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Olive oil intake and CHD in the European Prospective Investigation into Cancer and Nutrition Spanish cohort

Genevieve Buckland[1]*, Noemie Travier[1], Aurelio Barricarte[2,3], Eva Ardanaz[2,3], Conchi Moreno-Iribas[2,3], María-José Sánchez[3,4], Esther Molina-Montes[3,4], María Dolores Chirlaque[3,5], José María Huerta[3,5], Carmen Navarro[3,5], Maria Luisa Redondo[6], Pilar Amiano[3,7], Miren Dorronsoro[3,7], Nerea Larrañaga[3,7] and Carlos A. Gonzalez[1]

[1]*Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO-IDIBELL), Avda Gran Via 199-203, Barcelona 08907, Spain*
[2]*Public Health Institute of Navarra, Pamplona, Spain*
[3]*CIBER Epidemiología y Salud Pública (CIBERESP), Spain*
[4]*Andalusian School of Public Health, Granada, Spain*
[5]*Department of Epidemiology, Murcia Regional Health Council, Murcia, Spain*
[6]*Public Health Directorate, Asturias, Spain*
[7]*Public Health Department of Gipuzkoa, Basque Government, San Sebastián, Spain*

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Abstract

Olive oil is well known for its cardioprotective properties; however, epidemiological data showing that olive oil consumption reduces incident CHD events are still limited. Therefore, we studied the association between olive oil and CHD in the European Prospective Investigation into Cancer and Nutrition (EPIC) Spanish cohort study. The analysis included 40 142 participants (38 % male), free of CHD events at baseline, recruited from five EPIC-Spain centres from 1992 to 1996 and followed up until 2004. Baseline dietary and lifestyle information was collected using interview-administered questionnaires. Cox proportional regression models were used to assess the relationship between validated incident CHD events and olive oil intake (energy-adjusted quartiles and each 10 g/d per 8368 kJ (2000 kcal) increment), while adjusting for potential confounders. During a 10·4-year follow-up, 587 (79 % male) CHD events were recorded. Olive oil intake was negatively associated with CHD risk after excluding dietary mis-reporters (hazard ratio (HR) 0·93; 95 % CI 0·87, 1·00 for each 10 g/d per 8368 kJ (2000 kcal) and HR 0·78; 95 % CI 0·59, 1·03 for upper *v.* lower quartile). The inverse association between olive oil intake (per 10 g/d per 8368 kJ (2000 kcal)) and CHD was more pronounced in never smokers (11 % reduced CHD risk ($P=0·048$)), in never/low alcohol drinkers (25 % reduced CHD risk ($P<0·001$)) and in virgin olive oil consumers (14 % reduced CHD risk ($P=0·072$)). In conclusion, olive oil consumption was related to a reduced risk of incident CHD events. This emphasises the need to conserve the traditional culinary use of olive oil within the Mediterranean diet to reduce the CHD burden.

Key words: Olive oil: CHD: European Prospective Investigation into Cancer and Nutrition-Spain: Prospective cohort studies

The favourable effect of olive oil on CHD has long been suggested, as international comparisons noted that CHD mortality and incidence rates were lower in countries where olive oil consumption was higher[1–3]. In addition, large cohort studies set in Mediterranean countries have reported that the traditional Mediterranean diet (MD) reduces risk of CHD mortality[4] and incidence[5,6], CVD risk factors[7,8] and also secondary CHD events[9]. Although it is difficult to isolate the contribution of individual components within this dietary pattern, cumulative evidence suggests that olive oil, a key feature of the MD and the principal source of fat, plays an important role in these health benefits[8,10–13]. However, there are currently very few studies showing that consuming olive oil prevents incident CHD events.

For instance, case–control studies assessing the relationship between CHD and olive oil directly (not using MUFA as a proxy) are limited and conflicting, and have indicated inverse associations[14,15] or no association[16]. The Italian EPICOR study[17], to our knowledge the only cohort study to date that has prospectively studied olive oil and CHD risk

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; MD, Mediterranean diet; MI, myocardial infarction.

* **Corresponding author:** G. Buckland, fax +34 93 260 7787, email gbuckland@iconcologia.net

(but only in women), showed that olive oil intake in the upper quartile reduced risk of incident CHD events by 44% (*P*-trend 0·04).

Although intervention trials support the evidence that olive oil reduces CHD risk factors[7,18,19], there are still no results on primary CHD endpoints. However, experimental studies shed light on the biological mechanisms behind olive oil's cardioprotective role, attributing these benefits to its high MUFA oleic acid content (55–83% of total fatty acids) and to its highly bioactive micro-components (1–2% of total content)[10]. Most heavily implicated are its polyphenolic compounds, in particular hydroxytyrosol[20], which is found in high concentrations in extra-virgin olive oil. Polyphenols have been shown to have a broad spectrum of benefits including anti-inflammatory, antioxidant, anti-arrhythmic, anti-atherogenic and vasodialatory effects, favouring a less pro-thrombotic environment and greater endothelial protective capacity[8,19].

Although it is clear that olive oil improves many CHD risk factors, there is still limited evidence corroborating its role in preventing incident CHD events. Accordingly, recent reviews on olive oil and CVD[10,11,21] have concluded that further prospective studies and trials are needed to obtain more complete evidence for the primary prevention of CHD. Therefore, we aimed to prospectively study the relationship between olive oil consumption and risk of incident CHD events in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort study.

Methods

Study design and population

The EPIC is a large multi-centric European prospective cohort study designed to study the relationship between nutritional, lifestyle, metabolic and genetic factors and risk of cancer and other chronic diseases. The full methodological details have been published previously[22,23]. The present study makes use of the Spanish cohort of EPIC-Heart, the cardiovascular component of EPIC[24]. EPIC-Spain consists of 41 438 healthy volunteers (38% male), aged 29–69 years, recruited from 1992 to 1996 from five Spanish regions (Asturias, Granada, San Sebastian, Murcia and Navarra). Most participants (75%) were blood donors, and the study population covered a wide range of socio-economic and educational levels. At recruitment, participants signed an informed consent and the study was approved by the Ethics Committee of the Bellvitge Hospital (Barcelona).

Dietary and lifestyle questionnaires

All centres used an interview-administered computerised version of a dietary history questionnaire to collect information on usual food intake over the previous 12 months[25]. The validated dietary questionnaire was open, but was structured by occasions of intake and included a list of 662 common foods and recipes from each region[25,26]. The portions of each food consumed (including oil added to the salads and cooked foods (g/d)) were quantified using household and standard measures and thirty-five sets of pictures with simple foods, food mixtures and drinks[25]. A specific food composition table was used to calculate each participant's total daily energy and nutrient intake[27]. At recruitment, weight, height and waist circumference were measured and information on socio-demographic and lifestyle factors, including educational attainment, tobacco use, alcohol consumption, reproductive and medical history and physical activity was collected through interview-administered questionnaires[22,28].

Ascertainment and validation of CHD events

Incident CHD events were identified during a follow-up period that ran from recruitment until December 2004 (full details have been published previously[5]). Briefly, non-fatal and fatal coronary events were identified through the self-reported questionnaires at recruitment and at 3-year follow-up (all centres) and by record linkage with three sources of information (varying by centre): hospital discharge databases (Granada had limited access), population-based myocardial infarction (MI) registries and regional and national mortality registries (National Statistical Institute). All incident CHD events were validated by trained nurses/physicians who reviewed medical records and medico-legal autopsy reports to confirm and classify the events according to the American Heart Association Scientific Statement of 2003[29] and the multinational monitoring of trends and determinants in CVD (Multinational MONItoring of trends and determinants in CArdiovascular disease; MONICA) criteria.

Coronary events were classified as definite (fatal or non-fatal acute MI or unstable angina requiring revascularisation procedures such as coronary artery bypass graft or percutaneous transluminal coronary angioplasty) or possible (fatal or non-fatal MI that did not meet all diagnostic criteria and fatal CHD with insufficient information). Possible CHD events (*n* 101) were not considered as cases but were censored at the time of their coronary event. Participants with a definite coronary event recorded before recruitment were considered as prevalent cases and excluded.

Study exclusions and final sample

Of the initial 41 438 participants, 193 were excluded due to prevalent CHD, 806 for extreme total energy intake (lowest and highest 1% of the total energy intake to energy requirement ratio) and 297 for missing information on date of possible CHD event (*n* 12), hyperlipidaemia (*n* 195), diabetes (*n* 71) or hypertension (*n* 60). Thus, the final sample used for the analyses included 40 142 participants without history of coronary events at recruitment.

Statistical analysis

Olive oil is presented as a function of energy density (g/d per 8368 kJ (2000 kcal), excluding energy from alcohol)[30]. Participants' baseline characteristics were described according to olive oil intake using mean and standard deviation and

frequencies (%), and differences were tested using Kruskal–Wallis rank sum and χ^2 tests, respectively. The association between olive oil intake and CHD was assessed using Cox proportional hazards regression models. The models were stratified by age at recruitment (1-year intervals), sex and centre. Age was the primary time variable, with entry time defined as age at recruitment and exit time defined as age at diagnosis of first CHD event for cases and age at censoring or at death (whichever occurred first) for at-risk participants.

Olive oil was analysed as a categorical variable (quartiles) and a continuous variable (per 10 g/d per 8368 kJ (2000 kcal)). Linear trend tests were calculated for the categorical variable using the median of each quartile as a continuous variable. Four different models were created, the first was unadjusted, whereas the second model was partially adjusted for known CHD risk factors such as: BMI (<25, 25–30 and ≥30 kg/m^2), waist circumference (cm), educational level (none, primary school, secondary school, technical or professional training, university degree and not specified), smoking status (never, former, current ≤20 cigarettes/d, current >20 cigarettes/d and missing), physical activity level measured as total metabolic equivalents (MET)/h per week of recreational exercise (inactive, moderately inactive, moderately active and active), energy intake without alcohol (kJ/d), baseline alcohol intake (0, >0 to <6, ≥6 to <12, ≥12 to <24 and ≥24 g/d) and the presence of diabetes, hyperlipidaemia and hypertension (yes, no). Diabetes, hyperlipidaemia and hypertension were self-reported at recruitment or based on drug use. The third model (fully adjusted) was also adjusted for a MD score (full methodology has been described previously[5]) which included fruit, vegetables, cereals, fish, legumes, dairy products and meat but excluded olive oil and alcohol (14-unit, continuous variable). The final model (Goldberg exclusions) excluded participants with a poor concordance of energy intake to energy expenditure, identified using Goldberg criteria[31], from the fully adjusted model.

Subgroup analyses were carried out to evaluate CHD risk by type of olive oil intake: participants who consumed ordinary olive oil *v.* participants who exclusively consumed virgin olive oil (16% of olive oil consumers). Stratified analyses were also run by sex (female models were additionally adjusted for menopausal status (pre- and peri-menopausal and post-menopausal)), smoking status (ever *v.* never), waist circumference (men <102 cm and women <88 cm *v.* men ≥102 cm and women ≥88 cm) defined according to the National Cholesterol Education Program-Adult Treatment Panel III cut-offs[32] and lifetime alcohol consumption (never or light (0–5·9 g/d), moderate (6–23·9 g/d) and heavy (≥24 g/d) alcohol intake). Likelihood ratio tests were used to test for possible interaction between these variables and olive oil.

Sensitivity analyses were carried out by excluding the first 2 years of follow-up, subjects with hyperlipidaemia, hypertension and diabetes at recruitment and those from Granada (due to possible incomplete CHD events ascertainment). Schoenfeld residuals were used to ensure the proportional hazards assumption. All analyses were performed using STATA statistical software, version 10 (StataCorporation 2007) and statistical significance was set at $P<0·05$.

Results

The distribution of the 40 142 participants (38% male) across the five EPIC-Spain centres is shown in Table 1. During a mean follow-up of 10·4 (SD 1·3) years, 587 (79% male) incident CHD events were recorded. The mean olive oil intake in the whole cohort was 20·1 g/d per 8368 kJ (2000 kcal), which was highest in Navarra and Granada and lowest in Asturias (Table 1). A total of 14·8% of the participants did not consume olive oil.

The baseline characteristics of the cohort are described according to quartiles of olive oil intake in Table 2. Participants with a higher intake of olive oil were more likely to have a secondary school education or above, be hyperlipidaemic, have a narrower waist circumference, a lower energy intake and a higher MD score.

The hazard ratios (HR) for the association between olive oil and CHD events are shown in Table 3. Olive oil intake was inversely associated with CHD, but this association weakened after adjusting for lifestyle and dietary-related confounders. However, after excluding participants with poor concordance of energy intake to energy expenditure (Goldberg exclusions), there was a 22% decreased risk of a CHD for the upper *v.* the lower olive oil quartile and a 7% ($P=0·050$) reduction in incident CHD for each 10 g/d per 8368 kJ (2000 kcal) of olive oil.

Table 4 presents the results of the association between olive oil (each 10 g/d per 8368 kJ (2000 kcal) increment) and CHD events within different subgroups. After stratifying by type of olive oil intake, there appeared to be a greater decreased risk of a CHD event for consumption of virgin compared to ordinary olive oil (HR 0·86; 95% CI 0·72, 1·01 and HR 0·97; 95% CI 0·91, 1·03, respectively, for each 10 g/d per 8368 kJ (2000 kcal)). Although the inverse association was greater in females compared to males, the test for interaction was not significant. Olive oil intake was associated with a reduced risk of CHD in never smokers (HR 0·89; 95% CI 0·80, 1·00) but not in ever smokers. There was evidence of effect modification by lifetime alcohol intake, as there was an important significant negative association in never or light alcohol drinkers, with a 25% decreased risk of CHD ($P<0·001$) for each 10 g/d of olive oil consumption, while there was no evidence of an association in moderate or heavy drinkers (P-interaction=0·004).

In sensitivity analyses (data not shown), after excluding the first 2 years of follow-up, subjects with hyperlipidaemia, hypertension and diabetes at recruitment and those from the centre of Granada, the association did not materially change, i.e. HR 0·96 (95% CI 0·91, 1·03), HR 0·93 (95% CI 0·84, 1·02) and HR 0·97 (95% CI 0·91, 1·03), respectively, for each 10 g/d per 8368 kJ (2000 kcal).

Discussion

To our knowledge, this is the largest cohort study to assess the relationship between olive oil consumption and incident CHD

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Table 1. The distribution of participants, CHD and olive oil intake in the five centres of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort study
(Medians, percentages and percentiles)

EPIC-Spain centre	Cohort	Male (%)	Person-years	CHD events		CHD rates*	Olive oil intake (g/d per 8368 kJ (2000 kcal))					
							All		Male		Female	
				All	Male (%)	All	Median	P25–P75	Median	P25–P75	Median	P25–P75
Asturias	8305	36	86 511	124	77	143·33	17·2	5·1–24·8	18·2	5·8–25·7	16·5	4·8–24·2
Granada†	7599	23	77 261	44	55	56·95	22·3	15·3–30·3	21·4	14·7–29·5	22·5	15·5–30·7
Murcia	8232	31	84 248	109	62	129·38	18·6	12·0–25·0	19·0	11·3–25·6	18·5	12·1–24·7
Navarra	7838	48	81 844	145	90	177·17	26·5	12·1–36·7	25·1	6·7–36·8	27·3	16·0–36·7
San Sebastian	8168	49	85 875	165	88	192·14	17·9	0·1–28·3	17·1	0·0–28·8	18·3	4·0–27·7
Total	40 142	38	415 737	587	79	141·20	20·1	10·0–28·9	20·0	6·6–29·5	20·1	11·4–28·5

P25, 25th percentile; P75, 75th percentile.
* Crude CHD rates calculated per 100 000 person-years.
† Granada did not fully validate/ascertain CHD events in the cohort.

events. The present results in a Mediterranean population provide suggestive evidence that a greater consumption of olive oil was associated with a decreased risk of incident CHD events; after excluding participants with a poor concordance of energy intake to energy expenditure, there was a significant (7 %) reduction in CHD risk for each 10 g/d per 8368 kJ (2000 kcal) of olive oil and a non-significant (22 %) reduction for consumption in the upper quartile. This suggested that the protective effect may have been driven by the consumption of virgin olive oil, although further studies need to corroborate this.

The present results are in line with previous observational studies in Spain, Greece and Italy[14,15,17], although we observed a more modest reduction in CHD risk. In a Spanish hospital-based case–control study[14], the top quartile of energy-adjusted olive oil intake was associated with a 82 % (P=0·03) reduction in a first acute MI, and in a Greek hospital-based case–control study[15], exclusive olive oil users were 47 % less likely to have an acute coronary syndrome compared to non-users. An Italian cohort study reported a 44 % decreased risk of CHD in women whose olive oil consumption was in the upper quartile (>31·2 g/d)[17]. Less direct evidence comes from studies investigating mortality in patients with a previous MI. For instance, the Italian GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardio) Prevenzione trial showed that regular olive oil consumption significantly reduced mortality in MI patients by 24 %[12]. Although the EPIC-Greece study[13] did not find a significant association between each 21 g/d increment in olive oil and mortality in MI patients, there was a significant (18 %) reduction in mortality patients with a high MUFA:SFA ratio.

Differences in study designs and adjustment for confounding variables are likely to contribute to the differences in the magnitude of effect observed between studies. Olive oil intake is an indicator of a healthy MD and is usually correlated with foods such as vegetables; not adjusting for dietary factors may have led to an overestimation of the association. In addition, part of these differences might be explained by the type of olive oil (virgin *v.* ordinary) consumed across populations.

The present results are supported by strong mechanistic evidence[8,10] and results from experimental studies show that consuming olive oil improves important CHD risk factors. The PREDIMED (PREvención con DIeta MEDiterránea) dietary intervention trial has demonstrated that a MD enriched with extra virgin olive oil benefits blood pressure, glycaemic control in diabetics, endothelial function, oxidative stress and lipid profiles (decreasing TAG, increasing HDL- and lowering total and LDL-cholesterol) and reduces susceptibility of LDL to oxidation and concentrations of inflammatory markers such as C-reactive protein and IL-6[7,33,34]. In addition, the olive oil-rich diet was effective in the prevention of diabetes, the metabolic syndrome and weight gain[35,36]. The wide number of pathways by which olive oil intake could decrease CHD make a causal relationship probable.

Olive oil's benefits have been related to its high content of MUFA and its richness in bioactive micro-components such as polyphenols, abundant in virgin and extra-virgin olive oil but

Table 2. Participants' baseline characteristics according to olive oil intake

(Mean values and standard deviations; number of participants and percentages)

	Olive oil intake (g/d per 8368 kJ (2000 kcal))*							
	Quartile 1 (< 10·0 g)		Quartile 2 (≥ 10·0, < 20·1 g)		Quartile 3 (≥ 20·1, < 28·9 g)		Quartile 4 (≥ 28·9 g)	
Cohort characteristics	*n*	%	*n*	%	*n*	%	*n*	%
Sex								
Men	4437	44·21	3166	31·55	3507	34·94	3974	39·60
Women	5599	55·79	6869	68·45	6529	65·06	6061	60·40
Age at recruitment (years)								
Mean	49·58		48·88		48·97		49·57	
SD	7·94		8·13		8·07		7·95	
Educational level								
None	3502	34·89	3729	37·16	3442	34·30	3168	31·57
Primary	4272	42·57	3706	36·93	3694	36·81	3847	38·34
Technical/professional	821	8·18	698	6·96	817	8·14	965	9·62
Secondary	541	5·39	661	6·59	673	6·71	725	7·22
University	824	8·21	1181	11·77	1346	13·41	1258	12·54
Unknown	76	0·76	60	0·60	64	0·64	72	0·72
Smoking status								
Never	5475	54·55	5885	58·64	5611	55·91	5360	53·41
Former	1611	16·05	1650	16·44	1838	18·31	1924	19·17
Current	2943	29·32	2495	24·86	2583	25·74	2746	27·36
Unknown	7	0·07	5	0·05	4	0·04	5	0·05
Baseline alcohol consumption (g/d)								
0	3604	35·91	4099	40·85	3790	37·76	3650	36·37
1–5·9	1837	18·30	2248	22·40	2361	23·53	2207	21·99
6–11·9	835	8·32	931	9·28	978	9·74	900	8·97
12–23·9	1252	12·48	1126	11·22	1210	12·06	1161	11·57
≥ 24	2508	24·99	1631	16·25	1697	16·91	2117	21·10
Physical activity								
Inactive	2834	28·24	2943	29·33	2686	26·76	2679	26·70
Moderately inactive	2371	23·62	2560	25·51	2628	26·19	2362	23·54
Moderately active	2762	27·52	2668	26·59	2858	28·48	3015	30·04
Active	2069	20·62	1864	18·57	1864	18·57	1979	19·72
Menopausal status at recruitment†								
Peri-/pre-menopausal	3409	60·89	4373	63·66	4172	63·90	3734	61·61
Post-menopausal	2190	39·11	2496	36·34	2357	36·10	2327	38·39
BMI (kg/m^2)								
< 25	1951	19·44	2415	24·07	2356	23·48	2137	21·30
≥ 25	8085	80·56	7620	75·93	7680	76·52	7898	78·70
Waist circumference								
< 102 cm in men, < 88 cm in women	5678	56·58	5722	57·02	5893	58·72	5840	58·20
≥ 102 cm in men, ≥ 88 cm in women	4358	43·42	4313	42·98	4143	41·28	4195	41·80
Height (cm)								
Mean	162·10		160·44		161·19		161·72	
SD	8·66		8·18		8·44		8·45	
Energy intake excluding alcohol (kcal/d)								
Mean	2099·11		2067·63		2015·89		1958·57	
SD	619·54		607·99		587·87		571·28	
Energy intake excluding alcohol (kJ/d)								
Mean	8782·68		8650·96		8434·48		8194·66	
SD	2592·16		2543·83		2459·65		2390·24	
Total fat intake (g)								
Mean	85·56		83·47		82·59		85·88	
SD	32·21		31·87		30·34		30·13	
SFA intake (g)								
Mean	27·46		28·56		25·99		23·45	
SD	12·70		12·67		11·31		9·91	
MUFA intake (g)								
Mean	31·34		35·49		38·37		44·24	
SD	14·19		14·06		14·10		15·54	
PUFA intake (g)								
Mean	19·77		12·56		11·4		11·23	
SD	9·36		6·63		5·21		4·56	
Mediterranean diet score‡								
Low	4985	49·67	4824	48·07	3788	37·74	3052	30·41
Medium	3176	31·65	3275	32·64	3334	33·22	3443	34·31
High	1875	18·68	1936	19·29	2914	29·04	3540	35·28
Diabetes								
No	9514	94·80	9573	95·40	9558	95·24	9509	94·76
Yes	522	5·20	462	4·60	478	4·76	526	5·24
Hypertension								
No	7849	78·21	8104	80·76	8107	80·78	8014	79·86
Yes	2187	21·79	1931	19·24	1929	19·22	2021	20·14
Hyperlipidaemia								
No	8066	80·37	8116	80·88	7965	79·36	7881	78·54
Yes	1970	19·63	1919	19·12	2071	20·64	2154	21·46

* Apart from diabetes, all comparisons between baseline characteristics and olive oil intake (χ^2 or Kruskal–Wallis rank sum test) showed significant association at $P<0·05$.
† For women only.
‡ Excluding alcohol and olive oil.

Table 3. Multivariate hazard ratios (HR) for incident CHD events according to intake of olive oil in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort

(Hazard ratios (HR) and 95 % confidence intervals)

	Olive oil intake (g/d per 8368 kJ (2000 kcal))										
	Quartile 1		Quartile 2		Quartile 3		Quartile 4			Olive oil (10 g/d per 8368 kJ (2000 kcal))	
Models*	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	*P*-trend	HR	95 % CI
Cases (*n*)	202		109		136		140			587	
Crude	1	Referent	0·75	0·59, 0·96	0·89	0·71, 1·11	0·78	0·63, 0·98	0·043	0·94	0·89, 1·00
Partially adjusted†	1	Referent	0·79	0·62, 1·01	0·91	0·73, 1·14	0·81	0·65, 1·01	0·082	0·95	0·89, 1·00
Fully adjusted‡	1	Referent	0·79	0·62, 1·01	0·94	0·75, 1·18	0·85	0·68, 1·07	0·202	0·96	0·91, 1·02
Goldberg exclusions§	1	Referent	0·78	0·58, 1·03	0·88	0·67, 1·15	0·78	0·59, 1·03	0·079	0·93	0·87, 1·00

* Obtained from Cox regression models stratified by age at recruitment, centre and sex.
† Models adjusted for educational level, BMI, waist circumference, physical activity, smoking status, alcohol consumption, energy intake excluding alcohol, hyperlipidaemia, hypertension and diabetes.
‡ Models additionally adjusted for the Mediterranean diet score (excluding olive oil and alcohol).
§ Models adjusted as in fully adjusted but excluding 13 592 participants (171 cases; quartile 1 = 151 cases, quartile 2 = 79 cases, quartile 3 = 92 cases, quartile 4 = 94 cases) with improbable dietary values according to Goldberg criteria.

not in ordinary olive oil[8,10,20,37]. The EUROLIVE dietary intervention study showed that *in vivo* consumption of olive oil with three different phenolic concentrations increased HDL-cholesterol and decreased total and LDL-cholesterol, TAG and oxidative stress markers in a dose-dependent manner[10,38]. A key olive oil polyphenol is oleuropein (a compound that generates tyrosol and hydroxytyrosol), which accounts for approximately 80 % of olive oil phenolic content and is a potent scavenger of superoxide radicals and inhibits LDL oxidation[19,39]. The greater inverse association observed between olive oil and CHD risk when focusing on virgin olive oil consumers is consistent with the fact that olive oil is not just a MUFA and that other biologically active components are of importance.

The negative association between olive oil and CHD was more apparent in never or low alcohol drinkers and never smokers. As moderate alcohol intake is known to protect against CHD[40], the fact that the beneficial effect of olive oil on CHD was only apparent in never or light drinkers could be because the important protective effect of alcohol in

Table 4. Association between olive oil consumption and CHD in population subgroups in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Spain cohort

(Hazards ratios (HR) and 95 % confidence intervals)

			Olive oil intake (10 g/8368 kJ (2000 kcal) per d)		
Subgroups	Cases	Person-years	HR*	95 % CI	*P*-interaction
Olive oil type					
Ordinary olive oil	587	415 737	0·96	0·91, 1·02	N/A
Virgin olive oil	169	117 708	0·86	0·72, 1·01	N/A
Sex					
Male	464	156 080	0·98	0·92, 1·04	0·110
Female	123	259 657	0·87	0·76, 1·01	
Smoking status†					
Never	180	231 687	0·89	0·80, 1·00	0·101
Ever	406	183 822	0·99	0·92, 1·06	
Alcohol intake (lifetime) (g/d)					
0–5·9	157	212 364	0·75	0·65, 0·86	0·004
6–23·9	126	97 446	1·00	0·87, 1·15	
>24	298	103 059	1·00	0·93, 1·08	
Waist circumference‡					
Men <102 cm and women <88 cm	305	240 854	0·99	0·91, 1·08	0·310
Men ≥102 cm and women ≥88 cm	282	174 883	0·93	0·85, 1·01	
Mediterranean diet score§					
Low (0–6)	239	172 245	0·99	0·90, 1·09	0·528
Medium (7–8)	199	136 919	0·93	0·84, 1·03	
High (9–14)	149	106 573	0·95	0·85, 1·07	

N/A, not applicable.
* Models stratified by age, centre and sex, and adjusted for educational level, BMI, waist circumference, physical activity, smoking status, alcohol consumption, energy intake excluding alcohol, hyperlipidaemia, hypertension and diabetes and Mediterranean diet score (and menopausal status in the female model).
† Smoking status excludes twenty-one participants with unknown smoking status.
‡ Waist circumference cut-offs correspond to the National Cholesterol Education Program's Adult Treatment Panel III criteria.
§ Excluding alcohol and olive oil.

moderate or heavy drinkers masked the more subtle effect of olive oil, although this remains a hypothesis. Along the same line, the greater risk of CHD in smokers may have obscured any beneficial effect of olive oil and explain the differences observed between ever and never smokers. The inverse association was also stronger in women and could be explained by less olive oil intake misclassification error. Spanish women belonging to the generation included in the present cohort, recruited from 1992 to 1996, were usually responsible for preparing meals, and may have provided more accurate information on the quantity and type of oils used.

The strengths of the present study include its long follow-up period, large sample of initially healthy individuals and inclusion of validated incident definite CHD events. In addition, the mean olive oil intake in this Mediterranean population was relatively high, with 20·1 g/d per 8368 kJ (2000 kcal) overall and 38 g/d per 8368 kJ (2000 kcal) in the highest quartile of intake. We used the multivariate nutrient density model[30] to adjust for total energy intake and adjusted for adherence to the MD to separate the independent effect of olive oil on CHD from the rest of the MD components. In addition, we were able to explore the difference in effects between ordinary and virgin olive oil, which is seldom assessed in observational studies. Finally, we took into account possible dietary mis-reporting, applying a methodology identifying disparities between reported energy intakes and estimated requirements[41]. Interestingly, the association strengthened after restricting the analysis to those participants with more reliable dietary intakes.

The present study has some limitations too, such as although we adjusted for many lifestyle factors strongly related with CHD, we cannot rule out residual confounding. Also, olive oil and other dietary intakes were assessed using a single measurement taken at baseline and any changes during follow-up would not have been captured. In addition, participants with pre-clinical medical conditions at recruitment might have already changed their habitual diet to a healthier or olive-oil-richer diet, which could lead to reverse causality or dilute the real association. However, sensitivity analyses excluding the first 2 years of follow-up and participants with hyperlipidaemia, hypertension or diabetes showed similar results. Fewer cases of CHD were documented in Granada because of limited access to sources of ascertainment and incomplete follow-up, but excluding Granada from the main analyses resulted in minimal changes. Finally, some measurement error is unavoidable in nutritional epidemiology and it is especially difficult to accurately quantify added fats. However, the interview-administered validated dietary history questionnaire[25] used in the present study has been shown to have less measurement error than FFQ[42]. In addition, measurement error tends to introduce non-differential exposure misclassification, leading to effect dilution.

In conclusion, the results from this large Mediterranean cohort provide some evidence that olive oil consumption is associated with a reduction in primary incident CHD events. Previously published results in this cohort reported that high adherence to the entire MD was associated with a 40 % decreased risk of incident CHD events[5]. The present study therefore supports the contribution that olive oil makes within this dietary pattern in terms of reducing risk of CHD events. Our findings back the need to preserve the culinary use of olive oil within the Mediterranean dietary tradition.

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