Olive oil intake and mortality within the Spanish population (EPIC-Spain)\textsuperscript{1–3}

Genevieve Buckland, Ana Lucia Mayén, Antonio Agudo, Noemie Travier, Carmen Navarro, José Maríá Huerta, María Dolores Chirlaque, Aurelio Barricarte, Eva Ardanaz, Conchi Moreno-Iribas, Pilar Marin, J Ramón Quiroés, María-Luisa Redondo, Pilar Amiano, Miren Dorronsoro, Larraitz Arriola, Esther Molina, María-José Sanchez, and Carlos A Gonzalez

ABSTRACT

Background: Olive oil consumption is associated with a decreased risk of several chronic diseases, in particular cardiovascular disease (CVD). However, data on the effects of olive oil on overall mortality are scarce.

Objective: We evaluated the association between olive oil and overall and cause-specific mortality in the Spanish population in the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain).

Design: A total of 40,622 participants (62\% female) aged 29–69 years were recruited from 5 Spanish regions in 1992–1996. The association between olive oil (analyzed as a categorical and continuous variable) and overall and cause-specific mortality (CVD, cancer, and other causes) was analyzed by using Cox proportional hazards regression models adjusted for potential confounders.

Results: A total of 1915 deaths were reported during 13.4 years of follow-up: 416 CVD deaths, 956 cancer deaths, and 417 deaths from other causes (for 126 deaths the cause was not available). In comparison with nonconsumers, the highest quartile of olive oil consumption was associated with a 26\% (95\% CI: 13\%, 36\%) reduction in risk of overall mortality and a 44\% (95\% CI: 21\%, 60\%) reduction in CVD mortality. For each increase in olive oil of 10 g \cdot 2000 kcal\textsuperscript{-1} \cdot d\textsuperscript{-1}, there was a 7\% (95\% CI: 3\%, 10\%) decreased risk of overall mortality and a 13\% (95\% CI: 6\%, 20\%) decreased risk of CVD mortality. No significant association was observed between olive oil and cancer mortality.

Conclusions: Olive oil was associated with a decreased risk of overall mortality and an important reduction in CVD mortality in this large Mediterranean cohort. This provides further evidence on the beneficial effects of one of the key Mediterranean dietary components. Am J Clin Nutr 2012;96:142–9.

INTRODUCTION

Olive oil is one of the most characteristic features of the Mediterranean diet and is the main source of fat within this moderately high-fat dietary pattern. For centuries, olive oil has been recognized for its nutritional properties and has been considered an “elixir of youth and health” (1, 2). Epidemiologic studies have now confirmed that olive oil is related to a decreased risk of chronic diseases such as cardiovascular disease (CVD) and its risk factors and of certain cancers (3–5).

Several studies have reported that a Mediterranean dietary pattern reduces overall mortality (6, 7), and a study within the European Prospective Investigation into Cancer and Nutrition (EPIC)–Italy found that a dietary pattern including olive oil and salad significantly reduced mortality in the elderly (8). Although olive oil is believed to play a key role in these benefits (9–12), there is little direct epidemiologic evidence on the individual effects of olive oil on overall mortality. The Greek segment of the EPIC cohort study reported a negative but nonsignificant 4\% reduction for each 20 g/d of olive oil (13), although this study was primarily designed to study the entire Mediterranean dietary pattern. In contrast, an Italian study showed that regular consumption of olive oil, compared with no or infrequent consumption, significantly reduced mortality risk by 24\% in men and women with previous myocardial infarction (14); however, these results cannot be extrapolated to a healthy adult population.

The benefits that olive oil may have on reducing overall mortality could be partly explained by its important effects on CVD and its risk factors. The clinical randomized Mediterranean diet prevention trial (PREDIMED) has shown that an olive oil–enriched Mediterranean diet decreases blood pressure, improves

\textsuperscript{1} From the Unit of Nutrition, Environment, and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain (ALM, GB, AA, CAG, and NT); the Department of Epidemiology, Murcia Regional Health Council, Murcia, Spain (CN, JMH, and MDC); the Public Health Institute of Navarra, Pamplona, Spain (AB, EA, CM-I, and PM); the Health and Health Care Services Council, Asturias, Spain (JRQ and M-LR); the Public Health Department of Gipuzkoa, Basque Government, San Sebastián, Spain (PA, MD, and LA); the Andalusian School of Public Health, Granada, Spain (EM and M-JS); CIBER Epidemiología y Salud Pública (CIBERESP), Spain (CN, JMH, MDC, AB, EA, CM-I, PM, PA, MD, LA, EM, and M-JS); the Department of Public Health and Preventive Medicine, University of Murcia, Murcia, Spain (CN); and the Departments of Pediatrics, Obstetrics and Gynecology, and Preventive Medicine, Universidad Autónoma de Barcelona, Barcelona, Spain (CM-I).

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\textsuperscript{3} Address correspondence to G Buckland, Unit of Nutrition, Environment, and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO), Avda Gran Via 199-203, Barcelona, 08907, Spain. E-mail: gbuckland@iconcologia.net.


lipid profiles and endothelial function, and reduces metabolic syndrome (15). The high MUFA content and polyphenol constituents of olive oil are likely to be responsible for these health effects (11). For example the Eurovine study, a large crossover multicenter clinical trial, found that polyphenols in extra virgin olive oil improved lipid profiles in a dose-response manner (2).

Olive oil may also reduce mortality through its beneficial effect on risk of certain cancers. A recent review of epidemiologic studies on olive oil and cancer (5) showed that olive oil was inversely associated with risk of cancer of the upper aerodigestive tract and of breast and possibly colorectal cancer.

In conclusion, there is accumulating evidence that olive oil is associated with a decreased risk of several chronic diseases; however, it is still unclear whether olive oil, independent from the Mediterranean dietary pattern, is related to a reduction in mortality. Therefore, we studied the relation between olive oil intake and mortality (overall and cause-specific) in the EPIC-Spain cohort.

SUBJECTS AND METHODS

Study design and population

EPIC is a large, prospective, multicenter cohort study conducted in 10 European countries and designed to investigate the relation between dietary, nutritional, metabolic, and lifestyle factors and the risk of cancer and other chronic diseases. The full methodologic details have been published previously (16, 17).

This study includes the Spanish segment of EPIC, consisting of 41,438 participants (15,632 men and 25,806 women) aged 29–69 y who were recruited between 1992 and 1996 from 5 Spanish regions (Asturias, Granada, San Sebastian, Murcia, and Navarra) (18). Most of the population were blood donors (75%), and the participation rate varied from 55% to 89% between centers. The participants provided signed informed consent at recruitment, and the study was approved by the Ethics Committee of the Bellvitge Hospital (Barcelona).

Mortality ascertainment, cohort follow-up, and exclusions

Information on deaths occurring during follow-up (the date and underlying cause of death) was obtained through a record linkage between the EPIC-Spain database and the Spanish National Statistics Institute, which centralizes information from regional mortality registries. Cause of death was coded by using International Classification of Diseases (ICD)–9 until 1999 and ICD-10 from 1999 to 2009; codes 100–199 and D500–D890 for CVD and C00–C99 for cancer were used. All other causes of death, including codes D1–D48 for in situ/benign/uncertain or unknown behavior neoplasms, were categorized as “other causes.” The follow-up period for all-cause mortality began in 1992–1993 and ended between December 2006 and June 2009, depending on the center. A total of 816 participants with implausible dietary values, defined by the lowest and highest 1% of the total energy intake to energy requirement ratio, were excluded. The participants were not all free of disease at recruitment because no exclusions were made on the basis of current or previous health issues and because the main outcome was mortality. Thus, the final sample used for the analyses included 40,622 participants.

Lifestyle information

Information on sociodemographic and lifestyle factors, including questions about educational attainment, tobacco use, lifetime alcohol intake, reproductive history, physical activity, and medical history (medication use and history of diseases such as diabetes, cancer, and CVD), was obtained through an interviewer-administered lifestyle questionnaire (16, 19). Anthropometric data were also collected at recruitment by measuring each participant’s weight, height, and waist/hip circumference.

Dietary information

Each participant’s usual food intake over the previous year was obtained through individual interviews at recruitment by using a validated electronic dietary history questionnaire that contained ~600 food items (20, 21). The questionnaire was structured according to the different meals throughout the day, and participants were asked about what they ate and drank during these meals in a typical week of the year, taking into account seasonal variability. All of the foods consumed at least twice a month were registered (20).

The portions of each food consumed (g/d) were quantified by using household measures, standard measures, and 35 sets of pictures with simple foods, food mixtures, and drinks. Oil added to the salads and cooked foods was also measured by using standard household measures (20). A food-composition table was used to calculate each participant’s total energy intake (kcal/d) and daily nutrient intake (22).

Statistical analysis

Olive oil intake is presented as a function of energy density (g · 2000 kcal–1 · d–1), according to the multivariate nutrient density model (23). Olive oil was analyzed as a categorical variable [olive oil nonconsumers (reference group) and quantities of intake among consumers] and as a continuous variable (per 10 g · 2000 kcal–1 · d–1).

The distribution of baseline characteristics of the participants was described according to olive oil intake, and chi-square or Kruskal-Wallis rank-sum tests were used to assess differences between categories for categorical and continuous variables, respectively. Cox proportional hazards regression models were built to evaluate the association between olive oil intake and mortality (overall and cause-specific). Each participant’s entry time was defined according to his or her age at recruitment, and participants’ exit time was defined according to their age at death or last follow-up for participants at risk. The Cox models were stratified by age, center, and sex.

Three different models were built: 1) an unadjusted model that stratified by age, sex, and center; 2) a partially adjusted model that adjusted for nonnutritional confounding variables [BMI (in kg/m2): <25, 25–30, >30], educational status (no formal education, primary school, secondary school, technical or professional training, university degree, not specified), smoking status and number of cigarettes smoked per day (never; former; current, ≤20 cigarettes/d; current, >20 cigarettes/d; not specified), validated physical activity index (24) (inactive, moderately inactive, moderately active, and active), waist circumference (<102 cm in men and <88 cm in women compared with ≥102 cm in men and ≥88 cm in women) defined according to the
National Cholesterol Education Program–Adult Treatment Panel III cutoffs (25), alcohol intake (never drinkers, former drinkers, and current drinkers of <10, ≥10 and <20, ≥20 and <40, ≥40 g/d), and total energy intake (kcal/d)); and 3) a fully adjusted model that included the variables in the partially adjusted model plus the components of the Mediterranean diet score (26) that were identified as confounders by using the likelihood ratio test to assess whether there was a significant difference between models with and without each component, which resulted in the inclusion of fruit, vegetables, dairy, and meat in the model (g · 2000 kcal⁻¹ · d⁻¹; continuous) and exclusion of legumes, fish, and cereals. Linear trend tests were performed for categorical variables by assigning the median of each quartile category to all subjects and analyzing the new variable as a continuous variable.

Separate models were created to assess the association between olive oil and cause-specific mortality (CVD death, cancer death, and other causes of death) while censoring cases with a different cause of death from that being studied. Subgroup analyses were performed, stratifying the population by center and sex and known mortality risk factors and possible effect modifiers such as BMI, smoking status, and waist circumference. The likelihood ratio test was used to test for possible interaction between these subgroup categories by comparing models with and without an interaction term.

The association between mortality and different types of olive oil (10 g · 2000 kcal⁻¹ · d⁻¹) was assessed by separately analyzing participants who exclusively consumed virgin olive oil from those who exclusively consumed ordinary olive oil. Finally, the proportion of olive oil consumed relative to total fat intake was assessed (olive oil:total fat) and analyzed as a categorical variable [nonconsumers of olive oil (reference) and quartiles of the olive oil to total fat ratio], with adjustment for alcohol and for energy from total fat and energy from protein and carbohydrates, instead of total energy.

Three different sensitivity analyses were performed: 1) analysis excluding participants diagnosed with cancer, CVD, or diabetes before recruitment (self-reported at recruitment); 2) analysis excluding the first 2 y of follow-up; and 3) analysis excluding misreporters of energy intake according to the Goldberg et al classification (27). Schoenfeld residuals were used to test the assumption of proportional hazards, and all models met the criteria. Data were analyzed by using STATA statistical software (version 10; StataCorp LP).

### RESULTS

The distribution of participants in the 5 EPIC-Spain centers according to overall and cause-specific mortality is described in Table 1. A total of 40,622 participants (62% female) were followed up for 551,042 person-years. During this period 1915 deaths were recorded; 416 from CVD, 956 from cancer, and 417 from other causes (of which 27% were from external causes, 18% from respiratory system diseases, 12% from digestive system diseases, and 12% from nervous system diseases). Cause of death was undefined for 126 cases. Mean daily olive oil intake (g · 2000 kcal⁻¹ · d⁻¹) by center is also shown in Table 1. The highest intake was in Navarra followed by Granada, whereas the lowest was in Asturias.

The baseline characteristics of the EPIC-Spain cohort according to olive oil intake are described in Table 2. Nonconsumers of olive oil appeared to be a distinct group who did not fit the patterns of intake found among consumers. Participants with higher olive oil consumption were more likely to have a secondary education or greater, to be former smokers and never drink alcohol, and to consume more fruit and vegetables, less dairy, and fewer total calories.

HRs and 95% CIs (unadjusted, partially adjusted, and fully adjusted) for overall mortality according to olive oil intake (as a categorical and continuous variable) are presented in Table 3. In the partially adjusted model, including non-diet-related confounders plus energy and alcohol intake, there was a clear decreasing risk of mortality associated with increasing consumption of olive oil (P-trend < 0.001). There were minimal changes after dietary variables (fruit, vegetable, meat, and dairy intake) were additionally adjusted for in the fully adjusted model. In this model (which is applied in all of the subsequent Cox proportional hazards analyses), the highest quartile of olive oil consumption, in comparison with nonconsumers, was associated with a 26% reduction in risk of mortality (HR: 0.74; 95% CI: 0.64, 0.87), and there was a 7% (HR: 0.93; 95% CI 0.90, 0.97) decreased risk for each increase in olive oil of 10 g · 2000 kcal⁻¹ · d⁻¹.

The subgroup analysis for the association between olive oil intake (10 g · 2000 kcal⁻¹ · d⁻¹) and overall mortality is shown in Table 4. There was no evidence of interaction by sex. Olive oil was associated with a reduced risk of mortality in all of the centers, and there was no significant interaction. Although there seemed to be a greater decreased risk in never smokers, there was also no evidence of effect modification by smoking.

### Table 1

Distribution of participants by overall and cause-specific mortality and olive oil intake in the 5 centers of the EPIC-Spain cohort

<table>
<thead>
<tr>
<th>EPIC-Spain center</th>
<th>Cohort sample</th>
<th>Person-years</th>
<th>Total²</th>
<th>CVD</th>
<th>Cancer</th>
<th>Other</th>
<th>All</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asturias</td>
<td>8374 (36)</td>
<td>120,032</td>
<td>398 (58)</td>
<td>85</td>
<td>242</td>
<td>71</td>
<td>16.0±12.2</td>
<td>16.0±11.7</td>
<td>16.0±12.4</td>
</tr>
<tr>
<td>Granada</td>
<td>7725 (23)</td>
<td>108,403</td>
<td>368 (40)</td>
<td>76</td>
<td>143</td>
<td>69</td>
<td>23.0±12.0</td>
<td>21.5±11.5</td>
<td>23.5±12.1</td>
</tr>
<tr>
<td>Murcia</td>
<td>8348 (32)</td>
<td>110,056</td>
<td>322 (56)</td>
<td>77</td>
<td>141</td>
<td>80</td>
<td>17.9±10.3</td>
<td>17.5±10.5</td>
<td>18.0±10.2</td>
</tr>
<tr>
<td>Navarra</td>
<td>7924 (48)</td>
<td>109,291</td>
<td>390 (72)</td>
<td>79</td>
<td>210</td>
<td>93</td>
<td>23.8±15.8</td>
<td>21.6±16.0</td>
<td>25.8±15.3</td>
</tr>
<tr>
<td>San Sebastian</td>
<td>8251 (49)</td>
<td>103,260</td>
<td>437 (73)</td>
<td>104</td>
<td>220</td>
<td>104</td>
<td>16.5±13.8</td>
<td>15.5±14.0</td>
<td>17.4±13.6</td>
</tr>
<tr>
<td>Total</td>
<td>40,622 (38)</td>
<td>551,042</td>
<td>1915 (60)</td>
<td>416</td>
<td>956</td>
<td>417</td>
<td>19.3±13.3</td>
<td>18.2±13.6</td>
<td>20.1±13.1</td>
</tr>
</tbody>
</table>

1 CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition.
2 Cause of death was undefined for 126 cases.
3 Mean ± SD (all such values).
The association between olive oil intake and all-cause and cause-specific mortality is shown in Table 5. The greatest reduction in risk was observed for CVD mortality (for the highest olive oil quartile in comparison with nonconsumers—HR: 0.56; 95% CI: 0.40, 0.79). There was a gradual decreased risk of CVD mortality as olive oil intake increased (each increase of 10 g · 2000 kcal⁻¹ · d⁻¹ was related to a 13% decreased risk; HR: 0.87; 95% CI: 0.80, 0.94). There was also a significant inverse association between olive oil and death by causes other than CVD and cancer (for the highest olive oil quartile in comparison with nonconsumers—HR: 0.62; 95% CI: 0.44, 0.85). In contrast, there was no significant association between olive oil intake and cancer deaths. In further exploratory analyses (data not shown) that stratified diet-related cancers (n = 590; stomach and colorectal cancers, aerodigestive tract cancers, breast cancer, and prostate cancer) from non-diet-related cancers (n = 366), there was still no evidence of an association (for the upper quartile of olive oil consumers in comparison with nonconsumers in diet-related cancers—HR: 0.93; 95% CI: 0.70, 1.23).

The association between mortality and consumption of virgin olive oil compared with ordinary olive oil (data not shown) was similar [HR (95% CI): 0.93 (0.86, 1.00) and 0.93 (0.90, 0.97).
respectively, for each increase of 10 g · 2000 kcal\(^{-1}\) · d\(^{-1}\). There was a 19% (95% CI: 6%, 30%) reduction in mortality risk for the upper quartile of the ratio of olive oil to total fat consumption.

The inverse association between olive oil and overall mortality was similar in the sensitivity analyses (data not shown), after excluding the first 2 y of follow-up (for an increase of 10 g · 2000 kcal\(^{-1}\) · d\(^{-1}\)—HR: 0.93; 95% CI: 0.90, 0.97), excluding subjects with chronic diseases at baseline (cancer, CVD, diabetes; HR: 0.95; 95% CI: 0.90, 1.00) and misreporters of energy according to the Goldberg et al (27) criterion (HR: 0.94; 95% CI: 0.90, 0.97).

### DISCUSSION

To our knowledge, this is the first prospective study to show that olive oil consumption reduces the risk of mortality in a healthy Mediterranean population. In this Spanish cohort we found a significant 26% decrease in overall mortality and a 44% decrease in mortality risk for the upper quartile of the ratio of olive oil to total fat consumption.

### TABLE 3

<table>
<thead>
<tr>
<th>Olive oil intake (g · 2000 kcal(^{-1}) · d(^{-1}))</th>
<th>Total no. of subjects</th>
<th>Person-years</th>
<th>HR (95% CI)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonconsumers</td>
<td>Q1 (&lt;14.8)</td>
<td>Q2 (14.8 to &lt;21.7)</td>
<td>Q3 (21.7 to &lt;29.4)</td>
<td>Q4 (≥29.4)</td>
</tr>
<tr>
<td>Total no. of subjects</td>
<td>6016</td>
<td>8652</td>
<td>8651</td>
<td>8652</td>
</tr>
<tr>
<td>Person-years</td>
<td>80,652</td>
<td>117,618</td>
<td>117,808</td>
<td>117,291</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (referent)</td>
<td>0.85 (0.74, 0.98)</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.77 (0.67, 0.90)</td>
</tr>
<tr>
<td>Partially adjusted HR</td>
<td>1 (referent)</td>
<td>0.87 (0.75, 1.00)</td>
<td>0.82 (0.71, 0.96)</td>
<td>0.80 (0.69, 0.93)</td>
</tr>
<tr>
<td>Fully adjusted HR</td>
<td>1 (referent)</td>
<td>0.88 (0.76, 1.01)</td>
<td>0.83 (0.71, 0.96)</td>
<td>0.80 (0.69, 0.93)</td>
</tr>
</tbody>
</table>

1 EPIC, European Prospective Investigation into Cancer and Nutrition; Q, quartile.
2 All models were stratified by center, sex, and age and analyzed by Cox proportional regression analyses.
3 Adjusted for energy intake, BMI, waist circumference, educational status, smoking status, physical activity, and alcohol intake.
4 Adjusted for variables as in the partially adjusted model and additionally adjusted for intake of fruit, vegetables, meat, and dairy.

### TABLE 4

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cases</th>
<th>Person-years</th>
<th>HR (95% CI)</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1157</td>
<td>205,811</td>
<td>0.95 (0.91, 1.00)</td>
<td>0.922</td>
</tr>
<tr>
<td>Female</td>
<td>758</td>
<td>345,231</td>
<td>0.91 (0.86, 0.97)</td>
<td>0.158</td>
</tr>
<tr>
<td>Center</td>
<td></td>
<td></td>
<td></td>
<td>0.415</td>
</tr>
<tr>
<td>Asturias</td>
<td>398</td>
<td>120,032</td>
<td>0.86 (0.79, 0.94)</td>
<td></td>
</tr>
<tr>
<td>Granada</td>
<td>368</td>
<td>108,403</td>
<td>0.89 (0.81, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Murcia</td>
<td>322</td>
<td>110,056</td>
<td>0.87 (0.78, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Navarra</td>
<td>390</td>
<td>109,291</td>
<td>0.99 (0.92, 1.06)</td>
<td></td>
</tr>
<tr>
<td>San Sebastian</td>
<td>437</td>
<td>103,260</td>
<td>0.95 (0.89, 1.03)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td>0.816</td>
</tr>
<tr>
<td>Never</td>
<td>813</td>
<td>307,184</td>
<td>0.90 (0.85, 0.95)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>394</td>
<td>96,096</td>
<td>0.94 (0.87, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>595</td>
<td>126,520</td>
<td>0.96 (0.90, 1.03)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td>0.715</td>
</tr>
<tr>
<td>&lt;25 kg/m(^2)</td>
<td>319</td>
<td>121,106</td>
<td>0.92 (0.83, 1.02)</td>
<td></td>
</tr>
<tr>
<td>25–30 kg/m(^2)</td>
<td>881</td>
<td>264,956</td>
<td>0.94 (0.89, 0.99)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 kg/m(^2)</td>
<td>715</td>
<td>164,979</td>
<td>0.92 (0.87, 0.98)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, &lt;102 cm; women, &lt;88 cm</td>
<td>980</td>
<td>317,920</td>
<td>0.93 (0.88, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Men, ≥102 cm; women, ≥88 cm</td>
<td>935</td>
<td>233,122</td>
<td>0.94 (0.89, 0.99)</td>
<td></td>
</tr>
</tbody>
</table>

1 EPIC, European Prospective Investigation into Cancer and Nutrition.
2 Cox proportional hazards regression analysis stratified by center, age, and sex. Values were adjusted for physical activity, BMI, waist circumference, educational level, smoking status, energy intake, alcohol consumption, and intake of fruit, vegetables, meat, and dairy.
3 Former smokers were additionally adjusted for smoking duration; current smokers were additionally adjusted for number of cigarettes/d. A total of 1600 participants (including 113 cases) were excluded because smoking information was missing.
4 Waist circumference cutoffs correspond to the National Cholesterol Education Program–Adult Treatment Panel III criteria (25).
In our study olive oil was not related to death from cancer, which may be because this category groups together various types of cancer (diet-related and non-diet-related), although the results were similar when we analyzed these subgroups separately. A recent update of epidemiologic findings on olive oil and cancer showed that olive oil was associated with a reduced risk of certain cancers, in particular breast cancer (5). Therefore, it may be more relevant in the future to perform separate analyses by cancer site and to focus on incident data.

Cause-specific analyses also included other causes of death, and we found that olive oil was associated with an important reduction in mortality in this group. There was a 38% decreased risk of dying within the upper quartile of olive oil intake, and a dose-response effect was seen. Apart from the external causes of death, the main other causes of death were from respiratory, digestive, and nervous system diseases. Because this category is so broad, it is difficult to interpret our findings. However, olive oil is known for its antiinflammatory and antioxidant action, which could improve the outcome of a number of different diseases (2).

Although the biological pathways by which olive oil reduces mortality per se is unclear, it is likely that various different mechanisms are involved and are linked to the protective effect that olive oil has on the risk of chronic diseases such as CVD, specific types of cancer, diabetes, and metabolic syndrome (11, 30). Olive oil contains a high proportion of MUFAs, vitamin E, and diverse phenolic compounds that have been shown to have antiinflammatory, antioxidant, antiatherogenic, and possibly anticarcinogenic effects. Extra-virgin olive oil has been shown to have antiinflammatory, antioxidant, antiatherogenic, and possibly anticarcinogenic effects. Extra-virgin olive oil has been shown to decrease a range of CVD risk factors by improving lipid profiles and platelet function homeostasis, lowering blood pressure, and reducing the atherogenic process (2, 15, 31). Randomized controlled trials have also found that olive oil improves systemic inflammation and glycemic control (11).

The strengths of this study are its prospective cohort design, long follow-up period, and large sample size, and a relatively high

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**TABLE 5**

Association [HR (95% CI)] between olive oil intake and all-cause and cause-specific mortality in the EPIC-Spain cohort

<table>
<thead>
<tr>
<th>Mortality cause</th>
<th>Q1 (&lt;14.8)</th>
<th>Q2 (14.8 to &lt;21.7)</th>
<th>Q3 (21.7 to &lt;29.4)</th>
<th>Q4 (≥29.4)</th>
<th>P-trend</th>
<th>Olive oil intake (10 g · 2000 kcal⁻¹ · d⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause deaths (n)</td>
<td>376</td>
<td>426</td>
<td>373</td>
<td>378</td>
<td>362</td>
<td>1915</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (referent)</td>
<td>0.85 (0.74, 0.98)</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.77 (0.67, 0.90)</td>
<td>0.72 (0.62, 0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate HR</td>
<td>1 (referent)</td>
<td>0.88 (0.76, 1.01)</td>
<td>0.83 (0.71, 0.96)</td>
<td>0.80 (0.69, 0.93)</td>
<td>0.74 (0.64, 0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD deaths (n)</td>
<td>92</td>
<td>98</td>
<td>78</td>
<td>68</td>
<td>416</td>
<td>296</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (referent)</td>
<td>0.81 (0.60, 1.08)</td>
<td>0.72 (0.53, 0.98)</td>
<td>0.68 (0.50, 0.93)</td>
<td>0.56 (0.41, 0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate HR</td>
<td>1 (referent)</td>
<td>0.87 (0.64, 1.17)</td>
<td>0.77 (0.56, 1.06)</td>
<td>0.71 (0.52, 0.98)</td>
<td>0.56 (0.40, 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer deaths (n)</td>
<td>172</td>
<td>210</td>
<td>182</td>
<td>200</td>
<td>192</td>
<td>956</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (referent)</td>
<td>0.98 (0.79, 1.20)</td>
<td>0.90 (0.73, 1.12)</td>
<td>0.95 (0.77, 1.17)</td>
<td>0.88 (0.71, 1.08)</td>
<td>0.208</td>
</tr>
<tr>
<td>Multivariate HR</td>
<td>1 (referent)</td>
<td>0.99 (0.80, 1.22)</td>
<td>0.92 (0.74, 1.15)</td>
<td>0.97 (0.78, 1.20)</td>
<td>0.90 (0.72, 1.13)</td>
<td>0.361</td>
</tr>
<tr>
<td>Other deaths (n)</td>
<td>97</td>
<td>93</td>
<td>80</td>
<td>72</td>
<td>75</td>
<td>417</td>
</tr>
<tr>
<td>Unadjusted HR</td>
<td>1 (referent)</td>
<td>0.74 (0.55, 1.00)</td>
<td>0.69 (0.50, 0.93)</td>
<td>0.59 (0.43, 0.80)</td>
<td>0.59 (0.44, 0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate HR</td>
<td>1 (referent)</td>
<td>0.75 (0.56, 1.02)</td>
<td>0.71 (0.52, 0.97)</td>
<td>0.60 (0.44, 0.82)</td>
<td>0.62 (0.44, 0.85)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1. CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; Q, quartile.
2. Cause-specific mortality excluded 126 cases with no information on cause of death.
3. Cox proportional hazards regression analysis stratified by center, age, and sex.
4. Cox proportional hazards regression analysis stratified by center, age, and sex and adjusted for physical activity, BMI, waist circumference, educational level, smoking status, and intake of energy, alcohol, fruit, vegetables, meat, and dairy.

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Other causes of death (29.4 to 21.7) reduced the risk of all deaths by 7% and of CVD deaths by 13%. No significant association was found between olive oil intake and cancer mortality risk.

Previous studies have shown that the Mediterranean dietary pattern as a whole decreases overall mortality (6, 8), and our results support the important individual role that olive oil plays within this association, although other components, such as fruit and vegetables (28), are also of importance. The magnitude of the effect was similar to an Italian trial (14), which reported a significant 24% reduction in overall mortality for regular olive oil consumption in participants who had suffered a prior myocardial infarction. In our study we observed a 26% reduction in mortality in healthy adults in the upper quartile of olive oil consumption, which corresponded to an intake of >29.4 g · 2000 kcal⁻¹ · d⁻¹. These findings contrast with those reported in the EPIC-Greek cohort, which found that olive oil was not associated with overall mortality (13). However, because of its longer follow-up period, our study included more deaths and so may have had a greater statistical power to detect an association. In addition, differences in culture, lifestyle, and background diet may influence results.

In cause-specific analyses we found that olive oil intake had an even greater impact on CVD mortality. Furthermore, we found a dose-response effect, whereby the highest quartile of olive oil intake showed the greatest reduction in risk (reducing mortality risk by 44%). Although there is little direct previous evidence showing that olive oil decreases CVD mortality, other cohort studies have reported that olive oil decreases the risk of incident ischemic heart disease in Spanish and Italian populations (4, 26, 29). Our results are also supported by the findings from the clinical trials PREDIMED (15) and Eurolife (2), which show that olive oil reduces a number of CVD risk factors (2, 15).
number of deaths. We were able to adjust for a number of sociodemographic and lifestyle factors and take into account the potentially confounding effect of components of the Mediterranean dietary pattern that correlate with olive oil consumption (fruit, vegetable, meat, and dairy intake). We also controlled for the potentially confounding effect of total energy on olive oil intake by applying the multivariate nutrient density method (23).

Finally, we were able to analyze the effect of virgin and ordinary olive oil separately, although we did not observe any difference in their association with overall mortality. The type of olive oil consumed could be relevant because olive oils vary in the quantity of minor but biologically important active components, which are believed to be beneficial to human health. For example, polyphenols are present mainly in extra-virgin olive oil because they are partially lost during the refining process used to produce ordinary olive oil (32). The Euroriver clinical trial found that the consumption of olive oil with a higher phenolic content resulted in greater health benefits in terms of improving the LDL: HDL ratio and oxidized LDL decrement (2). Therefore, future analyses on extra-virgin olive oil (data not available in our study) and its effect on CVD mortality could be relevant.

Our study has some limitations, however; participants could have changed their dietary habits because of a preclinical or clinical stage of a chronic disease at recruitment, which would lead to reverse causality. Accordingly, sensitivity analyses were performed, with the exclusion of the first 2 y of follow-up and participants with chronic diseases at baseline. However, no substantial changes in the association were found. Another limitation could be a result of reporting bias; however, the association between olive oil intake and mortality did not change after the exclusion of subjects with implausible intakes according to Goldberg et al.’s cutoffs (27). The majority of the participants were blood donors, so the results cannot be entirely extrapolated to the general population. Nevertheless, the study population covered a wide range of socioeconomic levels and different geographical areas. A further limitation is measurement error, although an interview-administered, validated dietary history questionnaire was used that encompassed greater health benefits in terms of improving the LDL: HDL ratio and oxidized LDL decrement (2). Future analyses on extra-virgin olive oil (data not available in our study) and its effect on CVD mortality could be relevant.

In conclusion, our study highlights the independent effect that olive oil intake has on decreasing risk of mortality in a healthy Mediterranean population, and even a relatively small increase in olive oil consumption was seen to produce a beneficial effect. Our findings provide further evidence on the effects that one of the key components of the Mediterranean diet has on mortality and support the need to preserve the habitual use of olive oil within this healthy dietary pattern. This is especially important in light of the progressive loss of the Mediterranean diet and the increased intake of SFAs across many Mediterranean countries (34, 35).

The authors’ responsibilities were as follows—NT, GB, and ALM: statistical analysis; GB and AM: drafting of the manuscript; and AA, CAG, and GB: final content. All of the authors contributed to the different phases of manuscript preparation (including conception of the study, conducting the research, the study design, interpretation of the results, and drafting of the manuscript or revising it critically for important intellectual content). All of the authors read and approved the final manuscript. None of the authors declared a conflict of interest in relation to this article.

REFERENCES


