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Original Investigation

Consumption of Olive Oil and Risk of Total and Cause-Specific Mortality Among U.S. Adults

Marta Guasch-Ferré PhD [a, b], Yanping Li PhD [a], Walter C. Willett MD, DrPH [a, b, c], Qi Sun MD, ScD [a, b, c, d], Laura Sampson RD [a], Jordi Salas-Salvadó MD [e, f], Miguel A. Martínez-González MD [a, e, g], Meir J. Stampfer MD, DrPH [a, b, c], Frank B. Hu MD, PhD [a, b, c]

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Referred to by Susanna C. Larsson

Can Small Amounts of Olive Oil Keep the Death Away?*

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Abstract

Background

Olive oil consumption has been shown to lower cardiovascular disease risk, but its associations with total and cause-specific mortality are unclear.

Objectives

FEEDBACK

total and cause-specific mortality among 60,582 women (Nurses' Health Study, 1990-2018) and 31,801 men (Health Professionals Follow-up Study, 1990-2018) who were free of cardiovascular disease or cancer at baseline. Diet was assessed by a semiquantitative food frequency questionnaire every 4 years.

Results

During 28 years of follow-up, 36,856 deaths occurred. The multivariable-adjusted pooled HR for all-cause mortality among participants who had the highest consumption of olive oil (>0.5 tablespoon/day or >7 g/d) was 0.81 (95% CI: 0.78-0.84) compared with those who never or rarely consumed olive oil. Higher olive oil intake was associated with 19% lower risk of cardiovascular disease mortality (HR: 0.81; 95% CI: 0.75-0.87), 17% lower risk of cancer mortality (HR: 0.83; 95% CI: 0.78-0.89), 29% lower risk of neurodegenerative disease mortality (HR: 0.71; 95% CI: 0.64-0.78), and 18% lower risk of respiratory disease mortality (HR: 0.82; 95% CI: 0.72-0.93). In substitution analyses, replacing 10 g/d of margarine, butter, mayonnaise, and dairy fat with the equivalent amount of olive oil was associated with 8%-34% lower risk of total and cause-specific mortality. No significant associations were observed when olive oil was compared with other vegetable oils combined.

Conclusions

Higher olive oil intake was associated with lower risk of total and cause-specific mortality. Replacing margarine, butter, mayonnaise, and dairy fat with olive oil was associated with lower risk of mortality.

Central Illustration

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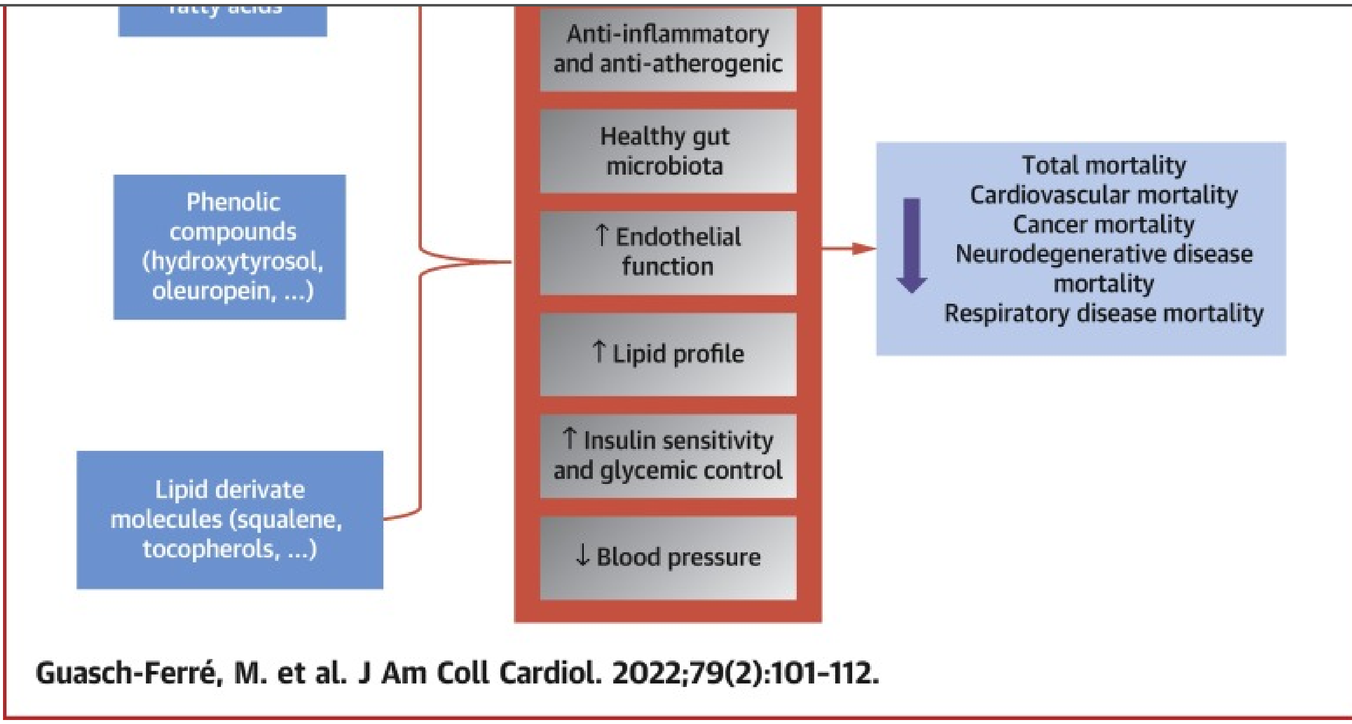

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Key Words

cause-specific mortality; nutrition; olive oil; plant oils; total mortality

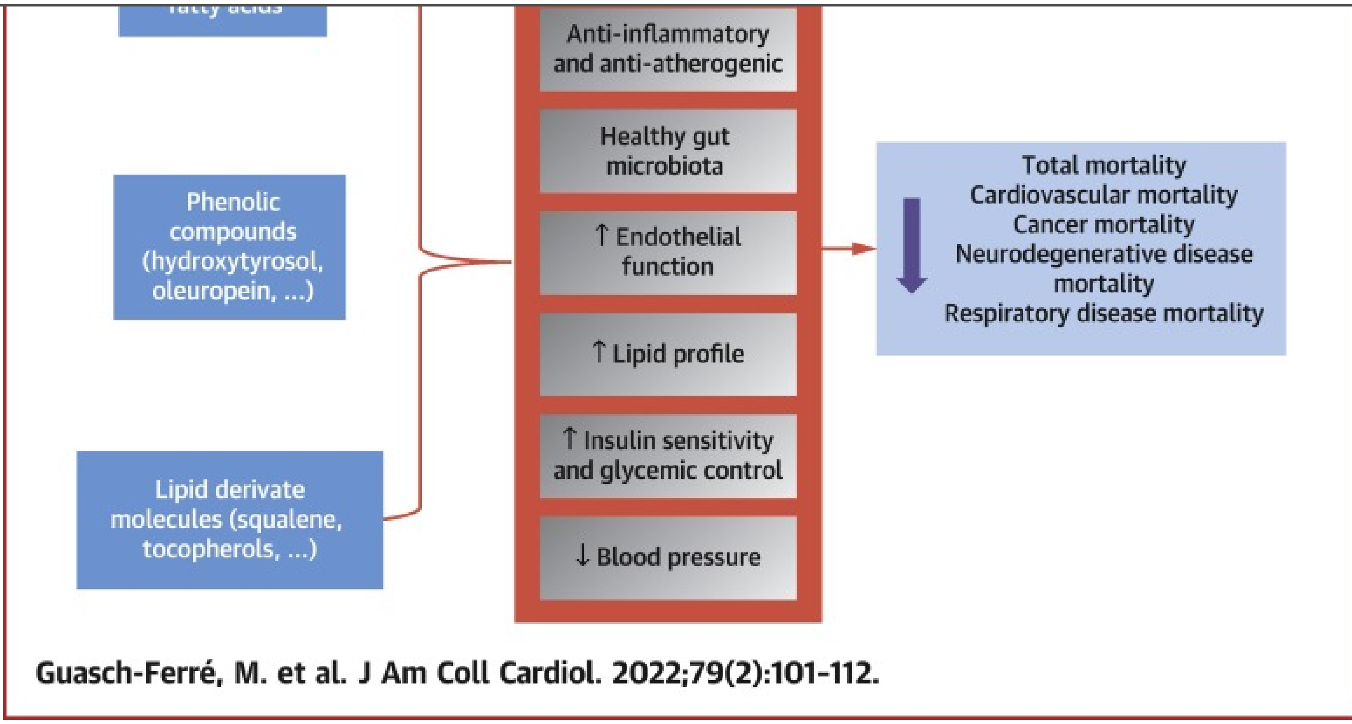
Abbreviations and Acronyms

AHEI, alternative healthy eating index; FFQ, food frequency questionnaire

Olive oil has been traditionally used as the main culinary and dressing fat in Mediterranean countries and is a key component of the Mediterranean diet. Well-known for its health benefits, it has become more popular worldwide in recent decades. Olive oil is high in mono

FEEDBACK

was associated with a lower risk of CVD (2). These findings were consistent with results from the PREDIMED (PREvención con DIeta MEDiterránea) trial showing that compared with a control diet, participants allocated to a Mediterranean diet supplemented with a free provision of extra virgin olive oil reduced the risk of a composite of CVD events by 31% (3). In a secondary analysis of the PREDIMED trial, baseline intake of olive oil was associated with lower risk of cardiovascular mortality (4). Other studies conducted in Mediterranean and European countries have also suggested that greater olive oil consumption is associated with a lower risk of all-cause and cardiovascular mortality (5, 6, 7). However, to date, no large prospective studies have examined the association between total olive oil consumption and total and cause-specific mortality in the U.S. population, where the average consumption of olive oil is considerably lower than that in Mediterranean countries (Central Illustration). Therefore, we examined the association between total consumption of olive oil and total and cause-specific mortality in 2 large cohorts of U.S. men and women. In addition, we used statistical substitution models to estimate the risk of total and cause-specific mortality when margarine, butter, mayonnaise, dairy fat, and vegetable oils were replaced by an equivalent amount of olive oil.



Central Illustration. Potential Mechanisms for Olive Oil Intake and Mortality

Olive oil is high in bioactive compounds and has been associated with lower risk of total and cause-specific mortality in 2 prospective cohorts including 92,383 U.S. men and women followed-up for up to 28 years. Potential mechanisms of these associations include olive oil being less susceptible to oxidation; having anti-inflammatory and antiatherogenic properties; and improving oxidative stress, endothelial function, lipid profile, insulin sensitivity, and blood pressure. ↑ = improvement; ↓ = worsening.

Methods

Study population

The analysis was conducted in 2 ongoing prospective cohort studies. The NHS was initiated in 1976 and included 121,701 women aged 30 to 55 years. The HPFS began in 1986, with 51,525 men aged 40 to 75 years. Both cohorts have been described previously (8,9). In both coh kcal/d for men). After exclusions, a total of 60,582 women and 31,801 men remained for the analysis. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Dietary assessment

Dietary intake was measured using a validated semiquantitative FFQ with >130 items, repeatedly administered every 4 years. The reproducibility and validity of these FFQs have been described in previous reports (10). Participants were asked how often, on average, they had consumed specific foods, as well as types of fats, oils, and brand or type of oils used for cooking and added at the table in the preceding year. Total olive oil intake was calculated from the sum of 3 items in the questionnaire pertaining to questions related to the consumption of olive oil: olive oil used for salad dressings, olive oil added to food or bread, and olive oil used for baking and frying at home. One tablespoon was considered to be equivalent to 13.5 g of olive oil. The consumed amount of other vegetable oils (eg, corn, safflower, soybean, canola) was calculated based on the participant's reported oil brand and type of fat used for cooking at home, including frying, sautéing, baking, and salad dressing. Data about homemade baked items and frying fats used at home were also incorporated. Total margarine was calculated based on the reported frequency of stick, tub, or soft margarine consumption and the amount of margarine added from baking and frying at home. The consumption of butter was calculated in the same manner. Intakes of dairy and other fats and nutrients were calculated based on the USDA and Harvard University Food Composition Database (11) and our biochemical analyses. Supplemental Table 1 shows the nutritional composition of olive oil and other types of fat.

Ascertainment of death

Deaths were identified from state vital statistics records and the National Death Index or by reports from next of kin or the postal authorities. The follow-up for mortality in these cohorts is >98% complete using these methods. Cause of death was determined by physician review of medical records, medical reports, autopsy reports, or death certificates. We used the International Classification of Diseases (ICD)-8th Revision in NHS and ICD-9 in HPFS, which were the ICD systems used at the time the cohorts began. Deaths were grouped into 5 major groups (CVD, cancer, neurodegenerative disease, respiratory disease, and all other causes, including suicide, injury, infections, diabetes, kidney disease, among others) (Supplemental Table 2).

Body mass index was calculated as weight in kilograms divided by the square of the height in meters. A modified Alternate Healthy Eating Index (AHEI) score, without the polyunsaturated fatty acids and the alcohol components, was used as an indicator of overall diet quality. This score was calculated based on 11 foods and nutrients that are predictive of chronic disease risk including fruit, vegetables, nuts and legumes, red and processed meat, whole grains, sodium, trans fat, and long chain omega-3 (12). A higher score denotes greater adherence to the AHEI and better diet quality.

Statistical analysis

Age-stratified Cox proportional hazards models were used to assess the associations between olive oil consumption and total and cause-specific mortality, separately for each cohort. Person time was calculated for each participant from baseline until the end of follow-up (June 30, 2018, for the NHS and January 31, 2018, for the HPFS) or death, whichever occurred first. We stopped updating dietary variables upon a report of cancer or CVD because changes in diet after the development of these conditions may confound the associations. Because most recent diet can have a stronger impact on mortality, we calculated the average of olive oil intake using the 2 most recent food frequency questionnaires (the average of 1990 and 1994 diets to predict death from 1994 to 1998, the average of 1994 and 1998 diets to predict death from 1998 to 2002, etc) using time-updated consumption. The cumulative average of olive oil from all available FFQs was used in a secondary analysis.

Olive oil consumption was categorized by frequency: never or <1 per month (reference), >0 to ≤4.5 g/d (>0 to ≤1 teaspoon), >4.5 to ≤7 g/d (>1 teaspoon to ≤1/2 tablespoon), and >7 g/d (>0.5 tablespoon), and linear trends were evaluated using the Wald test on a continuous variable representing median intakes of each category. Multivariable Cox proportional hazards regression models were used to estimate HRs and 95% CIs for total and cause-specific mortality according to olive oil intake categories. Model 1 adjusted for age and calendar time. Multivariable model 2 was further adjusted for ethnicity, Southern European/Mediterranean ancestry, marital status, living alone, smoking status, alcohol intake, physical activity, family history of diabetes, family history of myocardial infarction or cancer, personal history of hypertension or hypercholesterolemia, multivitamin use, aspirin use, in women postmenopausal status and menopausal hormone use, total energy intake, and body mass index. The categories for covariates are provided in the table footnotes. Model 3 was additionally adjusted for intake of red meat, fruits and vegetables, nuts, soda, whole grains (in quintiles), and *trans* fat.

terms based on olive oil intake (continuous variable) and the stratification variables.

We estimated the risk of total and cause-specific mortality in substitution analyses when replacing 10 g/d of other types of fats (margarine, butter, mayonnaise, other vegetable oils combined [corn, safflower, soybean, and canola], and dairy fat) with olive oil by including both continuous variables in the multivariable models and mutually adjusting for other types of fat. The difference in the coefficients from this multivariate model were used to estimate the HRs and 95% CIs for substituting 10 g/d of olive oil for the same amount of other fats.

Sensitivity analyses were conducted to test the robustness of the results. First, to account for potential confounding by socioeconomic status, the models were adjusted for census-tract median family income, median home value, and percentage with college degree. Second, to test whether the results were affected by selectively stopping updating diet, diet was continuously updated until the end of follow-up. Third, the models were adjusted for modified AHEI (without polyunsaturated fatty acids and alcohol components). Fourth, instead of using the average of the 2 most recent FFQ, the cumulative average of olive oil throughout follow-up was used. Fourth, the models were mutually adjusted for other types of fats. Fifth, the models were further adjusted for personal history of diabetes. Sixth, we conducted a sensitivity analysis excluding BMI from the models because BMI could be in the causal pathway. Seventh, we conducted a separate analysis for dementia-related death as the endpoint. Finally, we applied a competing risk regression model for cause-specific mortality by including olive oil as exposure and other risk factors as unconstrained covariates, allowing the effects of the covariates vary across cause-specific mortality (13).

Pooled HRs were obtained by combining data from both cohorts and stratifying by cohort (sex) and time period to increase statistical power and obtain summary estimates. Analyses were performed with the SAS statistical package version 9.4 (SAS Institute). Statistical tests were 2-sided, and *P* values <0.05 were considered statistically significant.

Results

During 28 years of follow-up, we documented 36,856 deaths (22,768 in NHS and 14,076 in HPFS). Mean consumption of olive oil increased from 1.6 g/d in 1990 to about 4 g/d in 2010, whereas margarine consumption decreased from around 12 g/d in 1990 to ~4 g/d in 2010; the intake of other fats remained stable (Supplemental Figure 1). The Spearman correlations between olive oil and other types of fat are presented in Supplemental Table 3. Baseline characteris baseline, and included 5% of the cohort participants.

Table 1. Age-Standardized Characteristics of the Study Population in 1990 by Olive Oil Consumption

	Never or <1 per mo	>0-≤4.5 g/d (>0 to ≤1 tsp)	>4.5-≤7 g/d (>1 tsp to ≤0.5 Tbsp)	>7 g/d (>0.5 Tbsp)
Nurses' Health Study				
Number of participants	32,360	22,684	2,393	3,145
Total olive oil, g/d	0.0 ± 0.0	1.5 ± 1.2	5.8 ± 0.5	9.0 ± 4.7
Age, y	56.2 ± 7.2	56.1 ± 7.0	56.3 ± 7.0	56.5 ± 7.0
Ethnicity, White	97.6	98.2	98.8	98.8
Southern European or Mediterranean ancestry	14.7	18.9	24.5	27.6
Family history of diabetes	30.5	29.3	28.0	30.2
Family history of cancer	14.5	14.6	14.3	14.0
Family history of myocardial infarction	19.0	19.5	19.8	19.8
Multivitamin use	36.8	38.9	39.1	37.6
Aspirin use	44.5	47.0	47.7	44.0
Baseline hypocholesterolemia	28.3	31.2	31.3	32.6
Baseline hypertension	18.3	18.3	17.2	17.6
Current menopausal hormone use	28.9	30.7	31.4	30.0
Current smoker	16.3	16.6	15.5	12.8
Former smoker %	35.8	41.7	46.1	48.0

Physical activity, MET-h/wk	14.4 ± 19.8	16.5 ± 22.9	18.3 ± 23.2	18.8 ± 25.9
Total calories, kcal/d	1,702 ± 497	1,762 ± 501	1,907 ± 512	1,989 ± 531
Red and processed meat, servings/d	0.9 ± 0.6	0.9 ± 0.6	0.8 ± 0.6	0.8 ± 0.6
Fruits and vegetables, servings/d	4.8 ± 1.9	5.3 ± 2	6.0 ± 2.1	6.4 ± 2.2
Total nuts, servings/d	0.1 ± 0.2	0.1 ± 0.2	0.2 ± 0.2	0.2 ± 0.2
Whole grains, servings/d	1.8 ± 1.5	1.9 ± 1.6	2.2 ± 1.7	2.3 ± 1.8
Soda, servings/d	0.8 ± 0.9	0.8 ± 0.9	0.7 ± 0.8	0.8 ± 0.9
AHEI score	41.7 ± 10.3	44.3 ± 10.2	46.5 ± 10.2	47.3 ± 10.2
Health Professionals Follow-up Study				
Number of participants	16,075	12,855	1,246	1,625
Total olive oil, g/d	0.0 ± 0.0	1.5 ± 1.1	5.8 ± 0.5	9.1 ± 4.5
Age, y	56.8 ± 9.5	56.8 ± 9.4	56.9 ± 9.4	56.9 ± 9.3
Ethnicity, White	95.4	95.7	95.2	97.0
Southern European or Mediterranean ancestry	20.6	23.8	31.6	37.9
Family history of diabetes	21.1	22.1	20.6	22.9
Family history of cancer	38.0	37.3	38.6	36.9
Family history of myocardial infarction	31.9	32.0	35.4	33.3
Multivitamin use	37.3	39.5	41.7	42.8
Aspirin use	29.8	30.0	27.5	29.8
Baseline hypocholesterolemia	19.8	21.2	22.0	23.8
Baseline hypertension	21.1	21.3	19.8	20.2
Current smoker	8.2	7.3	7.4	[illegible]

Alcohol intake, g/d	8.9 ± 13.8	11.2 ± 14.6	12.8 ± 15.0	13.3 ± 15
Physical activity, MET-h/wk	36.6 ± 42.7	37.8 ± 39.5	40.3 ± 37.4	43.6 ± 45.4
Total calories	1,897 ± 577	1,927 ± 582	2,063± 604	2,134 ± 605
Red and processed meat, servings/d	1.1 ± 0.8	1.0 ± 0.8	1.0 ± 0.8	0.8 ± 0.7
Fruits and vegetables, servings/d	5.2 ± 2.4	5.7 ± 2.4	6.6 ± 2.7	7.2 ± 2.9
Total nuts, servings/d	0.2 ± 0.3	0.3 ± 0.3	0.3 ± 0.4	0.3 ± 0.5
Whole grains, servings/d	1.0 ± 0.9	1.0 ± 0.9	1.1 ± 0.9	1.2 ± 1.1
Soda, servings/d	0.8 ± 0.9	0.7 ± 0.9	0.7 ± 0.9	0.7 ± 0.9
AHEI	41.1 ± 10.9	44.3 ± 10.5	47.2 ± 10.7	48.7 ± 10.7

Values are n, mean ± SD, or %, standardized to the age distribution of the study population.

AHEI = Alternative Healthy Eating Index (without the alcohol and polyunsaturated components, scored as 0-90, with higher scores representing healthier diets); BMI = body mass index; MET = metabolic equivalent task; Tbsp = tablespoon; tsp = teaspoon.

Age-adjusted and multivariable-adjusted models showed a consistent, significant, inverse association between olive oil intake and total and cause-specific mortality (Table 2). After adjusting for demographic and lifestyle factors, the pooled multivariable-adjusted HR for participants in the highest category of olive oil consumption, compared with those in the lowest category, were 0.81 (95% CI: 0.78-0.84) for total mortality, 0.81 (95% CI: 0.75-0.87) for cardiovascular mortality, 0.83 (95% CI: 0.78-0.89) for cancer mortality, 0.71 (95% CI: 0.64-0.78) for neurodegenerative mortality, and 0.82 (95% CI: 0.72-0.93) for respiratory mortality. Significant inverse associations for total mortality and cause-specific mortality were also observed for each 5 additional gram increase in olive oil intake as a continuous variable. Olive oil consumption was also inversely associated with other causes of death (Supplemental Table 4).

Table 2. HR (95% CI) of Total and Cause-Specific Mortality According to Categories of Total Olive Oil Intake

			Tbsp)		Trend	Olive Oil Intake
Total mortality						
NHS						
Mean total olive oil (g/d)	0.0 ± 0.0	1.6 ± 1.1	5.8 ± 0.7	14.0 ± 8.8		
N cases/person-years	10,158/527,372	8,266/603,179	1,570/117,489	2,774/238,877		
Age-adjusted model 1	1.00 (Ref.)	0.73 (0.71-0.75)	0.71 (0.67-0.75)	0.62 (0.59-0.65)	<0.001	0.90 (0.89-0.91)
Multivariable model 2	1.00 (Ref.)	0.86 (0.84-0.89)	0.85 (0.81-0.90)	0.79 (0.75-0.82)	<0.001	0.95 (0.94-0.96)
Multivariable model 3	1.00 (Ref.)	0.87 (0.84-0.89)	0.86 (0.81-0.91)	0.79 (0.75-0.82)	<0.001	0.95 (0.94-0.96)
HPFS						
Mean total olive oil (g/d)	0.0 ± 0.0	1.6 ± 1.1	5.7 ± 0.7	13.7 ± 8.5		
N cases/person-years	6,359/271,540	5,065/308,471	998/57,641	1,654/102,670		
Age-adjusted model 1	1.00 (Ref.)	0.77 (0.75-0.80)	0.75 (0.70-0.80)	0.68 (0.64-0.71)	<0.0001	0.91 (0.90-0.93)
Multivariable model 2	1.00 (Ref.)	0.91 (0.87-0.94)	0.88 (0.82-0.94)	0.84 (0.80-0.89)	<0.0001	0.96 (0.95-0.98)
Multivariable model 3	1.00 (Ref.)	0.92 (0.88-0.95)	0.89 (0.83-0.95)	0.86 (0.81-0.91)	<0.0001	0.97 (0.95-0.98)
Pooled model 3	1.00 (Ref.)	0.88 (0.86-0.90)	0.86 (0.82-0.90)	0.81 (0.78-0.84)	<0.001	0.96 (0.95-0.97)
Cardiovascular disease mortality						

N cases/person-years	2,263/527,372	1,655/603,179	266/117,489	553/238,877		
Age-adjusted model 1	1.00 (Ref.)	0.70 (0.66-0.75)	0.60 (0.53-0.69)	0.64 (0.59-0.71)	<0.001	0.91 (0.89-0.94)
Multivariable model 2	1.00 (Ref.)	0.82 (0.76-0.87)	0.73 (0.64-0.83)	0.84 (0.77-0.93)	0.002	0.98 (0.95-1.01)
Multivariable model 3	1.00 (Ref.)	0.83 (0.77-0.88)	0.74 (0.65-0.84)	0.85 (0.77-0.94)	0.006	0.98 (0.95-1.01)
HPFS						
N cases/person-years	1,993/275,615	1,383/311,810	269/58,305	439/103,761		
Age-adjusted model 1	1.00 (Ref.)	0.73 (0.68-0.78)	0.71 (0.63-0.81)	0.65 (0.59-0.72)	<0.0051	0.92 (0.89-0.95)
Multivariable model 2	1.00 (Ref.)	0.84 (0.78-0.90)	0.82 (0.72-0.94)	0.81 (0.72-0.90)	0.0005	0.97 (0.94-1.00)
Multivariable model 3	1.00 (Ref.)	0.84 (0.78-0.90)	0.81 (0.71-0.93)	0.79 (0.71-0.88)	0.0002	0.97 (0.94-1.00)
Pooled model 3	1.00 (Ref.)	0.82 (0.78-0.86)	0.77 (0.70-0.84)	0.81 (0.75-0.87)	<0.0001	0.97 (0.95-0.99)
Cancer mortality						
NHS						
N cases/person-years	2,431/527,372	2,033/603,179	450/117,489	794/238,877		
Age-adjusted model 1	1.00 (Ref.)	0.77 (0.73-0.82)	0.88 (0.79-0.97)	0.75 (0.69-0.81)	<0.001	0.95 (0.93-0.98)
Multivariable model 2	1.00 (Ref.)	0.84 (0.79-0.89)	0.96 (0.87-1.07)	0.84 (0.77-0.91)	0.02	0.98 (0.95-1.00)

model 3		0.90)	1.09)	0.93)		
HPFS						
N cases/person-years	1,290/229,084	1,880/387,235	258/59,343	336/74,094		
Age-adjusted model 1	1.00 (Ref.)	0.80 (0.75-0.86)	0.82 (0.72-0.93)	0.72 (0.64-0.80)	<0.0001	0.92 (0.89-0.95)
Multivariable model 2	1.00 (Ref.)	0.88 (0.82-0.94)	0.90 (0.79-1.03)	0.81 (0.72-0.90)	0.002	0.95 (0.91-0.98)
Multivariable model 3	1.00 (Ref.)	0.89 (0.82-0.95)	0.92 (0.81-1.05)	0.83 (0.74-0.93)	0.01	0.95 (0.92-0.99)
Pooled model 3	1.00 (Ref.)	0.86 (0.82-0.90)	0.94 (0.87-1.02)	0.83 (0.78-0.89)	0.001	0.97 (0.95-0.99)
Neurodegenerative disease mortality						
NHS						
N cases/person-years	1,901/527,372	1,315/603,179	267/117,489	399/238,877		
Age-adjusted model 1	1.00 (Ref.)	0.63 (0.58-0.67)	0.67 (0.59-0.76)	0.51 (0.45-0.56)	<0.0001	0.86 (0.83-0.89)
Multivariable model 2	1.00 (Ref.)	0.84 (0.78-0.90)	0.89 (0.78-1.01)	0.69 (0.62-0.77)	<0.0001	0.92 (0.89-0.95)
Multivariable model 3	1.00 (Ref.)	0.82 (0.76-0.88)	0.85 (0.74-0.97)	0.66 (0.59-0.74)	<0.0001	0.90 (0.87-0.94)
HPFS						
N cases/person-years	834/275,027	653/310,992	127/58,189	196/103,519		
Age-adjusted model 1	1.00 (Ref.)	0.77 (0.69-0.85)	0.71 (0.59-0.85)	0.59 (0.50-0.69)	<0.00001	0.87 (0.82-0.91)

model 2		1.14)	1.14)	1.03)		
Multivariable model 3	1.00 (Ref.)	1.03 (0.93-1.15)	0.95 (0.79-1.15)	0.89 (0.75-1.05)	0.11	0.96 (0.92-1.01)
Pooled model 3	1.00 (Ref.)	0.88 (0.83-0.94)	0.88 (0.78-0.98)	0.71 (0.64-0.78)	<0.0001	0.92 (0.89-0.94)
Respiratory disease mortality						
NHS						
N cases/person-years	867/527,372	713/603,179	121/117,489	204/238,877		
Age-adjusted model 1	1.00 (Ref.)	0.77 (0.70-0.86)	0.69 (0.57-0.84)	0.59 (0.50-0.68)	<0.0001	0.86 (0.82-0.91)
Multivariable model 2	1.00 (Ref.)	0.90 (0.81-0.99)	0.80 (0.66-0.97)	0.73 (0.62-0.85)	0.0001	0.91 (0.87-0.96)
Multivariable model 3	1.00 (Ref.)	0.95 (0.86-1.05)	0.88 (0.72-1.07)	0.80 (0.68-0.95)	0.008	0.94 (0.89-0.98)
HPFS						
N cases/person-years	487/276,475	386/312,247	73/58,426	118/103,937		
Age-adjusted model 1	1.00 (Ref.)	0.82 (0.72-0.94)	0.76 (0.59-0.98)	0.70 (0.57-0.85)	0.001	0.91 (0.85-0.97)
Multivariable model 2	1.00 (Ref.)	0.95 (0.83-1.09)	0.87 (0.68-1.12)	0.83 (0.67-1.02)	0.07	0.95 (0.89-1.01)
Multivariable model 3	1.00 (Ref.)	0.97 (0.85-1.12)	0.90 (0.70-1.16)	0.88 (0.71-1.09)	0.21	0.97 (0.91-1.03)
Pooled model 3	1.00 (Ref.)	0.95 (0.87-1.03)	0.88 (0.75-1.03)	0.82 (0.72-0.93)	0.002	0.94 (0.91-0.98)

hypercholesterolemia (yes/no), in women postmenopausal status and menopausal hormone use (premenopausal, postmenopausal [no, past, or current hormone use]), total energy intake (kilocalories/d) and body mass index (calculated as weight in kilograms divides by height in meters squared). Model 3 was additionally adjusted for red meat, fruits and vegetables, nuts, soda, whole grains intake (in quintiles), and trans fat. Results were pooled using a pooled dataset and stratifying by cohort (sex) and time period.

HPFS = Health Professionals Follow-up Study; NHS = Nurses' Health Study; other abbreviations as in Table 1.

Although participants were similar in education and occupation, in sensitivity analyses we adjusted for census-tract neighborhood median family income, home value, and percentage with college degree to control further for the potential confounding effects of socioeconomic status. However, these additional adjustments did not materially change the results (pooled HR for total mortality for high vs low olive oil intake was 0.81 (95% CI: 0.78-0.84) (Supplemental Table 5). In addition, consistent results were observed when we continuously updated the diet regardless of the development of intermediate outcomes (pooled HR for total mortality comparing high vs low intake: 0.93; 95% CI: 0.89-0.97; *P* trend = 0.02). When the models for total olive oil were adjusted for the modified AHEI (excluding polyunsaturated fatty acids and alcohol) instead of adjusting for food groups, the estimates for total and cause-specific mortality were consistent with those in the primary analysis (Supplemental Table 6). Olive oil intake was also inversely associated with the risk of total and cause-specific mortality when we used the cumulative average instead of using the average of the 2 most recent FFQs (Supplemental Table 7). Similarly, when the models for olive oil were mutually adjusted for other types of fat, the estimates remained largely unchanged (Supplemental Table 8). Results were also consistent when we further adjusted the models for personal history of diabetes (pooled HR for total mortality comparing high vs low intake: 0.81; 95% CI: 0.78-0.84; *P* trend <0.001) and when BMI was excluded from the models (pooled HR for total mortality comparing high vs low intake: 0.80; 95% CI: 0.78-0.84; *P* trend <0.001). The pooled HR for dementia-related mortality comparing high vs low intake of olive oil was 0.73 (95% CI: 0.66-0.81; *P* trend <0.001), after adjusting for potential confounders. Finally, when applying a competing risk regression model for cause-specific mortality, the results remained consistent with the primary analysis (Supplemental Table 9).

We found significant inverse associations for olive oil intake and total and cause-specific mortality in most of the prespecified subgroup analyses (Table 3). Participants reporting Southern European and/or Mediterranean ancestry had higher consumption of olive oil; they had a 6% (HR: 0.94; 95% CI: 0.92-0.96) lower risk of total mortality, slightly more pronounc

Oil Intake

	Adjusted HR (95% CI)				
	Total Mortality	CVD Mortality	Cancer Mortality	Neurodegenerative Mortality	Respiratory Mortality
Age					
Younger (<65 y)	0.97 (0.93-1.01)	0.90 (0.80-1.02)	0.99 (0.94-1.05)	0.99 (0.81-1.22)	0.85 (0.64-1.13)
Older (≥65 y)	0.89 (0.88-0.90)[a]	0.88 (0.86-0.90)	0.92 (0.90-0.94)[a]	0.83 (0.81-0.86)[a]	0.86 (0.83-0.90)[a]
Body mass index, kg/m^2					
<25	0.95 (0.94-0.96)	0.96 (0.93-0.99)	0.96 (0.94-0.99)	0.92 (0.88-0.95)	0.97 (0.92-1.02)
25-30	0.94 (0.92-0.97)	0.97 (0.92-1.01)	0.97 (0.94-1.01)	0.88 (0.82-0.94)	0.89 (0.81-0.98)
>30	0.95 (0.93-0.98)	0.97 (0.92-1.03)	0.98 (0.93-1.03)	0.88 (0.79-0.98)	0.89 (0.79-1.00)
Physical activity					
Below median (<18.5 MET-h/wk)	0.95 (0.94-0.96)	0.97 (0.95-0.99)	0.97 (0.95-1.00)	0.92 (0.88-0.95)	0.92 (0.88-0.96)
Above median (≥18.5 MET-h/wk)	0.94 (0.93-0.96)	0.97 (0.93-1.00)	0.94 (0.91-0.97)	0.93 (0.88-0.97)	0.90 (0.83-0.98)
Family history of myocardial infarction					
No	0.95 (0.94-0.97)	0.98 (0.96-1.00)	0.97 (0.95-0.99)	0.91 (0.88-0.94)	0.94 (0.90-0.98)

Ancestry					
Southern European/Mediterranean	0.94 (0.92-0.96)	0.96 (0.92-0.99)	0.96 (0.93-0.99)	0.91 (0.86-0.95)	0.95 (0.91-0.99)
Other ancestry	0.96 (0.94-0.97)	0.97 (0.94-0.99)	0.97 (0.95-0.99)	0.93 (0.90-0.96)	0.91 (0.84-0.99)
Baseline hypercholesterolemia					
No	0.96 (0.95-0.97)	0.98 (0.95-1.00)	0.97 (0.94-0.99)	0.92 (0.89-0.95)	0.95 (0.91-0.99)
Yes	0.95 (0.93-0.97)	0.94 (0.91-0.98)	0.98 (0.94-1.02)	0.94 (0.89-0.98)	0.92 (0.85-0.99)
Baseline hypertension					
No	0.96 (0.95-0.97)	0.98 (0.96-1.01)	0.97 (0.95-0.99)	0.92 (0.89-0.95)	0.94 (0.89-0.98)
Yes	0.96 (0.94-0.98)	0.94 (0.90-0.98)	0.98 (0.94-1.02)	0.93 (0.88-0.98)	0.96 (0.89-1.03)
Personal history of diabetes					
No	0.95 (0.94-0.96)	0.97 (0.95-1.00)	0.97 (0.95-0.99)	0.91 (0.88-0.94)	0.95 (0.92-0.99)
Yes	0.95 (0.93-0.97)	0.94 (0.90-0.99)	0.98 (0.93-1.03)	0.92 (0.86-0.99)	0.88 (0.78-0.98)
AHEI					
Below median (<44 points)	0.95 (0.94-0.96)	0.95 (0.91-0.98)	0.98 (0.95-1.01)	0.91 (0.86-0.95)	0.92 (0.87-0.98)
Above median (≥44 points)	0.97 (0.95-0.98)	0.98 (0.96-1.00)[a]	0.97 (0.94-0.99)	0.93 (0.90-0.96)	0.96 (0.91-1.00)
Total vegetable intake					

Above median (≥5 servings/d)	0.96 (0.95-0.97)	0.99 (0.97-1.02)[a]	0.98 (0.96-1.00)	0.94 (0.91-0.97)	0.97 (0.93-1.02)[a]
Green vegetable intake					
Below median (<1.4 servings/d)	0.95 (0.93-0.96)	0.94 (0.91-0.97)	0.98 (0.95-1.01)	0.93 (0.90-0.97)	0.90 (0.85-0.96)
Above median (≥1.4 servings/d)	0.96 (0.95-0.98)	0.99 (0.97-1.03)[a]	0.96 (0.94-0.99)	0.91 (0.87-0.95)[a]	0.98 (0.93-1.03)[a]
Lettuce intake					
Below median (<0.6 servings/d)	0.95 (0.94-0.96)	0.95 (0.92-0.98)	0.97 (0.95-1.00)	0.92 (0.89-0.96)	0.93 (0.88-0.98)
Above median (≥0.6 servings/d)	0.96 (0.95-0.98)	0.99 (0.97-1.03)	0.97 (0.94-0.99)	0.92 (0.88-0.96)	0.96 (0.91-1.01)
Total meat intake					
Below median (<1.3 servings/d)	0.96 (0.94-0.97)	0.98 (0.95-1.00)	0.96 (0.94-0.99)	0.93 (0.90-0.96)	0.96 (0.92-0.99)
Above median (≥1.3 servings/d)	0.95 (0.94-0.97)	0.97 (0.94-1.00)	0.97 (0.94-1.00)	0.91 (0.86-0.95)	0.97 (0.93-1.00)
Arachidonic acid					
Below median (<0.11 g/d)	0.98 (0.96-1.00)	0.97 (0.93-1.02)	0.99 (0.95-1.03)	0.97 (0.93-1.04)	0.86 (0.78-0.95)
Above median (>0.11 g/d)	0.96 (0.94-0.97)	0.97 (0.95-1.00)	0.97 (0.94-0.99)	0.90 (0.83-0.97)	0.97 (0.93-1.00)

Values are HR (95% CI). HRs for 5-g increase in olive oil intake in each subgroup category. Multivariable model was adjusted for age, ethnicity (White, non-White), Southern European/Mediterranean ancestry, married (yes/no), living alone (yes/no), smoking status (never, former, current smoker 1-14 cigarettes/d, 15-24 cigarettes/d, or ≥25 cigarettes/d), alcohol intake (0, 0.1-4.9, 5.0-9.9, 10.0-14.9, and ≥15.0 g/d), physical activity (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥27.0 MET task-h/wk), family history of diabetes, family history of myocardial infarction, family history of cancer, history of hypertension (yes/no), history of hypercholester significant interaction.

We estimated that replacing 10 g/d of margarine with 10 g/d of olive oil was associated with 13% lower risk of total mortality in multivariable-adjusted models (HR: 0.87; 95% CI: 0.85-0.89). The respective HR estimate for butter was 0.86 (95% CI: 0.83-0.88), for mayonnaise was 0.81 (95% CI: 0.78-0.84), and for dairy fat was 0.87 (95% CI: 0.84-0.89). These results were consistent for other causes of death including CVD, cancer, neurodegenerative disease, and respiratory disease mortality (Figure 1). HR and 95% CIs for all comparisons are reported in Supplemental Table 10. Substituting olive oil for other vegetable oils was not significantly associated with total or cause-specific mortality.

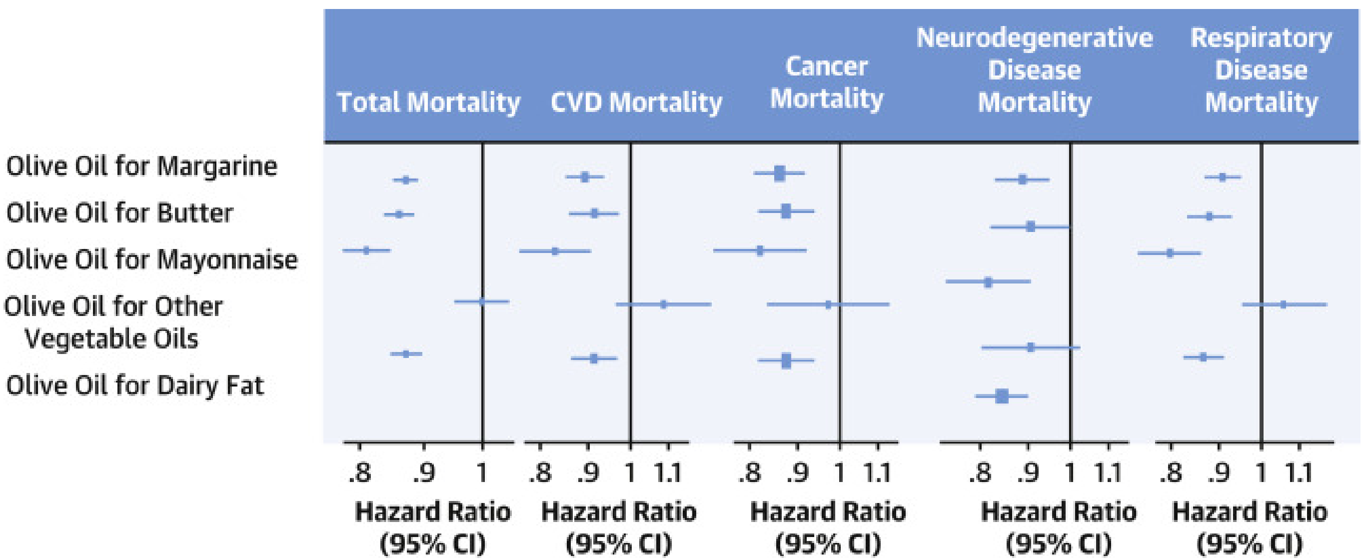


Figure 1. Mortality Associated With Olive Oil Substituted for Other Fats

HR (95% CI) for mortality substituting 10 g of olive oil for equivalent amount of other fats. Model was adjusted for age, ethnicity, ancestry, married, living alone, smoking status, alcohol intake, physical, family history of diabetes, myocardial infarction or cancer, multivitamin use, aspirin use, in women postmenopausal status and menopausal hormone use, energy intake, body mass index, red meat, fruits and vegetables, nuts, soda, whole grains, and the intake of trans fat, and mutually adjusted for the intake of other types of fat. Results were pooled using a pooled dataset and stratifying by cohort and time period. CVD = cardiovascular disease.

lifestyle factors and for potential dietary confounders. Compared with those who never or rarely consume olive oil, those in the highest category of olive oil consumption (>7 g/d) had 19% lower risk of total and CVD mortality, 17% lower risk of cancer mortality, 29% lower risk of neurodegenerative mortality, and 18% lower risk of respiratory mortality. Substituting 10 g/d of other fats, including margarine, butter, mayonnaise, and dairy fat, with olive oil was associated with reductions in the risk of total and cause-specific mortality. However, in general, no significant associations with total and cause-specific mortality were observed when other vegetable oils combined were substituted with olive oil. Overall, our data support current dietary recommendations to replace animal fats with unsaturated plant oils such as olive oil.

An inverse association between olive oil consumption and risk of CVD has been well established in large prospective cohort studies and large clinical trials, especially in Mediterranean and European countries (2,3,14). However, large prospective cohort studies evaluating whether olive oil intake affects total and cause-specific mortality were lacking. An Italian study of patients with a prior myocardial infarction showed a 24% (HR: 0.76; 95% CI: 0.64-0.91) lower risk of overall mortality for those consuming olive oil regularly compared with those who never consumed olive oil (5). The EPIC (European Prospective Investigation into Cancer and Nutrition)-Spanish cohort reported a 26% (HR: 0.74; 95% CI: 0.64-0.87) reduction in the risk of overall mortality for those in the highest quartile of total olive oil intake compared with the lowest quartile (6). The Three-City Study in France, including 8,973 participants, found that olive oil use was associated with lower risk of all-cause mortality in women but not men (7). In contrast, no associations were found between olive oil intake and all-cause mortality in a free-living Greek population (15) and in an ancillary analysis of the PREDIMED trial (16). Our study, with longer follow-up, a larger sample size, and repeated measurements of diet, showed that olive oil consumption was associated with lower risk of overall mortality in both men and women. Of note, our study showed that benefits of olive oil can be observed even when consumed in lower average amounts than in Mediterranean countries. The mean consumption of olive oil in our U.S. population was 10 g/d, whereas in Mediterranean populations, such as the Spanish participants of the PREDIMED study, the mean intake at baseline was 40 g/d (4).

Olive oil consumption may lower mortality risk in part through improving cardiometabolic risk factors (17). In line with previous observational studies conducted in Mediterranean and European countries, we observed that greater olive oil consumption was associated with 19% lower risk of CVD mortality in U.S. men and women. In the PREDIMED trial, baseline total olive oil intake was inversely associated with CVD mortality: each 10 g/d increase in tot and CVD mortality, no significant associations with the risk of cancer mortality were observed. This may be because of the relatively small number of cancer deaths in these studies. With 9,537 cancer deaths, we found that the consumption of more than one-half tablespoon per day of olive oil was associated with 16% lower risk of cancer mortality, compared with no olive oil. These associations were stronger in men than in women. Supporting our findings, a review of epidemiological studies suggested that olive oil can decrease the risk of upper digestive, respiratory, and breast cancer, and perhaps other sites (18). The PREDIMED trial showed that an intervention with Mediterranean diet supplemented with extra virgin olive oil substantially reduced the risk of breast cancer (19).

We also observed a lower risk of neurodegenerative and respiratory disease mortality. Few prior studies have reported on these associations; however, some evidence suggests that olive oil consumption may reduce cognitive decline (20,21). In the Three-City Study, participants who consumed more olive oil had a lower risk of cognitive deficit for verbal fluency and visual memory. For cognitive decline during the 4-year follow-up, the association with intensive use was significant for visual memory (adjusted OR: 0.83; 95% CI: 0.69-0.99) but not for verbal fluency (OR: 0.85; 95% CI: 0.70-1.03) in multivariate analysis (20). In 2 random subsamples of 285 and 522 participants of the PREDIMED-Navarra trial, participants allocated to the Mediterranean diet supplemented with extra virgin olive oil experienced better post-trial cognitive performance vs control in all cognitive domains and significantly better performance across fluency and memory tasks (21). Furthermore, adherence to Mediterranean diet has been associated with lower risk of cognitive impairment and Alzheimer's disease in several prospective cohort studies (22). Mechanistic evidence is accruing in support of the hypothesis that olive oil, particularly the virgin variety rich in bioactive polyphenols, also reduces the underlying pathology of Alzheimer's disease and other neurodegenerative diseases (23, 24, 25). However, further studies are needed to confirm the causality of these associations. The results for respiratory mortality are novel and to our knowledge no previous studies have evaluated these associations. One may speculate that mechanisms related to the anti-inflammatory and antioxidant properties of olive oil may have played a role in these findings, but more research is needed.

To our knowledge, this study is the first to estimate the impact of replacing specific types of fat with olive oil in relation to total and cause-specific mortality. We estimated that substituting 10 g/d of other fats including margarine, butter, mayonnaise, and dairy fat with olive oil was associated with reductions in the risk of total and cause-specific mortality. Controlled feeding studies of vegetable oils rich in monounsaturated fatty acids, including olive oil, high-oleic-acid from these cohorts, we found that higher olive oil intake was associated with lower levels of inflammatory biomarkers and a better lipid profile (2). Altogether, these potential mechanisms may have contributed to the observed inverse associations between olive oil intake and lower risk of mortality.

Study strengths and limitations

Strengths of our study include the large sample size, long-term and high rates of follow-up, detailed and repeated measurements of diet and lifestyle, and numerous sensitivity analyses that support the robustness of our results. As with any observational study, the possibility of residual confounding cannot be ruled out despite adjusting for diet and lifestyle factors in our analysis. Higher olive oil intake could be a marker of a globally healthier diet and higher socioeconomic status. However, when we adjusted for food groups, AHEI, and also for socioeconomic variables, the results remained largely unchanged. Also, our study was conducted among a predominantly non-Hispanic White population of health professionals, which minimizes potential confounding by socioeconomic factors but may limit generalizability. In our study, dietary assessment was conducted using validated self-reported FFQs, which inevitably includes measurement errors. However, the use of averaged measurements reduced random measurement errors caused by within-person variation. Unfortunately, we could not distinguish between olive oil varieties containing different amounts of polyphenols and other nonlipid bioactive compounds.

Conclusions

We found that greater consumption of olive oil was associated with lower risk of total and cause-specific mortality. Replacing other types of fat, such as margarine, butter, mayonnaise, and dairy fat, with olive oil was associated with a lower risk of mortality. Our results support current dietary recommendations to increase the intake of olive oil and other unsaturated vegetable oils in place of other fats to improve overall health and longevity.

Perspectives

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: In cohort studies of U.S. adults, replacing margarine, butter, mayonnaise, and dairy fat with olive oil is associated with lower risks of total and cause-specific mortality.

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Appendix

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Supplemental Figure 1 and Supplemental Tables 1–10.

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