradient, in that women and less educated persons are more likely to be frail (3). As a result, frailty is considered to be an emerging public health priority (4).

Diabetes increases the risk of frailty by accelerating the rate of muscle loss and by increasing the incidence of several chronic diseases (5). In addition, oral antidiabetic therapy may aggravate frailty by contributing to muscle loss (6). Frailty also influences an individual's ability to effectively manage several diseases frequently associated with diabetes, such as cardiovascular disease (CVD), cancer, and chronic obstructive lung disease, and worsens the prognosis of these diseases (7, 8). Therefore, preventive strategies that help reduce the incidence of frailty in diabetic patients need to be identified.

There is emerging evidence that links diet to frailty; specifically, adherence to a Mediterranean diet and other healthy dietary patterns, which include high amounts of vegetables and fruit, whole grains, a high content of polyunsaturated oils, and high amounts of proteins from fish, poultry, beans, or nuts, have been

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Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: aMED, alternate Mediterranean diet; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; FRAIL, fatigue, resistance, aerobic, illnesses, loss of weight; NHS, Nurses' Health Study.

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related to a lower risk of frailty in older adults (9–11). Healthy diets have also been shown to improve glycemic control and reduce insulin sensitivity, to improve lipid profile, and to reduce the risk of CVD in diabetic individuals (12–14). Because patients with type 2 diabetes are at higher risk of frailty, it is of interest to examine the impact of nutritional factors in this population. Therefore, in this study, we investigated whether greater adherence to a Mediterranean-style diet, adapted to the American population from the traditional diet pattern in the Mediterranean countries, was associated with a lower risk of frailty among women with type 2 diabetes from the Nurses' Health Study (NHS).

METHODS

Study design and participants

The NHS was established in 1976 with an enrollment of 121,700 female nurses aged 30–55 y at study entry (15). Participants completed baseline and follow-up questionnaires reporting medical history, health-related behaviors, and dietary intake. For this analysis, we included women aged ≥60 y who reported physician-diagnosed type 2 diabetes on any questionnaire between 1992 and 2010 (1949 women with prevalent diabetes in 1992 and 7021 women with incident diabetes during the follow-up), with complete information for the exposure and outcome variables (**Supplemental Figure 1**). We examined the relation between habitual diet and frailty occurrence up to 2012. The Harvard School of Public Health and Brigham and Women's Hospital Human Subjects Committee Review Board approved the protocol of the study.

Ascertainment of type 2 diabetes

A supplementary questionnaire was mailed to women who indicated on any biennial questionnaire that they had been diagnosed as having diabetes. In accordance with the National Diabetes Data Group (16), diagnosed cases were required to meet 1 of the following criteria: *1*) an elevated glucose concentration (fasting plasma glucose ≥7.8 mmol/L, random plasma glucose ≥11.1 mmol/L, or plasma glucose ≥11.1 mmol/L after an oral glucose load) and ≥1 symptom related to diabetes (excessive thirst, polyuria, weight loss, or hunger), *2*) no symptoms other than elevated glucose concentrations on 2 occasions, or *3*) treatment with insulin or oral hypoglycemic medication. For cases of type 2 diabetes identified after 1998, the cutoff used for fasting plasma glucose concentration was lowered to 7.0 mmol/L following the American Diabetes Association criteria (17). Our validation study showed a high level of confirmation (98%) of self-reported type 2 diabetes (18).

Dietary assessment

Food-frequency questionnaires (FFQs) were sent to the participants in 1990, 1994, 1998, 2000, 2006, and 2010. In each questionnaire, participants were asked how often, on average, during the previous year they had consumed each food (with the specification of standard portion sizes). The participants could choose from several responses, depending on the type of food. With the use of the USDA National Nutrient Database for Standard Reference corresponding to the year when the dietary questionnaire was administered, we estimated total energy and nutrient intakes derived from the foods reported. These nutrients were energy-adjusted with the use of the residual method. Previous validation studies showed good correlations between energy-adjusted nutrients or food assessed by the FFQ and multiple weeks of food records completed over the preceding year in the NHS (19).

Adherence to a Mediterranean-style diet was derived from the information obtained with the FFQs with the use of the alternate Mediterranean diet (aMED) score (20). This adapted score considers the singularities of the diet of the American population, including a low consumption of olive oil and wine and a high consumption of refined cereals in the form of snacks and breakfast foods. Therefore, the score rewards 1 point if intakes are above the cohort-specific median for vegetables (without considering potatoes), legumes, fruit, nuts, whole-grain cereals, fish, and the monounsaturated to saturated fat ratio and 1 point for intakes below the cohort-specific median for red and processed meats. In addition, alcohol intake of 5–15 g/d, defining moderate consumption, receives 1 point. Thus, a higher score corresponds to a higher adherence to the Mediterranean diet, with a final score ranging from 0 to 9 points. To best represent long-term diet during follow-up and to account for changes in food consumption, we used the cumulative average of the aMED score from all available dietary questionnaires from the diagnosis of type 2 diabetes through the end of follow-up.

Ascertainment of frailty

Because the NHS lacks performance-based measures, we used a scale comprising 5 self-reported frailty criteria: fatigue, low resistance, low aerobic capacity, having several illnesses, and a significant loss of weight during the previous year (FRAIL) (21). The FRAIL scale has been shown to be correlated ($r = 0.617$, $P < 0.001$) with the Fried scale (22), the most widely used scale for frailty assessment, which includes both self-reported and performance-based measures.

In 1992, 1996, 2000, 2004, 2008, and 2012, participants completed the Medical Outcomes Study Short-Form 36 (SF-36), a 36-item questionnaire with 8 health concepts, including physical and mental components (23). From the SF-36, we assessed the first 3 frailty criteria with the following questions:

1) For fatigue: "Did you have a lot of energy?" with replies "some of the time" or "none of the time," or with the question "I could not get going," with responses of "moderate amount" or "all of the time."

2) For low resistance: "In a normal day, is your health a limitation to walk up 1 flight of stairs?" with responses of "yes" or "a lot."

3) For low aerobic capacity: "In a normal day, is your health a limitation to walk several blocks or several miles?" with responses of "yes" or "a lot."

In addition, the illnesses criterion was ascertained from the question "In the last 2 years, have you had any of these physician-diagnosed illnesses?" Participants who reported ≥5 of the following diseases (in addition to type 2 diabetes) were considered to meet this criterion: cancer, hypertension, myocardial infarction, stroke, angina, asthma, arthritis, chronic lung disease, Parkinson disease, kidney disease, congestive heart failure, and depression. Finally, the weight-loss criterion was defined as a ≥5% decrease in weight reported in 2 consecutive follow-up cycles. At the end of each follow-up cycle, incident cases of frailty were defined as participants meeting ≥3 criteria in the FRAIL scale.

Ascertainment of mortality

Deaths were reported by next of kin or the postal system or ascertained through the National Death Index. Follow-up for death was >98% complete (24). We obtained copies of death certificates and medical records to determine causes of death (classified according to the categories of the International Classification of Diseases, Ninth Revision). Death records were reviewed and coded by physicians.

Medical history, anthropometric data, and lifestyle factors

On the baseline questionnaire (1992), we collected information on age, weight and height, smoking status, and medication use. This information has been updated on each of the subsequent biennial questionnaires. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Leisure-time physical activity was reported as the average time spent per week during the preceding year in specific activities (e.g., walking outdoors, jogging, and bicycling). The time spent in each activity was multiplied by its typical energy expenditure, expressed in metabolic equivalent tasks, and then summed over all activities. Detailed information on the validity and reproducibility of self-reported weight and physical activity has been published elsewhere (25, 26).

Statistical analysis

We calculated person-years from the return date of the questionnaire in which a type 2 diabetes diagnosis was first reported until the occurrence of frailty, death, or the end of the study period (1 June 2012), whichever came first. Women identified as frail at baseline in 1992 were excluded from follow-up.

Participants were classified into 4 groups according to quartiles of the aMED score. We used Cox proportional hazards models to investigate the association between the score and frailty, adjusting for potential confounders updated at each 4-y time period. Multivariable models were adjusted for age, BMI, smoking status, energy intake, and time since diabetes diagnosis, and for medication use, including postmenopausal hormone replacement therapy, aspirin, diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other antihypertensive medication, statins and other cholesterol-lowering drugs, insulin, and oral hypoglycemic medication. We adjusted the estimates for leisure-time physical activity in a secondary analysis because physical activity is highly related to the outcome. To test for a linear dose-response relation, we considered the aMED score as a continuous variable. In addition, we calculated the risk of frailty associated with a 2-point increase in the aMED score (corresponding to 1 SD difference). The population for analysis included all participants with <3 frailty criteria at baseline (non-frail participants). We also conducted these analyses among those with none of the criteria at baseline (robust participants) to understand whether the effect of this diet pattern on frailty may differ depending on the baseline status.

We performed additional analyses assessing the association between the aMED score and each component of the FRAIL scale, to understand the effect of the diet pattern on the individual frailty criteria. Finally, we examined the association of each food component of the aMED score with the risk of frailty by using multivariable models that were also adjusted for each of the other food components of the aMED score. Analyses were performed with SAS software, version 9.4 (SAS Institute). This article follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (27).

RESULTS

Adherence to the aMED score among diabetic women was low to moderate and remained stable over the different waves in the follow-up: mean ± SD scores were 3.9 ± 1.8 in 1990, 4.3 ± 1.9 in 1994, 4.2 ± 1.8 in 1998, 4.1 ± 1.9 in 2002, 3.8 ± 1.9 in 2006, and 3.7 ± 1.9 in 2010. In **Table 1**, we show that women in the lowest quartile of the aMED score (i.e., worst adherence) had a higher BMI and were more likely to be smokers and less physically active than women in the highest quartile. The use of medication was similar across categories of the diet score; however, among those women with a higher score, the use of postmenopausal hormone replacement therapy, some antihypertensive drugs (calcium channel blockers and angiotensin-converting enzyme inhibitors), and statins was greater.

Over 22 y of follow-up, we identified 569 incident frailty cases. Overall, the aMED score was inversely associated with the risk of frailty (**Table 2**). The age-adjusted HR of frailty among diabetic women in the higher quartile of adherence to the diet score was 0.60 (95% CI: 0.47, 0.77) compared with women in the lowest quartile. After adjustment for many potential confounders, including time since diabetes diagnosis and medication use, the results did not substantially change (HR: 0.54, 95% CI: 0.42, 0.71). However, adjustment for leisure-time physical activity somewhat attenuated the association, although it remained significant. A 2-point increase in the aMED score was associated with a 28% (95% CI: 19%, 36%) lower risk of frailty. When we repeated the analyses among the robust individuals, we found a 29% (95% CI: 17%, 39%) reduced risk of frailty associated with a 2-point increase in the aMED score (Table 2). These results also held when we adjusted the models for alcohol consumption of >15 g/d.

Table 3 shows the association between the aMED score and the risk of each frailty criterion**.** Each of these was inversely associated with the diet score, in both age-adjusted models and in multivariable models without adjustment for physical activity, except for having "≥5 illnesses." Finally, when we assessed the individual dietary components included in the aMED score, we observed the largest reduction in the risk of frailty among those who consumed the greatest amount of vegetables and fruit, as well as for alcohol intake (**Table 4**). A sensitivity analysis assessing the association between moderate alcohol consumption (5–15 g/d) and risk of frailty also showed an inverse association (adjusted HR: 0.72; 95% CI: 0.55, 0.94). Adjustment for physical activity attenuated most of the associations.

DISCUSSION

In this study we found an inverse association between the aMED score and frailty in older women with type 2 diabetes.

TABLE 1
Baseline characteristics of women aged ≥60 y with type 2 diabetes according to quartiles of the aMED score in the NHS[1]

	Quartile				
	1	2	3	4	*P*-trend
Participants, *n*	2213	2520	1945	2292	
Age, y	65.2 ± 7.9	65.6 ± 7.7	66.5 ± 7.4	66.9 ± 7.1	<0.001
aMED score	2.12 ± 0.64	3.58 ± 0.36	4.68 ± 0.29	6.13 ± 0.70	<0.001
BMI, kg/m^2	30.6 ± 6.2	30.2 ± 5.9	30.4 ± 6.1	29.5 ± 5.9	<0.001
Current smoker, %	11	8	6	5	<0.001
Energy intake, kcal/d	1470 ± 495	1637 ± 522	1787 ± 534	1956 ± 530	<0.001
Leisure-time physical activity, MET-h/wk	11.3 ± 14.8	14.2 ± 18.5	16.9 ± 19.8	20.9 ± 23.4	<0.001
Number of frailty criteria, %					
0	46	52	53	55	<0.001
1	39	36	35	36	0.13
2	15	13	11	10	<0.001
Medication use,[2] %					
Aspirin	14	12	13	13	0.36
Postmenopausal hormone replacement therapy	19	23	23	26	<0.001
Diuretics	21	21	24	22	0.01
β-Blockers	25	25	25	23	0.52
Calcium channel blockers	14	15	16	16	0.002
ACE inhibitors	13	16	17	16	0.007
Other blood pressure medication	13	11	12	12	0.87
Statins	35	35	39	40	<0.001
Other cholesterol-lowering drugs	7	8	9	8	0.06
Insulin	1	1	1	1	0.70
Oral hypoglycemic drugs	15	15	14	14	0.11
Foods in the score					
Vegetables, servings/d	1.8 ± 0.8	2.6 ± 1.2	3.4 ± 1.4	4.3 ± 1.9	<0.001
Legumes, servings/d	0.6 ± 0.9	0.6 ± 0.8	0.8 ± 0.9	0.9 ± 0.9	<0.001
Fruit, servings/d	1.4 ± 0.8	2.0 ± 1.1	2.5 ± 1.1	3.2 ± 1.5	<0.001
Nuts, servings/d	0.2 ± 0.3	0.3 ± 0.4	0.3 ± 0.4	0.4 ± 0.4	<0.001
Whole grains, servings/d	0.6 ± 0.6	1.0 ± 0.8	1.2 ± 0.8	1.6 ± 1.0	<0.001
Fish, servings/d	0.2 ± 0.1	0.2 ± 0.2	0.3 ± 0.2	0.4 ± 0.3	<0.001
Monounsaturated-to-saturated fat ratio	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	<0.001
Red and processed meats, servings/d	0.9 ± 0.5	0.8 ± 0.5	0.8 ± 0.6	0.7 ± 0.5	<0.001
Alcohol intake, g/d	2.7 ± 7.2	3.5 ± 7.3	3.7 ± 6.8	4.1 ± 6.1	<0.001

[1] Values are means ± SDs unless otherwise indicated; $n = 8970$. Data correspond to different periods based on the diagnosis of type 2 diabetes during follow-up (1992–2008). Data, except for age, were directly standardized to the age distribution of the entire cohort. *P*-trend values were calculated from linear regressions with the use of quartile ordinal as the predictor variable. ACE, angiotensin-converting enzyme; aMED, alternate Mediterranean diet; MET-h, metabolic equivalent task hour; NHS, Nurses' Health Study.
[2] ≥1 time/wk.

Specifically, we observed a 28% reduction in the risk of frailty with each 2-point increase in the diet score. Moreover, among the participants who at baseline did not meet any of the criteria for frailty, a higher adherence to the aMED score was associated with a similar lower risk as in those who already presented ≥2 frailty criteria. Overall, our results indicate that adherence to a Mediterranean-style diet results in a substantial reduction in frailty risk, regardless of the number of frailty criteria at baseline.

There are a variety of scales and instruments to ascertain frailty (28). Scales with self-reported items, such as the FRAIL scale, tend to produce higher estimates of frailty than those that include performance-based measures, such as the Fried scale (29). In addition, scales with a larger number of items are more finely graded to predict health outcomes (30) but are more difficult to use in the clinical setting or in prospective cohort studies (31). There is also some discussion on whether frailty is only a physical syndrome (1, 21) or if should also include cognition and psychosocial risk factors (30). However, although more research is needed for better understanding the health consequences of the different operational definitions of frailty, most of them perform well in predicting adverse health outcomes in older individuals (32), and have allowed researchers to establish that frailty can be prevented or treated with exercise, protein-calorie supplementation, vitamin D, and reduction in polypharmacy (28).

The role of dietary patterns on the risk of frailty is still uncertain. Macronutrient needs are similar throughout adulthood, but the need of energy is substantially reduced in old age. Thus, older adults might find it difficult to follow a diet that provides a sufficient macronutrient intake to prevent sarcopenia and that also has a low caloric content to prevent obesity. In addition, older adults sometimes suffer from dental problems and swallowing difficulties, which may impair adequate nutrition (33). Also, for patients with diabetes, some antidiabetic medications and kidney disease may increase malnutrition risk (6). Thus, our results associating a higher adherence to a Mediterranean-style diet with a lower risk of frailty suggest that this diet pattern may contribute to address the nutritional challenges of older people with diabetes. In addition, our results extend the knowledge of the health

TABLE 2
Association between aMED score (in quartiles) and frailty among women aged ≥60 y with incident type 2 diabetes in the NHS (1992–2012)[1]

	Quartile					
	1	2	3	4	*P*-trend	HR (95%CI) for a 2-point increase in aMED score
All nonfrail (0, 1, or 2 frailty criteria at baseline)						
Participants (total $n = 8970$), n	2213	2520	1945	2292		
Person-years	8819	10,086	7825	9193		
Frailty events (total $n = 569$), n	167	171	118	113		
HR (95% CI)						
Age-adjusted	1.0	0.91 (0.73, 1.13)	0.74 (0.58, 0.94)	0.60 (0.47, 0.77)	<0.001	0.76 (0.68, 0.85)
Multivariable model[2]	1.0	0.90 (0.72, 1.12)	0.71 (0.55, 0.90)	0.57 (0.44, 0.73)	<0.001	0.73 (0.65, 0.82)
Multivariable model[3]	1.0	0.88 (0.71, 1.10)	0.69 (0.53, 0.88)	0.54 (0.42, 0.71)	<0.001	0.72 (0.64, 0.81)
Multivariable model[4]	1.0	1.00 (0.80, 1.25)	0.83 (0.65, 1.07)	0.76 (0.58, 0.99)	0.02	0.85 (0.75, 0.96)
Robust (0 frailty criteria at baseline)						
Participants (total $n = 6777$), n	1584	1880	1471	1842		
Person-years	6308	7540	5918	7382		
Frailty events (total $n = 348$), n	97	105	71	75		
HR (95% CI)						
Age-adjusted	1.0	0.95 (0.71, 1.26)	0.70 (0.51 0.95)	0.64 (0.47, 0.88)	<0.001	0.75 (0.65, 0.87)
Multivariable model[2]	1.0	0.95 (0.71, 1.26)	0.67 (0.48, 0.92)	0.61 (0.44, 0.84)	<0.001	0.73 (0.62, 0.85)
Multivariable model[3]	1.0	0.95 (0.71, 1.27)	0.65 (0.47, 0.90)	0.58 (0.42, 0.82)	<0.001	0.71 (0.61, 0.83)
Multivariable model[4]	1.0	1.06 (0.79, 1.42)	0.77 (0.55, 1.08)	0.79 (0.56, 1.12)	0.04	0.83 (0.70, 0.97)

[1]ACE, angiotensin-converting enzyme; aMED, alternate Mediterranean diet; MET-h, metabolic equivalent task hour; NHS, Nurses' Health Study.
[2]Model adjusted for age (1-y increment), BMI (kg/m^2; <25.0, 25.0–29.9, or ≥30.0), smoking status (never; past; current: 1–14, 15–24, or ≥25 cigarettes/d), and energy intake (quintiles of kilocalories per day).
[3]Model additionally adjusted for years since diagnosis of type 2 diabetes (<5, 5–10, 11–14, or ≥15 y) and medication use (aspirin, postmenopausal hormone replacement therapy, diuretics, β-blockers, calcium channel blockers, ACE inhibitors, other blood pressure medication, statins and other cholesterol-lowering drugs, insulin, and oral hypoglycemic medication).
[4]Model additionally adjusted for a potential intermediate: leisure-time physical activity (quintiles of MET-h/wk).

benefits of the Mediterranean diet, which has already been shown to improve glycemic control and cardiovascular risk factors, and to lower combined endpoints for CVD events and stroke, in diabetic patients (12–14).

To construct the Mediterranean diet adherence score, we assigned equal weights to each component, although their health effects might be different. The foods included in the aMED score that were most associated with a reduction in the risk of frailty were vegetables and fruit. This is consistent with previous results among older nondiabetic populations. For example, in 3 different European populations, the consumption of 3 portions of fruit/d and 2 portions of vegetables/d was associated with a lower short-term risk of frailty (34). With regard to alcohol intake, our results are in line with those obtained in older adults from the general population, in whom a "Mediterranean drinking pattern" characterized by moderate alcohol intake (<40 g/d in men and <24 g/d in women), with a preference of wine and drinking only with meals, has been associated with a lower risk of frailty during a 3.3-y follow-up (35). In addition, vegetable and fruit consumption is part of most high-quality diets, including the Alternative Healthy Eating Index–2010 and the Dietary Approaches to Stop Hypertension (DASH) score (36, 37). Our results corroborate the essential role of these foods on health.

There is a close relation between diabetes, insulin resistance, low-grade inflammation, and sarcopenia and muscle deterioration. Specifically, insulin resistance is associated with a decrease in muscle strength, due to alterations in muscle glucose handling, intracellular energy production, and muscle contraction. All of these factors reduce protein synthesis, modulating the balance toward higher proteolytic activity and muscle weakness (38, 39). In addition, diabetes contributes to frailty through well-known macro- and microvascular complications as well as cognitive impairment (40, 41). Of note is the evidence that a Mediterranean diet improves insulin resistance, reduces chronic inflammation, lowers cardiovascular risk, and may improve cognition (42); thus, these mechanisms could help explain the inverse association between this dietary pattern and frailty in our study.

A strength of this study is the use of updated information on diet. Although patients with diabetes tend to underreport diet, the use of average cumulative consumption from several measurements over the years, and the adjustment for energy intake and BMI, may have accounted for differences in intake reporting among participants. In addition, some methodologic limitations should be mentioned. First, we used an adapted score to capture the adherence to a Mediterranean-style diet pattern in the American population. Definitions of the traditional Mediterranean diet vary across countries and the scores developed to measure adherence to this diet have differences (43). However, all of them were created to capture the uniqueness of this diet, defined by a high consumption of fruit and vegetables and legumes and nuts,

TABLE 3
Association between aMED score (in quartiles) and each frailty criterion among women with incident type 2 diabetes in the NHS (1992–2012)[1]

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-trend	HR (95%CI) for a 2-point increase in aMED score
Participants, *n*	2213	2520	1945	2292		
Fatigue						
Events (total $n = 1122$), *n*	294	344	225	259		
HR (95% CI)						
Age-adjusted	1.0	1.06 (0.91, 1.24)	0.86 (0.72, 1.03)	0.86 (0.72, 1.01)	0.007	0.90 (0.84, 0.98)
Multivariable model[2]	1.0	1.07 (0.91, 1.25)	0.85 (0.71, 1.02)	0.85 (0.71, 1.02)	0.006	0.90 (0.83, 0.98)
Multivariable model[3]	1.0	1.10 (0.94, 1.30)	0.89 (0.74, 1.07)	0.92 (0.76, 1.10)	0.06	0.94 (0.86, 1.02)
Low resistance						
Events (total $n = 465$), *n*	141	140	88	96		
HR (95% CI)						
Age-adjusted	1.0	0.86 (0.67, 1.09)	0.69 (0.53, 0.90)	0.64 (0.49, 0.83)	<0.001	0.79 (0.70, 0.89)
Multivariable model[2]	1.0	0.87 (0.69, 1.11)	0.68 (0.51, 0.89)	0.65 (0.49, 0.86)	<0.001	0.79 (0.69, 0.90)
Multivariable model[3]	1.0	0.95 (0.74, 1.21)	0.78 (0.59, 1.03)	0.83 (0.62, 1.10)	0.08	0.90 (0.78, 1.03)
Low aerobic capacity						
Events (total $n = 946$), *n*	261	281	190	214		
HR (95% CI)						
Age-adjusted	1.0	0.91 (0.76, 1.07)	0.79 (0.65, 0.95)	0.74 (0.62, 0.89)	<0.001	0.84 (0.77, 0.91)
Multivariable model[2]	1.0	0.90 (0.76, 1.07)	0.77 (0.63, 0.93)	0.75 (0.61, 0.91)	<0.001	0.83 (0.76, 0.91)
Multivariable model[3]	1.0	0.96 (0.80, 1.14)	0.85 (0.70, 1.03)	0.89 (0.73, 1.08)	0.12	0.90 (0.82, 0.99)
≥5 illnesses						
Events (total $n = 331$), *n*	70	79	88	94		
HR (95% CI)						
Age-adjusted	1.0	1.04 (0.75, 1.44)	1.34 (0.98, 1.85)	1.25 (0.91, 1.70)	0.06	1.18 (1.02, 1.35)
Multivariable model[2]	1.0	0.95 (0.68, 1.33)	1.19 (0.86, 1.66)	1.03 (0.74, 1.44)	0.46	1.08 (0.93, 1.27)
Multivariable model[3]	1.0	0.99 (0.71, 1.38)	1.28 (0.91, 1.78)	1.12 (0.79, 1.58)	0.23	1.13 (0.96, 1.33)
Weight loss ≥5%						
Events (total $n = 1513$), *n*	394	437	309	373		
HR (95% CI)						
Age-adjusted	1.0	0.94 (0.82, 1.08)	0.87 (0.75, 1.01)	0.89 (0.77, 1.03)	0.07	0.94 (0.88, 1.01)
Multivariable model[2]	1.0	0.90 (0.78, 1.04)	0.83 (0.71, 0.97)	0.78 (0.67, 0.91)	<0.001	0.89 (0.83, 0.96)
Multivariable model[3]	1.0	0.91 (0.79, 1.04)	0.83 (0.71, 0.97)	0.78 (0.67, 0.92)	0.002	0.89 (0.83, 0.96)

[1]ACE, angiotensin-converting enzyme; aMED, alternate Mediterranean diet; MET-h, metabolic equivalent task hour; NHS, Nurses' Health Study.
[2]Model adjusted for age (1-y increment), BMI (kg/m^2; <25.0, 25.0–29.9, or ≥30.0), smoking status (never; past; current: 1–14, 15–24, or ≥25 cigarettes/d), energy intake (quintiles of kilocalories per day), years since diagnosis of type 2 diabetes (<5, 5–10, 11–14, or ≥15 y) and medication use (aspirin, postmenopausal hormone replacement therapy, diuretics, β-blockers, calcium channel blockers, ACE inhibitors, other blood pressure medication, statins and other cholesterol-lowering drugs, insulin, and oral hypoglycemic medication).
[3]Model additionally adjusted for a potential intermediate: leisure-time physical activity (quintiles of MET-h/wk).

a high fat intake, moderate consumption of fish, and a low intake of meat and meat products, with moderate alcohol consumption, usually as wine consumed with meals. Second, frailty and physical activity are closely related. In fact, in all definitions of frailty, physical activity is included to some extent. For example, in the operational definition of frailty by Fried et al. (1), individuals are categorized into quintiles of self-reported physical activity measured with standard questionnaires, and the lowest quintile defines the cutoff of the "Low activity" criterion. Similarly, in the FRAIL scale (21), physical activity was assessed with a question about the ability to walk several blocks or miles. For this reason, it is unclear whether frailty analyses should be adjusted for physical activity. When we accounted for this factor in secondary analyses, the beneficial effects of the Mediterranean diet were attenuated but the association remained significant, suggesting that the inverse association between diet quality and frailty is not fully explained by physical activity levels. Third, we adjusted for updated information on the use of medication, in order to account for the severity of the diabetes and other cardiometabolic disorders. The fact that women with a higher Mediterranean diet score also had greater medication use might indicate that women in this cohort improved diet quality when they were diagnosed with a chronic disease. We also adjusted for a wide range of other potential confounders, although we were not able to account for the degree of social support received or unknown factors that might also have had an impact on the association found; therefore, we cannot rule out some residual confounding. Fourth, our results should be confirmed with the use of other operational definitions of frailty, including the Fried scale (1) and the Frailty index (30), because the latter represents an alternative conceptual model of frailty (e.g., cumulative deficit model). Finally, given that results were obtained from a relatively homogeneous cohort of female health professionals with diabetes, with a similar socioeconomic level and access to health care, extrapolation to patients other than those included in the study should be made with caution.

In conclusion, a Mediterranean-style diet pattern was associated with a reduced risk of frailty in older women with type 2 diabetes. This finding is of relevance because frailty reflects a

TABLE 4

Association between dietary components included in the aMED score (in quartiles) and frailty among women aged ≥60 y with incident type 2 diabetes in the NHS (1992–2012)[1]

	Quartile				
	1	2	3	4	*P*-trend
Vegetables, servings/d					
Participants, *n*	2242	2242	2244	2242	
Frailty events, *n*	173	147	122	127	
HR (95% CI)					
Age-adjusted	1.0	0.85 (0.68, 1.06)	0.70 (0.56, 0.89)	0.72 (0.57, 0.91)	0.003
Multivariable model[2]	1.0	0.87 (0.68, 1.10)	0.68 (0.53, 0.91)	0.71 (0.53, 0.95)	0.02
Multivariable model[3]	1.0	0.91 (0.72, 1.16)	0.75 (0.58, 0.99)	0.82 (0.61, 1.10)	0.16
Legumes, servings/d					
Participants, *n*	2227	2222	2284	2237	
Frailty events, *n*	150	124	147	148	
HR (95% CI)					
Age-adjusted	1.0	0.83 (0.65, 1.05)	0.96 (0.76, 1.21)	1.05 (0.83, 1.33)	0.25
Multivariable model[2]	1.0	0.89 (0.69, 1.15)	1.08 (0.84, 1.40)	1.18 (0.92, 1.53)	0.07
Multivariable model[3]	1.0	0.94 (0.73, 1.20)	1.16 (0.89, 1.49)	1.24 (0.96, 1.60)	0.05
Fruit, servings/d					
Participants, *n*	2241	2244	2244	2241	
Frailty events, *n*	161	133	139	136	
HR (95% CI)					
Age-adjusted	1.0	0.74 (0.58, 0.93)	0.71 (0.56, 0.90)	0.66 (0.52, 0.83)	0.002
Multivariable model[2]	1.0	0.78 (0.61, 0.99)	0.76 (0.59, 0.98)	0.70 (0.53, 0.93)	0.02
Multivariable model[3]	1.0	0.83 (0.65, 1.06)	0.82 (0.63, 1.06)	0.78 (0.59, 1.04)	0.12
Nuts, servings/d					
Participants, *n*	2250	2219	2260	2241	
Frailty events, *n*	154	140	126	149	
HR (95% CI)					
Age-adjusted	1.0	0.94 (0.74, 1.19)	0.81 (0.64, 1.03)	0.99 (0.79, 1.25)	0.91
Multivariable model[2]	1.0	0.97 (0.76, 1.24)	0.89 (0.68, 1.12)	1.02 (0.80, 1.31)	0.78
Multivariable model[3]	1.0	0.99 (0.78, 1.26)	0.91 (0.71, 1.16)	1.07 (0.83, 1.37)	0.54
Whole grains, servings/d					
Participants, *n*	2249	2230	2250	2241	
Frailty events, *n*	151	131	131	156	
HR (95% CI)					
Age-adjusted	1.0	0.83 (0.66, 1.05)	0.79 (0.63, 1.01)	0.87 (0.69, 1.09)	0.49
Multivariable model[2]	1.0	0.89 (0.70, 1.14)	0.91 (0.70, 1.17)	0.93 (0.72, 1.21)	0.93
Multivariable model[3]	1.0	0.94 (0.73, 1.20)	0.96 (0.75, 1.25)	1.00 (0.77, 1.29)	0.75
Fish, servings/d					
Participants, *n*	2225	2242	2264	2239	
Frailty events, *n*	164	143	130	132	
HR (95% CI)					
Age-adjusted	1.0	0.92 (0.73, 1.15)	0.85 (0.67, 1.08)	0.86 (0.68, 1.08)	0.20
Multivariable model[2]	1.0	0.95 (0.75, 1.20)	0.95 (0.74, 1.22)	1.01 (0.78, 1.32)	0.88
Multivariable model[3]	1.0	1.00 (0.79, 1.26)	1.00 (0.78, 1.28)	1.09 (0.83, 1.41)	0.52
Monounsaturated-to-saturated fat ratio					
Participants, *n*	2241	2243	2244	2242	
Frailty events, *n*	157	144	152	116	
HR (95% CI)					
Age-adjusted	1.0	0.89 (0.71, 1.12)	0.96 (0.76, 1.20)	0.72 (0.56, 0.92)	0.01
Multivariable model[2]	1.0	0.98 (0.77, 1.24)	1.06 (0.83, 1.34)	0.87 (0.67, 1.12)	0.36
Multivariable model[3]	1.0	0.99 (0.78, 1.26)	1.07 (0.84, 1.36)	0.87 (0.67, 1.13)	0.39
Red and processed meats, servings/d					
Participants, *n*	2245	2243	2239	2243	
Frailty events, *n*	140	137	145	147	
HR (95% CI)					
Age-adjusted	1.0	1.02 (0.80, 1.30)	1.16 (0.91, 1.47)	1.25 (0.98, 1.58)	0.04
Multivariable model[2]	1.0	0.95 (0.74, 1.22)	1.01 (0.78, 1.30)	1.02 (0.78, 1.33)	0.77
Multivariable model[3]	1.0	0.95 (0.74, 1.22)	0.98 (0.76, 1.26)	0.94 (0.72, 1.24)	0.74
Alcohol intake, g/d					
Participants, *n*	3301	1156	2270	2243	
Frailty events, *n*	258	81	129	101	
HR (95% CI)					
Age-adjusted	1.0	0.75 (0.58, 0.97)	0.72 (0.58, 0.89)	0.54 (0.43, 0.68)	<0.001
Multivariable model[2]	1.0	0.73 (0.56, 0.96)	0.70 (0.56, 0.88)	0.54 (0.42, 0.69)	<0.001
Multivariable model[3]	1.0	0.77 (0.59, 1.00)	0.75 (0.60, 0.94)	0.60 (0.47, 0.77)	<0.001

[1]ACE, angiotensin-converting enzyme; aMED, alternate Mediterranean diet; MET-h, metabolic equivalent task hour; NHS, Nurses' Health Study.

[2]Model adjusted for age (1-y increment), BMI (kg/m^2; <25.0, 25.0–29.9, or ≥30.0), smoking status (never; past; current: 1–14, 15–24, or ≥25 cigarettes/d), energy intake (quintiles of kilocalories per day), years since diagnosis of type 2 diabetes (<5, 5–10, 11–14, or ≥15 y) and medication use (aspirin, postmenopausal hormone replacement therapy, diuretics, β-blockers, calcium channel blockers, ACE inhibitors, other blood pressure medication, statins and other cholesterol-lowering drugs, insulin, and oral hypoglycemic medication). Food components were mutually adjusted for each other.

[3]Model additionally adjusted for a potential intermediate: leisure-time physical activity (quintiles of MET-h/wk).

state of decreased physiologic reserve and vulnerability as well as comorbidity and thus has emerged as a main target to maintain or improve well-being in the older population. Future research should assess if interventions with a Mediterranean-style diet can effectively prevent frailty and reduce the subsequent risk of falls, hospitalization, disability, and institutionalization, which already represent a great burden for individuals, families, and health- and social-care organizations.

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