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Meta-analyses

Effect of olive oil consumption on cardiovascular disease, cancer, type 2 diabetes, and all-cause mortality: A systematic review and meta-analysis

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SUMMARY

Background: Some large prospective studies on olive oil consumption and risk of chronic disease suggested protective effects.
Objective: We conducted an outcome-wide systematic review and meta-analysis of prospective cohort studies and randomized controlled trials (RCT) assessing the association between olive oil consumption and the primary risk of 4 different outcomes: cardiovascular disease (CVD), cancer, type 2 diabetes (T2D) or all-cause mortality through January 2022.
Methods: Thirty-six studies were included in the systematic review and twenty-seven studies (24 prospective cohorts and 3 different reports from one RCT) were assessed in 4 quantitative random-effects meta-analyses. They included a total of 806,203 participants with 49,223 CVD events; 1,285,064 participants with 58,892 incident cases of cancer; 680,239 participants with 13,389 incident cases of T2D; and 733,420 participants with 174,081 deaths. Olive oil consumption was most frequently measured with validated food frequency questionnaires. Studies follow-up ranged between 3.7 and 28 years.
Results: A 16% reduced risk of CVD (relative risk [RR]: 0.84; 95% confidence interval [CI]: 0.76 to 0.94), standardized for every additional olive oil consumption of 25 g/d was found. No significant association with cancer risk was observed (RR: 0.94; 95% CI: 0.86 to 1.03, per 25 g/d). Olive oil consumption was associated with a 22% lower relative risk of T2D (RR: 0.78; 95% CI: 0.69 to 0.87, per 25 g/d) without evidence of heterogeneity. Similarly, it was inversely associated with all-cause mortality (RR: 0.89; 95% CI: 0.85 to 0.93, per 25 g/d). Only the results for T2D were homogeneous. Specific sources of heterogeneity for the other 3 outcomes were not always apparent.
Conclusions: Prospective studies supported a beneficial association of olive oil consumption with CVD, T2D and all-cause mortality, but they did not show any association with cancer risk.

1. Introduction

The most effective way to reduce the global burden of disease is to apply primary prevention interventions to reduce the incidence of major cardiovascular disease (CVD) and other chronic diseases [1,2]. Adherence to high-quality nutritional eating patterns has shown to be associated with reductions in the rates of clinical CVD events [3–5]. The traditional Mediterranean dietary pattern, represents not only the most widely tested model [5], but also a highly palatable and sustainable approach [6]. A relationship was reported between changes in diet quality over time (measured as the Alternate Mediterranean diet score) and the risk of mortality, showing a reduction in mortality associated with improved adherence to the Mediterranean diet (MedDiet) over time [3]. Epidemiological studies have reported that the MedDiet has positive effects on cardiometabolic features and a preventive effect on primary CVD events [4]. In this context, a systematic review and

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meta-analysis of prospective studies and RCTs showed that participants with better adherence to the MedDiet exhibited lower incidence of CVD and lower cardiovascular mortality [7]. Beneficial effects on CVD outcomes were reported to be attributable to fruits, vegetables, legumes, and olive oil [5]. However, some of the available systematic reviews or meta-analyses evaluating the effect of the MedDiet on CVD outcomes, had limitations (low-quality of the design and conduction of studies, inappropriate statistical methods, publication bias, others) that should be considered [5].

The largest trial testing the MedDiet, the PREDIMED trial, in one of its 3 arms, specifically tested a MedDiet supplemented with free provision of extra-virgin olive oil (EVOO) [8]. Reported results for this arm of the PREDIMED trial were salient with respect to significant and clinically meaningful reductions (versus control group) in hard end-points, including major CVD events [8], atrial fibrillation [9], peripheral artery disease [10], type 2 diabetes (T2D) [11] and breast cancer [12]. Additionally, a previous meta-analysis conducted in 2014 reported inverse associations between olive oil consumption and CVD events, particularly stroke [13]. Thereafter, several large and well conducted observational studies have reported beneficial associations for overall CVD, but with variable specific effects for only stroke or only coronary heart disease (CHD) [14–16].

Given the substantial proportion of calories (even up to 20–25% of total energy intake) provided by olive oil in the traditional MedDiet, and in light of the substantial number of recent publications in this active research field, there is a need for an updated synthesis of the evidence on the effect of dietary olive oil consumption and the risk of major chronic disease, by conducting a systematic review and meta-analysis of the published prospective studies [4]. As proposed by Vanderweele, we adopted an outcome-wide perspective to consider several end-points potentially related to the consumption of olive oil [17].

2. Materials and methods

This review was conducted according to the Cochrane Handbook (https://training.cochrane.org/handbook) [18] and the PRISMA guidelines for reporting systematic reviews [19] (Supplementary material). The protocol has been registered in PROSPERO, the international Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/, identifier: CRD42021253760).

2.1. Literature search

We performed an outcome-wide systematic search using PubMed and Web of Science databases through January 19th, 2022 to identify published cohort studies or RCT evaluating the association between olive oil and CVD, cancer, T2D, and all-cause mortality, with no restrictions in the calendar date. Keywords and MeSH terms relating to olive oil consumption 'olive oil' combined with cardiovascular events ('cardiovascular disease' or 'cardiac heart disease' or 'myocardial ischemia' or 'brain ischemia' or 'cerebro vascular'); all cause-mortality ('death' or 'mortality'); cancer events ('neoplasm*' or 'cancer') and type 2 diabetes mellitus ('diabetes mellitus' or 'diabetes mellitus, type 2') were used in the search strategy. The language of publication was restricted to English, Spanish, Italian, French or Portuguese. Furthermore, the reference lists of the studies retrieved were checked to identify further relevant studies. The complete search strategy is presented in Supplemental Tables S1–S2.

2.2. Inclusion and exclusion criteria

Articles eligible for inclusion were manually evaluated. Two investigators (VB–V and CS-O) independently reviewed all titles and abstracts identified by the search. Then also these two investigators (VB–V and CS-O) independently reviewed the full texts. Situations with discrepant decisions were solved by consensus and in consultation with a third researcher (MB-R). Included studies had to meet all the following 3 criteria: 1) the study design was a cohort with prospective follow-up >3 years or a RCT conducted only in human participants; 2) prospective studies that considered olive oil consumption as exposure; and assessed as an outcome of interest incident cases of major CVD (including CHD or stroke), any cancer, T2D or all-cause death; and, 3) reported relative risks (RR), hazard ratios (HR) or odds ratios (OR) with 95% CI for at least 2 categories of olive oil consumption, or for olive oil consumption as a continuous variable. We excluded ecological studies, cross-sectional designs, case–control studies, case-cohort studies, and studies which were written in languages other than English, Spanish, Italian, French or Portuguese. We also excluded articles only reporting protocols, reviews, editorials, comments, letters, conference or abstracts of meeting presentations, and studies dealing with other exposures (e.g. 'oil', 'vegetable oil' or eating patterns that included olive oil merely as one of many components of a dietary pattern or a set of dietary elements, without providing specific estimates for olive oil). Additionally, when results from a study population were reported more than once, we used the results with the longest follow-up time.

2.3. Data extraction

Two reviewers (VB–V and CS-O) extracted independently the following information from each study: authors, year of publication, study name, country of origin, study design, main participants' characteristics (sample size, sex and age), dietary assessment method, type of oil consumed and categories of consumption, years of follow-up, definition of end-points, number of cases of each end-point, covariates adjusted for in the multivariable analyses; RR, HR or OR with 95% CI for all categories of oil consumption considering "non-consumption" (or the lowest category of consumption of olive oil) as the comparator. If it was available, the substitution of olive oil for another type of fat, was also extracted.

2.4. Outcomes definitions

Most of the included studies defined CVD using the ICD-10 codes as follows: Cerebrovascular disease: I60–I69 and G45-G46 (ICD-9 codes: 430–438); ischemic heart disease: I20-25 (ICD-9 codes: 410–414); cardiac arrest: I46 [20]. Other studies used diagnostic criterion of World Health Organization (WHO) [21], or the modified criteria of the WHO Expert Committee, or the simplified version developed by the American Heart Association [22]. Cancer cases were identified with the following ICD-10 codes as follow: C16 for gastric cancer, C50 for breast cancer, C18–C20 for colorectal cancer, we did not include cancers with benign prognosis (non-melanoma skin cancer) as well as studies that did not include initially healthy participants. For mortality, fatalities were confirmed through medical death certificates, or civil registry information. Finally, for T2D all studies used the definition of the American Diabetes Association [23].

2.5. Risk of bias assessment

Two independent reviewers (VB–V and CS-O) assessed the quality of the included studies. Risk of bias of cohort studies was assessed using a 9-point scoring system according to the Newcastle–Ottawa Scale (NOS) [24]. The score ranged from 0 to 9, and a high-quality study in the present analysis was defined by a threshold of $\geq$7 points. For RCTs, we applied the Cochrane Risk of Bias tool-2 (RoB 2) that is structured into five domains, assigning judgments of "Low", "high", and "some concerns" within each domain [25].

2.6. Statistical analysis

RRs and their 95% CI were taken as the magnitude of the association for all studies, and HRs were considered equivalent to RRs. Results stratified by sex were treated as two separate reports. Owing to the distinct cut-off points for olive oil categories in different articles, effect estimates were standardized by computing a RR with 95% CI for each additional consumption of 25 g/d of olive oil for each report, standardizing all RRs to this amount. Median or mean olive oil consumption in each category was used as the corresponding dose of consumption. We used preferentially the median, and when it was not reported, we used the mean. The midpoint of the upper and lower boundaries was considered as the dose of each category if the median or mean intake for that category was not available. If the highest category was open-ended, the midpoint of that category was set at the mean point between the lower boundary and 100 g. Exploratory meta-regression analyses were conducted using the "metareg" command. Covariates explored in the meta-regression analyses were geographical origin (Mediterranean and non-Mediterranean countries), number of participants (<10,000 *vs* ≥ 10,000), length of the follow-up period (<10 *vs* ≥ 10 years), exposure assessment (olive oil quantified vs olive oil in categories), mean intake of olive oil (≥12 g/d vs < 12 g/d). The meta-regressions were conducted when at least 10 studies were available for each covariate. Then, between-study heterogeneity using Cochran's Q x^2 test, were conducted and the proportion of heterogeneity with the I^2 statistic was quantified. The I^2 statistic represents the percentage of the total variation in the RR estimates that is due to true heterogeneity rather than chance. As heterogeneity was apparent, we used a random-effects model (DerSimonian and Laird method). To investigate the influence of each single study on the overall estimation we conducted another sensitivity analysis omitting one study at a time, using Stata's user-written function "metaninf". We considered a particular study was influential if the pooled estimate without that study was not within the 95% confidence interval of the overall estimation. Forest plots were used to examine the overall effect.

As interventions in the PREDIMED study (the only large RCT that was conducted with the free provision of olive oil) were also based on changes in the overall adherence to the traditional pattern of the MedDiet, it is possible that the effects of the PREDIMED interventions cannot be solely attributed to olive oil. For this reason, we also run sensitivity analyses after excluding the results of PREDIMED.

Potential publication bias and evidence for small-study effects was tested using the "metafunnel" and "metabias" functions of Stata which produce funnel plots and the Egger statistical test. The assessment of publication bias was only conducted when there were at least 10 studies included in the meta-analysis [18]. Statistical analyses were conducted using Stata SE V.16.

3. Results

3.1. Search results

The results of the literature research and study selection are shown in Fig. 1. Initially, a total of 508 records were identified in PubMed and 1463 in the Web of Science until January 19th, 2022. After the exclusion of 188 duplicate records and screening the titles of the remaining 1783 records, we excluded 1609 records that were clearly not relevant or did not meet at least one of the inclusion criteria. The abstracts and full text of the 174 eligible reports were read, and this also helped us to identify eighteen additional articles that were not captured in our first search. We excluded 156 reports that did not meet the inclusion criteria (reasons of exclusion of each report are available at Supplemental Table S3). Thus, thirty-six articles were included in the systematic review and twenty-seven studies were included in the quantitative meta-analysis.

3.2. Characteristics of the studies

Study characteristics are shown in Table 1 for cohort studies and in Table 2 for RCT. The present meta-analyses included a total of 806,203 participants with 49,223 CVD events; 1,285,064 participants with 58,892 cases of cancer (considering both incident cases

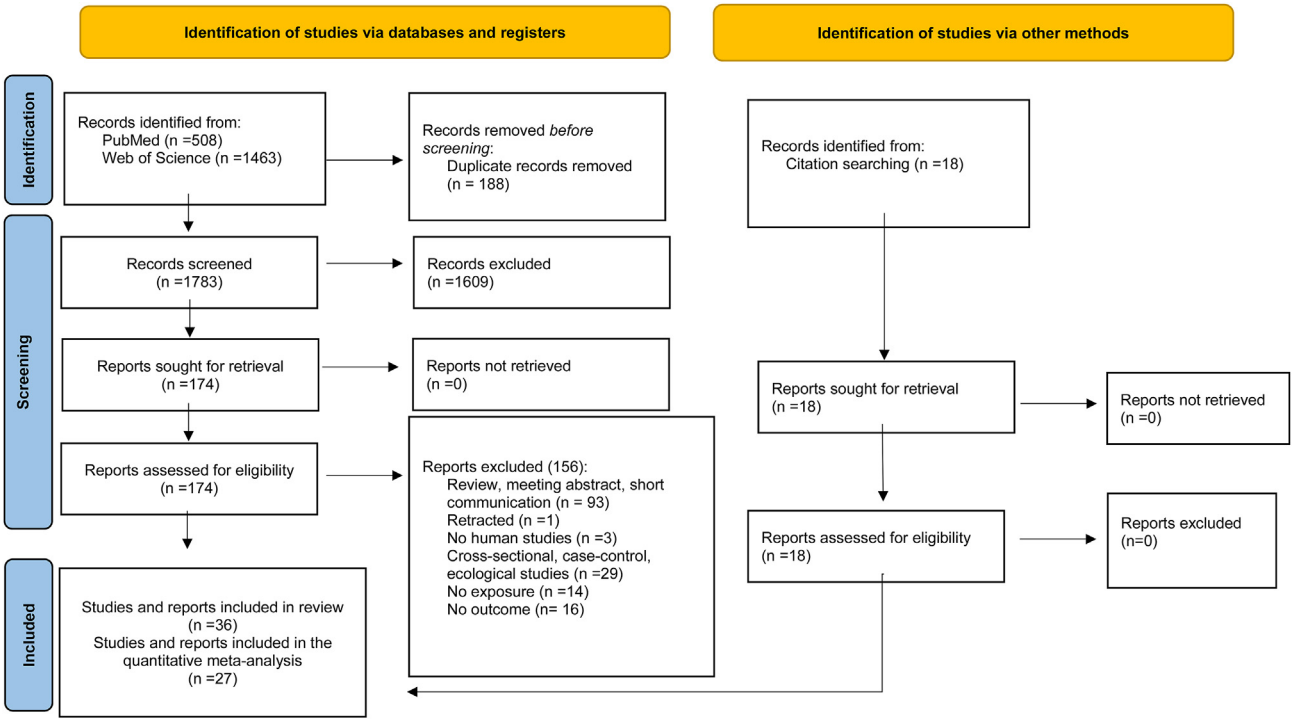

Fig. 1. Flow chart for selection of articles relating olive oil with cardiovascular disease, cancer, type 2 diabetes or all-cause mortality.

Table 1
General study characteristics of the cohort studies investigating the effects of olive oil consumption on cardiovascular disease, cancer, type 2 diabetes mellitus and all-cause mortality.

Author, Publication year	Study, Country/ region	Study population and baseline age	Outcomes	Dietary assessment	Exposures	Intake categories	Follow-up period	Events	RR (95% CI)	Covariables adjusted for in the fully adjusted model	RR 95%CI substituting another type of oil for olive oil
Cardiovascular disease											
Samieri C, 2011 [26]	Three-City Study, France	7625 ≥65 years	Stroke	FFQ and 24 h dietary recall in one center (Bordeux)	Olive oil use	No olive oil use Moderate olive oil use Intensive olive oil use	5.25 yrs	Stroke event:148	**Stroke event:** No use: 1.00 Ref Moderate use: 0.80 (0.53−1.20) Intensive use: 0.59 (0.37−0.94)	Age, sex, education, center, consumption of fish, meat, pulses, raw vegetables, raw fruit, cooked fruits and vegetables, cereals, regular use of omega-3 rich oils, omega-6 rich oil, butter, goose, or duck fat, alcohol consumption, physical activity, systolic blood pressure, antihypertensive therapy, diabetes, smoking, history of CVD, AF, BMI, triglyceridemia and hypercholesterolemia.	NA
Bendinelli B, 2011 [27]	EPICOR Study, Italy	29,689 35−74 years	CHD	FFQ (217−154 food items)	Total olive oil consumption	Quartiles of consumption	7.85 yrs	CHD event: 144	***CHD event:*** Q1: 1.00 Ref Q2: 1.06 (0.70−1.61) Q3: 0.81 (0.50−1.30) Q4: 0.56 (0.31−0.99)	Energy intake, educational level, smoking status, alcohol consumption, height, weight, waist circumference, daily non-alcohol caloric intake, hypertension, menopausal status, total physical activity, total meat consumption, vegetable consumption.	NA
Misirli G, 2012 [28]	EPIC Study Greece	23,601 25−86 years	Stroke Stroke mortality	FFQ (150 items)	Total olive oil consumption	Increment increase in 23 g/day	10.6 yrs	Stroke event: 395 Stroke mortality: 196	Stroke ***event:*** 0.80 (0.70−0.90) Stroke ***mortality:*** 0.89 (0.73−1.08)	Sex, age, education, smoking status, BMI, physical activity, hypertension, diabetes, total energy intake	NA
[a]Buckland G, 2012 (a) [29]	EPIC study, Spain	40,622 29−69 years	CVD mortality	Dietary history questionnaire (600 foods items)	Total olive oil consumption	Olive oil as a function of energy density (g/d per 2000)	13.4 yrs	CVD mortality: 416	***CVD mortality*** Non-consumers: 1.00 Ref. Q1: 0.87 (0.64−1.17) Q2: 0.77 (0.56−1.06) Q3: 0.71 (0.52−0.98) Q4: 0.56 (0.40−0.79) Olive oil 10 g: 0.87 (0.80−0.94)	Physical activity, BMI, waist circumference, educational level, smoking status, energy intake, alcohol, fruit, vegetables, meat and dairy, stratified by center, age, and sex.	NA
Dilis V, 2012 [30]	EPIC study, Greece	Total: 23,929 14,189 women; 9740 men 20−86 years	CHD CHD mortality	FFQ (200 items)	Total olive oil consumption	1 SD of increment of olive oil	10 yrs	CHD event: 636 CHD mortality: 240	***CHD event:*** Men: 1.09 (0.97−1.23) Women: 1.10 (0.90−1.34) ***CHD mortality:*** Men: 1.11 (0.91−1.36) Women: 1.42 (1.02−1.96)	BMI, height, physical activity, years of schooling, energy intake, alcohol consumption, smoking status, blood pressure.	NA
[a]Buckland G, 2012 (b) [31]	EPIC Study, Spain	40,142 29−69 years	CHD	Dietary history questionnaire (662 food items)	Olive oil as a function of energy density (g/d per 2,000 kcal)	Quartiles of olive oil intake (g/d per 2000 kcal)	10.4 yrs	CHD event: 587	***CHD event:*** Q1: 1.00 Ref. Q2: 0.79 (0.62−1.01) Q3: 0.94 (0.75−1.18) Q4: 0.85 (0.68−1.07) Olive oil 10 g: 0.96 (0.91−1.02)	Educational level, BMI, waist circumference, physical activity, smoking status, alcohol consumption, energy intake excluding alcohol, hyperlipidaemia,	NA

										hypertension, diabetes, Mediterranean diet score (excluding olive oil and alcohol). Stratified by age, centre and sex.	
[a]Guasch-Ferre M, 2014 [32]	PREDIMED Observational Study, Spain	7216 55–80 years	CVD CVD mortality	FFQ (137 items)	Total olive oil consumption	Energy adjusted tertiles of total olive oil consumption	4.8 yrs	CVD event: 277 CVD mortality: 81	***CVD event:*** T1: 1.00 Ref. T2: 0.78 (0.58–1.04) T3: 0.65 (0.47–0.89) Olive oil 10 g: 0.87 (0.81–0.94) ***CVD mortality:*** T1: 1.00 Ref. T2: 0.69 (0.40–1.18) T3: 0.52 (0.29–0.93) Olive oil 10 g: 0.84 (0.73–0.96)	Age, sex intervention group, BMI, smoking status, alcohol intake, educational level, leisure-time physical activity, prevalence of diabetes, hypertension, hypercholesterolemia or use of medication, Mediterranean diet adherence, stratified by recruitment center	NA
Atkins JL, 2014 [33]	British Regional Heart Study	3269 men 60–79 years	CVD CHD CVD mortality	FFQ (Use in the WHOs Monitoring Trends and Determinants in CDV Survey)	Total olive oil consumption	Lowest (score 1) vs highest (score 4) Compliance with EDI score	11.3 yrs	CVD event: 570 CHD event: 301 CVD mortality: 317	***CVD mortality:*** 0.43 (0.24–0.80) ***CVD event:*** 0.58 (0.40–0.86) ***CHD event:*** 0.55 (0.32–0.95)	Age, energy intake, smoking, alcohol, physical activity, social class, BMI, and a modified version of the HDI/EDI score not containing the individual component of interest.	NA
Stefler D, 2017 [34]	HAPIEE, Czech Republic, Poland and Russian Federation	19,333 45–69 years	CVD CHD Stroke	FFQ (covering 136, 148 and 147 items)	Olive oil usage	Yes/No	7 yrs	CVD event:438 CHD event: 226 Stroke event: 109	***CVD event:*** 1.07 (0.73–1.55) ***CHD event:*** 1.23 (0.71–2.16) ***Stroke event:*** 1.58 (0.72–3.50)	Age, sex, cohort, education, marital status, household amenities score, smoking, physical activity, total energy intake and vitamin supplement intake.	NA
[a]Bazal P, 2019 [35]	SUN Study, Spain	18,118 Mean age: 37.5 years	AF	FFQ (136 items)	Total olive oil intake	Low intake Low-moderate intake Moderate-high intake High intake	10.1 yrs	AF event: 94	***AF event:*** Low: 1.00 Ref. Low-moderate: 1.52 (0.93–2.48) Moderate-high: 1.44 (0.83–2.47) High: 1.27 (0.56–2.86)	Age, sex BMI, physical activity, diabetes, arterial hypertension, CVD, adherence to Mediterranean diet, sleep apnea, height, and alcohol consumption.	NA
Kouli G-M, 2019 [36]	ATTICA Study, Greece	2020 18–87 years	CVD	FFQ (190 items)	Total olive oil consumption	No use Mixed use with other oils Exclusive use	8.41 yrs	Fatal and non-fatal CVD event: 317	***Total CVD fatal and non-fatal***: No use: 1.00 Ref. Mixed: 2.02 (0.69–5.90) Exclusive: 0.24 (0.02–2.54)	Age, sex, BMI, smoking habits, physical activity, education level, history of hypertension, hypercholesterolemia, diabetes, metabolic syndrome, fibrinogen.	NA
Guasch-Ferre M, 2020 [14]	NHS I and II and HPFUS, USA	NHSI and II: 61,181 HPFUS: 31,797 NHS I: 30–55 years NHSII: 25–42 years HPFUS: 40–75 years	CVD CHD Stroke	FFQ (130 items)	Total olive oil consumption	Never or less than 1 per month. >0 to ≤4.5 g/d >4.5 to ≤7 g/d >7 g/d	24 yrs	***Total CVD fatal and non-fatal event***: NHS: 1971 HPFS: 1696 ***CHD fatal and non-fatal event:*** NHS: 1078 HPFS: 1310 ***Stroke, fatal and non-fatal event:*** NHS: 906 HPFS: 386	**Total CVD fatal and non- fatal event:** Never: 1.00 Ref. >0-≤4.5 g/d: 0.89 (0.85–0.93) >4.5-≤7 g/d: 0.83 (0.76–0.91) >7 g/d: 0.86 (0.79–0.84) Olive oil 5 g: 0.94 (0.92–0.97) **CHD fatal and non-fatal event:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.85 (0.81–0.89) >4.5- ≤7 g/d: 0.81 (0.73–0.91)	Age, ethnicity, Southern European and/or Mediterranean ancestry, smoking status, alcohol intake, physical activity, family history of diabetes, family history of myocardial infarction, cancer, baseline diabetes mellitus, hypertension or antihypertensive medication use, hypercholesterolemia or cholesterol-lowering medication use, multivitamin use, aspirin use, in women,	***CVD*** ***For margarine:*** *0.94 (0.91-0.97)* ***For butter:*** *0.95 (0.91-1.00)* ***For mayonnaise:*** *0.93 (0.89-0.98)* ***For other vegetable oils:*** *0.98 (0.92-1.04)* ***For dairy fat:*** *0.95 (0.92-0.98)* ***For other fats:*** *0.94 (0.91-0.97)* ***CHD*** ***For margarine:*** *0.93 (0.89-0.97)* ***For butter:*** *0.94 (0.89-1.01)*

(*continued on next page*)

Table 1 (*continued*)

									>7 g/d: 0.82 (0.73–0.91) Olive oil 5 g: 0.93 (0.89–0.97) **Stroke, fatal and non-fatal event:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.99 (0.97–1.02) >4.5- ≤7 g/d: 0.90 (0.80–1.01) >7 g/d: 0.95 (0.85–1.12) Olive oil 5 g: 0.96 (0.92–1.01)	postmenopausal status and menopausal hormone use, total energy intake, BMI, red meat, fruits and vegetables, nuts, soda, whole grain intake, and trans-fat.	***For mayonnaise:*** *0.94 (0.88-1.00)* ***For other vegetable oils:*** *0.96 (0.89-1.04)* ***For dairy fat:*** *0.93 (0.89-0.97)* ***For other fats:*** *0.93 (0.91-0.97)* ***Stroke*** ***For margarine:*** *0.96 (0.91-1.02)* ***For butter:*** *0.96 (0.89-1.04)* ***For mayonnaise:*** *0.94 (0.87-1.02)* ***For other vegetable oils:*** *0.99 (0.99-1.01)* ***For dairy fat:*** *0.98 (0.93-1.04)* ***For other fats:*** *097 (0.92-1.02)*
Sadeghi M, 2021 [37]	ICS study, Iran	5432 ≥35 years	CVD Stroke Myocardial infarction IHD	Persian FFQ	Olive oil	Quartiles of olive oil intake	11.25 yrs	CVD event: 751 Stroke event: 157 Myocardial infarction event: 156 Ischemic heart disease event: 245	***CVD event:*** Q1: 1.00 Ref. Q2: 1.05 (0.83–1.32) Q3: 0.93 (0.69–1.25) Q4: 0.95 (0.74–1.21) ***Stroke event:*** Q1: 1.00 Ref. Q2: 1.01 (0.60–1.69) Q3: 1.10 (0.57–2.10) Q4: 1.35 (0.81–2.28) ***Myocardial infarction:*** Q1: 1.00 Ref. Q2: 0.79 (0.48–1.32) Q3: 0.73 (0.39–1.37) Q4: 1.07 (0.63–1.82) ***Ischemic heart disease event (myocardial infarction and sudden cardiac death)*** Q1: 1.00 Ref. Q2: 1.24 (0.81–1.88) Q3: 1.26 (0.75–2.13) Q4: 1.26 (0.75–2.13) ***CVD mortality event:*** Q1: 1.00 Ref. Q2: 1.36 (0.83–2.25) Q3: 1.62 (0.87–3.03) Q4: 1.07 (0.60–1.90)	Age, sex, education, residency, smoking status, daily physical activity, family history of cardiovascular disease, diabetes mellitus, hypertension, hypercholesterolemia, aspirin use and post menopause in women, BMI, dietary factor including red meat, fish, fruit and vegetable, hydrogenated vegetable oil, non-hydrogenated oil, olive oil, ghee oil, animal fats, fast food, cereals, legumes, nuts and seeds, animal fats, sweets, soft drink and beverages.	NA
Zhang, 2021 [15]	NIH-AARP Diet and Health Study	521,120 50–71 years	CVD mortality	FFQ (124 item)	Olive oil intake	Olive oil intake (g/d per 2000 kcal) Non-consumers T1: ≤0.7 g/d T2: 0.8–1.8 g/d T3: ≥1.9 g/d	Average of 16 yrs	CVD mortality 38,747 CHD mortality 33,142 Stroke mortality 5605	**CVD mortality:** Non-consumers: 1.0 Ref. T1: 0.93 (0.89–0.97) T2: 0.95 (0.92–0.98) T3: 0.95 (0.92–0.99) **Heart disease:** Non-consumers: 1.0 Ref. T1: 0.92 (0.88–0.97) T2: 0.96 (0.93–1.00) T3: 0.96 (0.92–0.99) **Stroke:** Non-consumers: 1.0 Ref. T1: 0.95 (0.85–1.06) T2: 0.89 (0.81–0.99) T3: 0.92 (0.84–1.00)	Age, sex, race, marital status, education, household income, BMI, alcohol, smoking, vigorous physical activity, usual activity at work, perceived health condition, and history of cancer, heart disease, stroke, and diabetes, Healthy Eating Index-2015, total energy intake, and consumption of remaining oils where appropriate (butter, margarine, lard, corn oil, canola oil, olive oil, and other vegetable oils).	NA
Donat-Vargas C, 2021 (a,b) [16]	SUN study EPIC study Spain	SUN (18,266), mean age: 38 years	CVD	FFQ and dietary history questionnaire	Total olive oil consumption	0 to <10 g/d 10 to <20 g/d	SUN study: Average of 10.8 yrs	CVD event SUN study CVD:150	**SUN study** **CVD event:** 0 to <10 g/d:	Age, sex, total energy intake, years of university (SUN	NA

		EPIC-Spain (39,393), mean age: 49 years				20 to <30 g/d ≥30 g/d	EPIC-Spain Average of 22.8 yrs	EPIC-Spain CVD: 2159	1.00 Ref. 10 to <20 g/d: 0.97 (0.65−1.47) 20 to <30 g/d 0.83 (0.51−1.37) ≥30 g/d: 0.73 (0.38−1.40) **EPIC-Spain** **CVD event:** 0 to <10 g/d: 1.00 Ref. 10 to <20 g/d: 0.90 (0.79−1.02) 20 to <30 g/d: 0.87 (0.76−0.98) ≥30 g/d: 0.95 (0.84−1.08) **CHD event:** <10 g/d: 1.00 Ref. 10 to <20 g/d: 0.94 (0.80−1.10) 20 to <30 g/d: 0.90 (0.77−1.05) ≥30 g/d: 0.99 (0.84−1.17) **Stroke event:** <10 g/d: 1.00 Ref. 10 to <20 g/d: 0.84 (0.70−1.02) 20 to <30 g/d: 0.80 (0.66−0.96) ≥30 g/d: 0.89 (0.74−1.07)	study), education level (EPIC study), smoking status, number of cigarettes per day (SUN study), number of packs per day (EPIC study), physical activity, BMI, alcohol consumption, dietary fiber, fruits and vegetables, sodium intake, systolic and diastolic blood pressure, hypercholesterolemia, hypertension, diabetes, stratified by center (EPIC study) or calendar year recruitment (SUN study)	
[a]Guasch-Ferre M, 2021 [38]	NHS and HPFUS, USA	NHS 60,582 30−55 years HPFUS 31,801 40−75 years	CVD mortality	FFQ (130 items)	Total olive oil consumption	Never or less than 1 per month. >0 to ≤4.5 g/d >4.5 to ≤7 g/d >7 g/d	28 yrs	**NHS** CVD mortality 4915 **HPFUS** CVD mortality 4084	**NHS** **CVD mortality:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.83 (0.77−0.88) >4.5- ≤7 g/d: 0.74 (0.65−0.84) >7 g/d: 0.85 (0.77−0.94) HR per 5 g/d increment 0.98 (0.95−1.01) **HPFUS** **CVD mortality:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.84 (0.78−0.90) >4.5- ≤7 g/d: 0.81 (0.71−0.93) >7 g/d: 0.79 (0.71−0.88) HR per 5 g/d increment 0.97 (0.94−1.00) **Pooled** **CVD mortality:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.82 (0.78−0.86) >4.5- ≤7 g/d: 0.77 (0.70−0.84) >7 g/d: 0.81 (0.75−0.87) HR per 5 g/d increment 0.97 (0.95−0.99)	Adjusted for age and calendar time, 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, body mass index, intake of red meat, fruits and vegetables, nuts, soda, whole grains, and trans-fat. Pooled dataset was stratified by cohort (sex) and time period.	NA

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Donat-Vargas C, 2021 (c) [39]	ENRICA study, Spain	12,161 18–96 years	CVD mortality	Dietary history ENRICA (DH-E)>	Total olive oil intake	HR per 10 g in daily intakes of olive oil	10.7 yrs	CVD mortality 143	**CVD mortality:** 0.87 (0.73–1.04)	Sex, age, total energy intake, educational level, smoking status, BMI, physical activity in home activities and free time, TV time, alcohol consumption, fiber intake, number of medications, hypertriglyceridemia, hypercholesterolemia, high blood pressure, number of self-reported chronic conditions, adherence to Mediterranean diet.	NA
Cancer											
Trichopoulou, 2010 [40]	EPIC Study, Greece	14,807 women 20–86 years	Breast cancer	FFQ (150 items)	Total olive oil consumption	HR per 21 g in daily intakes of olive oil	Average of 9.8 yrs	Breast cancer: 240	**Breast cancer:** Cohort 1.93 (0.80–1.08) Premenopausal 1.00 (0.82–1.22)** Postmenopausal 0.85 (0.69–1.06)***	Age at enrollment, educational level, smoking status, BMI, height, metabolic equivalents of task per day, energy intake, age of menarche, parity, age at first delivery, menopausal status, age at menopause, hormone replacement therapy and an interaction term for the BMI by menopausal status, **without menopausal status, age at menopause, and the interaction term for BMI by menopausal status, ***without variables denoting menopausal status and the interaction term for BMI by menopausal status.	NA
Buckland G, 2012 (a) [29]	EPIC study, Spain	40,622 29–69 years	Cancer mortality	Dietary history questionnaire (600 foods items)	Total olive oil consumption	Olive oil as a function of energy density (g/d per 2,000 kcal)	13.4 yrs	Cancer mortality: 956	***Cancer mortality*** Non-consumers: 1.00 Ref. Q1: 0.99 (0.80–1.22) Q2: 0.92 (0.74–1.15) Q3: 0.97 (0.78–1.20) Q4: 0.90 (0.72–1.13) Olive oil 10 g: 0.98 (0.93–1.04)	Physical activity, BMI, waist circumference, educational level, smoking status, energy intake, alcohol, fruit, vegetables, meat and dairy stratified by center, age, and sex.	NA
Buckland G, 2012 (c) [42]	EPIC study, Spain, Greece, Italy,	62,284 29–69 years	Breast cancer	FFQ or Dietary history questionnaire (country/specific)	Total olive oil consumption	Tertiles of olive oil intake (g/d per 2000 kcal)	9 yrs	Breast cancer: 1256	***Breast cancer*** T1: 1.00 Ref. T2: 1.06 (0.92–1.21) T3: 1.06 (0.92–1.21)	educational level, BMI, height, physical activity, smoking status, alcohol consumption and energy intake excluding alcohol stratified by age and center.	NA
Guasch-Ferre M, 2014 [32]	PREDIMED Study, Spain	7216 55–80 years	Cancer mortality	FFQ (137 items)	Total olive oil consumption	Energy adjusted tertiles of total olive oil consumption	4.8 yrs	Cancer mortality:130	***Cancer mortality:*** T1: 1.00 Ref T2: 1.13 (0.74–1.72) T3: 0.84 (0.52–1.37) Olive oil 10 g: 0.95 (0.85–1.07)	Age, sex intervention group, BMI, smoking status, alcohol intake, educational level, leisure time physical activity, prevalence of diabetes, hypertension, hypercholesterolemia or use of medication, Mediterranean diet	NA

										adherence, stratified by recruitment center.	
[a]Mahamat-Saleh Y, 2019 [45]	E3N study, France	67,322 40–65 years	Skin cancer	FFQ (208 food items) and 24-h dietary recall	Olive oil	Non-consumers Consumers	15 yrs	Skin cancer: 2003	***Skin cancer:*** Non-consumers: 1.00 Ref. Consumers: 1.04 (0.95–1.13)	age, skin sensitivity to sun exposure, number of nevi, number of freckles, skin color, hair color, family history of skin cancer, levels of residential sun exposure at birth and at baseline, BMI, physical activity, smoking status, education level, energy intake, coffee intake, and other dietary components of the Mediterranean score stratified by birth cohort.	NA
Zhang, 2021 [15]	NIH-AARP Diet and Health Study USA	521,120 50–71 years	Cancer mortality	FFQ (124 item)	Olive oil intake	Olive oil intake (g/d per 2000 kcal) Non-consumers T1: ≤0.7 g/d T2: 0.8–1.8 g/d T3: ≥1.9 g/d	Average of 16 yrs	Cancer mortality 45,783	**Cancer mortality:** Non-consumers: 1.0 Ref. T1: 1.03 (0.99–1.07) T2: 1.01 (0.98–1.05) T3: 1.02 (0.99–1.05)	Age, sex, race, marital status, education, household income, BMI, alcohol, smoking, vigorous physical activity, usual activity at work, perceived health condition, and history of cancer, heart disease, stroke, and diabetes, Healthy Eating Index-2015, total energy intake, and consumption of remaining oils where appropriate (butter, margarine, lard, corn oil, canola oil, olive oil, and other vegetable oils).	NA
Guasch-Ferre M, 2021 [38]	NHS and HPFUS, USA	NHS 60,582 30–55 years HPFUS 31,801 40–75 years	Cancer mortality	FFQ (130 items)	Olive oil intake	Never or less than 1 per month. >0 to ≤4.5 g/d >4.5 to ≤7 g/d >7 g/d	28 yrs	**NHS** Cancer mortality 5708 **HPFUS** Cancer mortality 3764 146	**NHS** **Cancer mortality** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.85 (0.80–0.90) >4.5- ≤7 g/d: 0.98 (0.88–1.09) >7 g/d: 0.86 (0.78–0.93) HR per 5 g/d increment 0.98 (0.96–1.01) **HPFUS** **Cancer mortality:** Never: 1.00 Ref. >0-≤4.5 g/d: 0.89 (0.82–0.95) >4.5-≤7 g/d: 0.92 (0.81–1.05) >7 g/d: 0.83 (0.74–0.93) HR per 5 g/d increment 0.95 (0.92–0.99) **Pooled** **Cancer mortality:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.86 (0.82–0.90) >4.5- ≤7 g/d: 0.94 (0.87–1.02)	Adjusted for age and calendar time, 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, body mass index, intake of red meat, fruits and vegetables, nuts, soda, whole grains, and trans-fat. Pooled dataset was stratified by cohort (sex) and time period.	NA

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								>7 g/d: 0.83 (0.78–0.89) HR per 5 g/d increment 0.97 (0.95–0.99)		
Sex, age, total energy C, 2021 (c) [39]	ENRICA study, Spain	12,161 18–96 years	Cancer mortality	Dietary history ENRICA (DH-E)	Total olive oil intake	HR per 10 g in daily intakes of olive oil	10.7 yrs	Cancer mortality	**Cancer mortality:** 0.97 (0.83–1.12)	Sex, age, total energy intake, educational level, smoking status, BMI, physical activity in home activities and free time, TV time, alcohol consumption, fiber intake, number of medications, hypertriglyceridemia, hypercholesterolemia, high blood pressure, number of self-reported chronic conditions, adherence to Mediterranean diet.	NA
Buckland G, 2010 [41]	EPIC Study, United Kingdom, France, Denmark, Sweden, Germany, Italy, Spain, the Netherlands, Norway, and Greece.	485,044 35–70 years	Gastric adenocarcinoma	FFQ or Dietary history questionnaire (country/specific)	rMED dietary score g.1000 $kcal^{-1}$ d^{-1}	No consumers <Median: 3.6 g/d >Median: 3.6 g/d	8.9 yrs	Gastric adenocarcinoma 449	**Gastric adenocarcinoma:** No consumers: 1.00 Ref. <Median: 1.05 (0.74–1.46) >Median: 1.15 (0.78–1.69)	stratified by center and age and adjusted for sex (in overall model), BMI, educational level, smoking status, cigarette smoking intensity, and total energy intake.	NA
Agnoli C, 2013 [43]	EPIC Study, Italy	45,275 Mean age: 50.5	Colorectal cancer	FFQ (140 items)	Total olive oil consumption	T1: 0–19.3 g/d T2: 19.4–29.8 g/d T3: 29.9–160.4 g/d	11.28 yrs	Colorectal cancer 435	**Colorectal cancer** T1: 1.00 Ref. T2: 0.86 (0.68–1.09) T3: 0.88 (0.68–1.14)	Adjusted for non-alcoholic energy intake, gender (analysis of entire cohort only), age, BMI, smoking, education and total physical activity; stratified for centre.	NA
[a]Gnagnarella P, 2013 [44]	COSMOS Study, Italy	4336 Median age: 57 years (range:50–84)	Lung cancer	FFQ (188 items from the EPIC study)	Total olive oil consumption	Quartiles of olive oil consumption	5.7 yrs	Lung cancer 178	**Lung cancer** Q1: 1.00 Ref. Q2: 0.86 (0.58–1.28) Q3: 0.77 (0.51–1.18) Q4: 0.64 (0.39–1.04)	Baseline lung cancer risk probability, total energy intake, fruits and vegetables, fish, red meat, tea and wine consumption.	NA
Type 2 diabetes											
Marí-Sanchis A, 2011 [46]	SUN study, Spain	10,491 Mean age: 38.9 (11.4)	T2D	FFQ (136 items)	Total olive oil consumption	Quintiles of consumption	5.7 yrs	T2D: 42	**Incident T2D:** Q1: 1.00 Ref. Q2: 0.41 (0.13–1.25) Q3: 0.44 (0.15–1.30) Q4: 0.98 (0.39–2.48) Q5: 1.11 (0.45–2.78)	Age, sex, BMI, physical activity, family history of diabetes, gestational diabetes, hypercholesterolemia, hypertension, total energy intake, smoking status, alcohol consumption, trans fatty acid, fruits juice consumption, sugar sweetened beverages consumption, sleep apnea and caffeine intake.	NA
Guasch-Ferre M, 2015 [47]	NHS I–NHSII, USA	145,087 26–65 years	T2D	FFQ (130 items)	Total olive oil consumption	Never/almost never >0–4 g/d >4–8 g/d >8 g/d	22 yrs	Incident T2D: 9654	**Incident T2D:** Never/almost never: 1.00 Ref. >0–4 g/d: 0.99 (0.94–1.04) >4–8 g/d: 0.94 (0.88–1.01) >8 g/d: 0.90 (0.82.-0.99) Olive oil 8 g: 0.94 (0.90–0.99)	Age, ethnicity, ancestry, smoking status, alcohol intake, physical activity, family history of diabetes, history of hypertension, history of hypercholesterolemia, multivitamin use, postmenopausal	NA

										status, menopausal hormones use, quintiles of the AHEI score, total energy intake, BMI.	
Zhang, 2021 [15]	NIH-AARP Diet and Health Study USA	521,120 50–71 years	Diabetes mortality	FFQ (124 item)	Olive oil intake	Olive oil intake (g/d per 2000 kcal) Non-consumers T1: ≤0.7 g/d T2: 0.8–1.8 g/d T3: ≥1.9 g/d	Average of 16 yrs	Diabetes mortality 3512	**Diabetes mortality:** Non-consumers: 1.0 Ref. T1: 0.84 (0.72–0.98) T2: 0.94 (0.83–1.06) T3: 0.87 (0.77–0.99)	Age, sex, race, marital status, education, household income, BMI, alcohol, smoking, vigorous physical activity, usual activity at work, perceived health condition, and history of cancer, heart disease, stroke, and diabetes, Healthy Eating Index-2015, total energy intake, and consumption of remaining oils where appropriate (butter, margarine, lard, corn oil, canola oil, olive oil, and other vegetable oils).	NA
All cause-mortality											
Trichopoulou, 2003 [48]	EPIC Study, Greece	22,043 20–86 years	All-cause mortality	FFQ (150 items)	Olive oil intake	HR per 20 g in daily intakes of olive oil	3.7 yrs	All cause-mortality 275	**All cause-mortality:** 0.96 (0.83–1.10)	Sex, age, waist-to-hip ratio, energy-expenditure score, years of education, smoking status, BMI, and total energy intake.	NA
[a]Masala, 2007 [49]	EPIC Study, Italy	5611 ≥60 years	All-cause mortality	FFQ (more than 120 food items and different versions were applied in Naples and Ragusa)	Olive oil and salad pattern (high consumption of olive oil as culinary fat, raw vegetables, soups and white meat)	Quartiles of olive oil and salad pattern intake considered in the factor analysis	Average of 6.2 yrs	All cause-mortality 152	**All cause-mortality:** Q1: 1.00 Ref. Q2: 0.78 (0.50–1.21) Q3: 0.76 (0.48–1.20) Q4: 0.50 (0.29–0.86)	Sex, age, BMI waist, smoking status, years of education, civil status, hypertension at enrolment, index of physical activity and caloric intake stratified by recruitment center.	NA
Buckland G, 2012 (a) [29]	EPIC study, Spain	40,622 29–69 years	All cause-mortality	Dietary history questionnaire (600 foods items)	Total olive oil consumption	Olive oil as a function of energy density (g/d per 2,000 kcal)	13.4 yrs	All-cause mortality: 1915	***All-cause mortality*** Non-consumers: 1.00 Ref. Q1: 0.88 (0.76–1.01) Q2: 0.83 (0.71–0.96) Q3: 0.80 (0.69–0.93) Q4: 0.74 (0.64–0.87) Olive oil 10 g: 0.93 (0.90–0.97)	Physical activity, BMI, waist circumference, educational level, smoking status, energy intake, alcohol, fruit, vegetables, meat and dairy stratified by center, age, and sex.	NA
[a]Barzi, 2013 [50]	GISSI-Prevenzione study, Italy	11,246 19–90 years	All-cause mortality	Dietary questionnaire	Total olive oil consumption	Never/sometimes Often Regularly	42 months	All cause-mortality: 1660	**All cause-mortality** Never/sometimes: 1.00 Ref. Often: 0.77 (0.62–0.94) Regularly: 0.71 (0.60–0.84)	Age, sex, hypertension, HDL-cholesterol, diabetes, smoking, claudication, electrical instability, left ventricular dysfunction, residual myocardial ischemia, dietary supplementation (vitamin E, n-3 PUFA and the interaction), pharmacological therapies (aspirin, beta-blockers, angiotensin-converting enzyme inhibitors).	NA
[a]Guasch-Ferre M, 2014 [32]	PREDIMED Observational Study, Spain	7216 55–80 years	All-cause mortality	FFQ (137 items)	Total olive oil consumption	Energy adjusted tertiles of total olive oil consumption	4.8 yrs	All-cause mortality: 323	***All-cause mortality:*** T1: 1.00 Ref. T2: 0.90 (0.69–1.18) T3: 0.78 (0.58–1.05)	Age, sex intervention group, BMI, smoking status, alcohol intake, educational level, leisure-time physical	NA

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									Olive oil 10 g: 0.94 (0.87–1.00)	activity, prevalence of diabetes, hypertension, hypercholesterolemia or use of medication, Mediterranean diet adherence, stratified by recruitment center.	
Atkins JL, 2014 [33]	British Regional Heart Study, UK	3269 men 60–79 years	All cause-mortality	FFQ (Use in the WHOs Monitoring Trends and Determinants in CVD Survey)	Total olive oil consumption	Lowest (score 1) vs highest (score 4) Compliance with EDI score	11.3 yrs	All-cause mortality: 907	***All-cause mortality:*** 0.68 (0.51–0.91)	Age; energy intake, smoking, alcohol, physical activity, social class, BMI, and a modified version of the HDI/EDI score not containing the individual component of interest.	NA
Chrysohoou C, 2016 [51]	Ikara study of the Blue Zones, Greece	673 ≥65 years	All-cause mortality	MEDIS-FFQ (validated for older adults)	Total olive oil consumption	Daily use vs no regular use	4 yrs	All cause-mortality: 53	**All cause-mortality:** No regular use: 1.00 Ref. Daily use: 0.92 (0.95–0.98)	Age at entry, sex, BMI, history of diabetes, hypertension, hypercholesterolemia, pulse pressure, heart rate, physical activity, smoking status, urea, history of CVD.	NA
Letois F, 2016 [52]	Three-City study, France	8937 Mean age: 74.2 years	All-cause mortality	FFQ and 24 h dietary recall in on center (Bordeux)	Olive oil use	No olive oil use Moderate olive oil use Intensive olive oil use	8.85 yrs	All-cause mortality: 2016	***All-cause mortality:*** No use: 1.00 Ref Moderate use: 0.97 (0.83–1.15) Intensive use: 0.90 (0.76–1.06)	Sex, center, education, monthly income, occupation, smoking, alcohol consumption, history of cardiovascular diseases, BMI, depression, diabetes, hypertension, hypercholesterolemia, dependence, self-rated health, self-rated diet quality, number of medications, number of chronic diseases and physical activity.	NA
Stefler D, 2017 [34]	HAPIEE, Czech Republic, Poland and Russian Federation	19,333 45–69 years	All cause-mortality	FFQ (covering 136, 148 and 147 items)	Olive oil usage	Yes/No	7 yrs	All-cause mortality: 1314	***All-cause mortality*** 1.11 (0.92–1.34)	Age, sex, cohort, education, marital status, household amenities score, smoking, physical activity, total energy intake and vitamin supplement intake.	NA
Sadeghi M, 2021 [37]	ICS study, Iran	5432 ≥35 years	All-cause mortality	Persian FFQ	Olive oil	Quartiles of olive oil intake	11.25 yrs	All-cause mortality: 458	***All-cause mortality:*** Q1: 1.00 Ref. Q2: 0.86 (0.63, 1.17) Q3: 0.83 (0.57, 1.20) Q4: 0.81 (0.56, 1.16)	Age, sex, education, residency, smoking status, daily physical activity, family history of cardiovascular disease, diabetes mellitus, hypertension, hypercholesterolemia, aspirin use and post menopause in women, BMI, dietary factor including red meat, fish, fruit and vegetable, hydrogenated vegetable oil, non-hydrogenated oil, olive oil, ghee oil, animal fats, fast food, cereals, legumes, nuts and seeds, animal fats, sweets, soft drink and beverages.	NA

Zhang, 2021 [15]	NIH-AARP Diet and Health Study, USA	521,120 50–71 years	All cause-mortality	FFQ (124 item)	Olive oil intake	Olive oil intake (g/d per 2000 kcal) Non-consumers T1: ≤0.7 g/d T2: 0.8–1.8 g/d T3: ≥1.9 g/d	Average of 16 yrs	All cause-mortality 129,328	**All-cause mortality:** Non-consumers: 1.0 Ref. T1: 0.96 (0.94–0.99) T2: 0.97 (0.95–0.98) T3: 0.96 (0.95–0.98).	Age, sex, race, marital status, education, household income, BMI, alcohol, smoking, vigorous physical activity, usual activity at work, perceived health condition, and history of cancer, heart disease, stroke, and diabetes, Healthy Eating Index-2015, total energy intake, and consumption of remaining oils where appropriate (butter, margarine, lard, corn oil, canola oil, olive oil, and other vegetable oils)	NA
Guasch-Ferre M, 2021 [38]	NHS and HPFUS, USA	NHS 60,582 30–55 years HPFUS 31,801 40–75 years	All-cause mortality	FFQ (130 items)	Total olive oil consumption	Never or less than 1 per month. >0 to ≤4.5 g/d >4.5 to ≤7 g/d >7 g/d	28 yrs	**NHS** All-cause mortality 22,768 **HPFUS** All-cause mortality 14,076	**NHS** **All-cause mortality:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.87 (0.84–0.89) >4.5- ≤7 g/d: 0.86 (0.81–0.91) >7 g/d: 0.79 (0.75–0.82) HR per 5 g/d increment 0.95 (0.94–0.96) **HPFUS** **All-cause mortality:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.92 (0.88–0.95) >4.5- ≤7 g/d: 0.89 (0.83–0.95) >7 g/d: 0.86 (0.81–0.91) HR per 5 g/d increment 0.97 (0.95–0.98) **Pooled** **All cause-mortality:** Never: 1.00 Ref. >0- ≤4.5 g/d: 0.88 (0.86–0.90) >4.5- ≤7 g/d: 0.86 (0.82–0.90) >7 g/d: 0.81 (0.78–0.84) HR per 5 g/d increment 0.96 (0.95–0.97)	Adjusted for age and calendar time, 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, body mass index, intake of red meat, fruits and vegetables, nuts, soda, whole grains, and trans-fat. Pooled dataset was stratified by cohort (sex) and time period.	**All cause-mortality (pooled)** ***For margarine:*** 0.87 (0.85–0.89) ***For butter:*** 0.86 (0.83–0.88) ***For mayonnaise:*** 0.81 (0.78–0.84) ***For dairy fat:*** 0.87 (0.84–0.89)

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Donat-Vargas C, 2021 (c) [39]	ENRICA study, Spain	12.161 18–96 years	All-cause mortality	Dietary history ENRICA (DH-E)	Total olive oil consumption	HR per 10 g in daily intakes of olive oil	10.7 yrs	All-cause mortality 739	**All-cause mortality:** 0.94 (0.87–1.01)	Sex, age, total energy intake, educational level, smoking status, BMI, physical activity, alcohol consumption, fiber intake, number of medications, hypertriglyceridemia, hypercholesterolemia, high blood pressure, number of self-reported chronic conditions, adherence to Mediterranean diet.	NA

Abbreviations: RR, relative risk; CI, confidence interval; 3C study, Three-city: EPICOR, European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts in Italy, EPIC, European Prospective Investigation into Cancer and Nutrition; PREDIMED, PREvención con Dieta MEDiterránea; HAPIEE: Health Alcohol and Psychosocial factors in Eastern Europe; SUN, Seguimiento Universidad de Navarra; NHS, Nurses' Health Study; HPFUS: Health Professionals' Follow-up Study; ICS, Isfahan Cohort Study; NIH-AARP, National Institutes of Health–American Association of Retired Persons; ENRICA, Estudio de Nutrición y Riesgo Cardiovascular; E3N; Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education National; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; FFQ, food frequency questionnaire; CVD, cardiovascular disease; AF, atrial fibrillation; IHD, ischemic heart disease; CHD, coronary heart disease; T2D, type 2 diabetes; BMI, body mass index; HDI, Healthy Diet Indicator; rMED, relative Mediterranean diet; EDI, Elderly Dietary Index; WHO, World Health Organization; SD, standard deviation; HDL, high density lipoprotein; n3-PUFA, omega-3 polyunsaturated fatty acids; MEDIS-FFQ, MEDiterranean Islands frequency food questionnaire.
Buckland G, 2012: Cancer mortality = a, CHD = b, breast cancer = c; Donat-Vargas C, 2021: SUN Study = a, EPIC study = b, ENRICA Study = c.
[a] Several of the 36 studies included in the systematic review were not included in the quantitative meta-analysis. Five studies were excluded from the quantitative meta-analysis on CVD for the following reasons: results were reported more than once [29,31,32,38] or they did not include any of the assessed outcomes [35]. Two from the meta-analysis on cancer: the studies on skin cancer were also excluded because of its benign prognosis [45], as well as the study on lung cancer as it did not include initially healthy participants (it only included heavy smokers) [44]. In the meta-analysis on overall mortality, three studies were excluded for these reasons: reported more than once (Guasch-Ferre, 2014, which was conducted with the same subjects as the RCT by Estruch-PREDIMED, 2018, but following an observational design), olive oil as a part of a salad pattern and it was not quantified [49], all participants were patients with myocardial infarction [50].

and fatal cases); 680,239 participants with 13,389 incident cases of T2D, and 733,420 participants with 174,081 deaths. The study durations ranged from 3.7 to 28 years for prospective studies, and between 4.1 and 4.8 years for RCTs, while the age of participants ranged from 18 to 96 years. Most studies were conducted in European countries, but also four studies were conducted in USA [14,15,38,47] and one study in Iran [32]. Also, all studies adjusted their estimates for potential confounders. Twenty-four prospective cohort studies and three reports from the PREDIMED trial [8,11,12] were included in the quantitative meta-analysis. Moreover, according to the NOS tool applied for prospective cohort studies, most observational cohort studies showed high quality (Table 3). Regarding RCT, the RoB 2 score indicated low risk of bias for all studies (Table 4). Olive oil consumption was assessed in g/d in most studies, using validated food frequency questionnaires as the most frequent dietary assessment tool (Tables 1 and 2).

3.2.1. Main outcomes

3.2.1.1. Association between olive oil consumption and the risk of CVD. A total of twenty estimates from thirteen eligible studies were included in the meta-analysis of olive oil consumption and the risk of CVD: twelve cohort studies and one RCT (PREDIMED study). The pooled results using the random effects model showed a 16% reduced relative risk of CVD (RR: 0.84; 95% CI: 0.76 to 0.94 for every additional 25 g/d of olive oil consumption). There was evidence of substantial heterogeneity ($I^2 = 67.9\%$, $P < 0.001$), but it was only moderate within subgroups (Fig. 2). The funnel plot (Supplementary Fig. S1) might suggest some degree of publication bias because there is some asymmetry, especially in the lower right section of the plot, however the Egger test did not reach statistical significance for combined CVD events ($p = 0.159$). When excluding from the meta-analysis the RCT, a 14% reduced relative risk of CVD (RR: 0.86; 95% CI: 0.77 to 0.95 for every additional 25 g/d of olive oil consumption) was observed.

3.2.1.2. Association between olive oil consumption and the risk of cancer. Nine reports of cohort studies and one RCT were included in the meta-analysis assessing cancer as end-point. The random-effects pooled estimate showed no significant association between olive oil consumption and the composite outcome of cancer incidence or mortality (RR = 0.94; 95% CI: 0.86 to 1.03 for every additional consumption of 25 g/d), with significant heterogeneity ($I^2 = 55.8\%$) (Fig. 3). No evidence of publication bias was found with the Egger's test ($p = 0.148$) or funnel plot (Supplemental Fig. S2). When excluding data from the RCT, the results were similar (RR = 0.96; 95% CI: 0.89 to 1.03 for every additional consumption of 25 g/d).

3.2.1.3. Association between olive oil consumption and the risk of T2D. Four studies were included in the meta-analysis. The random-effects model showed that an increment of 25 g/d in olive oil consumption was associated with a significant 22% relative reduction in the risk of T2D (RR: 0.78; 95% CI: 0.69 to 0.87) with no evidence of heterogeneity, $I^2 = 0.0\%$ ($P = 0.506$) (Fig. 4). Furthermore, no evidence of publication bias was found as suggested by the Egger test ($p = 0.897$). When excluding data from the PREDIMED trial, the pooled RR was 0.81; 95% CI: 0.71 to 0.91 for every additional consumption of 25 g/d.

3.2.1.4. Association between olive oil consumption and the risk of all-cause mortality. The meta-analysis included ten cohort studies and one RCT. The summary estimates revealed that for each 25 g/d of olive oil consumption the overall relative risk of all-cause mortality was reduced by 11% (RR: 0.89; 95% CI: 0.85 to 0.93). However, heterogeneity was substantial; ($I^2 = 65.2\%$, $P = 0.001$) (Fig. 5). The

Table 2
General study characteristics of the randomized controlled trials investigating the effects of olive oil consumption on cardiovascular disease, cancer, type 2 diabetes and all-cause mortality.

Author, Publication year	Study, Country/region	Study population and baseline age	Outcomes	Dietary assessment	Exposures	Intake categories	Follow-up period	Events	RR (95% CI)	Covariables in the fully adjusted model	RR 95% CI replacing one type oil by other type
Cardiovascular disease											
[a]Martínez-González MA, 2014 [9]	PREDIMED Study, Spain	6705	Atrial fibrillation	FFQ (137 items)	MedDiet + EVOO = Mediterranean diet supplemented with extra-virgin olive oil	MedDiet + EVOO (MedDiet + nuts)	4.7 yrs	Atrial Fibrillation MedDiet + EVOO: 72	***Atrial fibrillation*** Control diet: 1.00 Ref	Age, sex, smoking, educational level, baseline height, BMI, waist to height ratio, diabetes mellitus, hypertension, low-density lipoprotein cholesterol, baseline systolic blood pressure, diastolic blood pressure, antihypertensive treatment, statin use, baseline adherence to MedDiet, pre-existing arrhythmias stratified by centre.	NA
		55–80 years			Control diet = low-fat diet (reduced all types of fat)	Control diet		Control diet: 89	MedDiet + EVOO: 0.62 (0.44–0.85)		
Estruch PREDIMED group, 2018 [8]	PREDIMED Study, main results, Spain	7447	Myocardial infarction and stroke	FFQ (137 items)	MedDiet + EVOO = Mediterranean diet supplemented with extra-virgin olive oil	MedDiet + EVOO	4.8 yrs	Primary endpoint (myocardial infarction, stroke, and death) MedDiet + EVOO: 96 Control diet: 109 Stroke event	***Primary endpoint:*** Control diet: 1.00 Ref MedDiet + EVOO: 0.69 (0.53–0.91) ***Stroke event*** Control diet: 1.00 Ref	Age, smoking status, family history of premature coronary heart disease, BM, waist-to-height ratio, physical activity, hypertension at baseline, dyslipidemia at baseline, diabetes at baseline, and propensity scores to estimate the probability assignment to each of the intervention groups, stratified according to sex, recruiting site, and educational level.	NA
						MedDiet + nuts		MedDiet + EVOO:49	MedDiet + EVOO: 0.65 (0.44–0.95)		
		55–80 years			Control diet = low-fat diet (reduced all types of fat)			Control diet: 58 Myocardial infarction event MedDiet + EVOO:37	***Myocardial infarction event*** Control diet: 1.00 Ref MedDiet + EVOO: 0.82 (0.52–1.30)		
						Control diet		Control diet: 38 CVD mortality MedDiet + EVOO:26 Control: 30	***CVD mortality*** Control diet: 1.00 Ref MedDiet + EVOO: 0.62 (0.36–1.06)		
[a]Papadaki A, 2019 [53]	PREDIMED Study, Spain	7403	Heart failure	FFQ (137 items)	MedDiet + EVOO = Mediterranean diet supplemented with extra-virgin olive oil	MedDiet + EVOO	4.8 yrs	Heart failure event MedDiet + EVOO: 29	***Heart failure event:*** Control diet: 1.00 Ref	Adjusted for age, smoking, waist-to-height ratio, physical activity, dyspnea symptoms at baseline, non-atrial fibrillation arrhythmias at baseline, history of diabetes, history of hypertension, history of dyslipidemia, family history of premature coronary heart disease and baseline prevalence of atrial fibrillation, baseline energy intake, stratified according to centre, sex and education.	NA
		55–80 years			Control diet = low-fat diet (reduced all types of fat)	Control diet		Control diet: 32	MedDiet + EVOO: 0.73 (0.43–1.24)		
Cancer											
Toledo E, 2015 [12]	PREDIMED Study, Spain (d)	4152	Breast cancer	FFQ (137 items)	MedDiet + EVOO = Mediterranean diet supplemented with extra-virgin olive oil	MedDiet + EVOO	4.8 yrs	Breast cancer: MedDiet + EVOO: 8	***Breast cancer:*** Control diet: 1.00 Ref	Age, BMI, waist-to-height ratio, use of hormone therapy, leisure-time physical activity, total energy intake, alcohol consumption, age at menopause, baseline adherence to the MedDiet stratified by center and educational level	NA
		55–80 years			Control diet = low-fat diet (reduced all types of fat)	Control diet		Control diet: 17	MedDiet + EVOO: 0.31 (0.13–0.77)		

(*continued on next page*)

Table 2 (*continued*)

Type 2 diabetes										
[a]Salas-Salvadó J, 2011 [54]	PREDIMED-Reus, Spain	418 55–80 years	T2D	FFQ (137 items)	MedDiet + EVOO = Mediterranean diet supplemented with extra-virgin olive oil Control diet = low-fat diet (reduced all types of fat)	MedDiet + EVOO Control diet	4 yrs	MedDiet + EVOO: 14 Control diet: 24	**Incident T2D:** Control diet: 1.00 Ref. MedDiet + EVOO: 0.49 (0.25–0.97)	Sex, age, baseline energy intake, BMI, waist circumference, physical activity, smoking status, fasting serum glucose, use of lipid lowering drugs, Mediterranean diet score, and weight changes during the study	NA
Salas-Salvadó J, 2014 [11]	PREDIMED, Spain (e)	3541 55–80 years	T2D	FFQ (137 items)	MedDiet + EVOO = Mediterranean diet supplemented with extra-virgin olive oil Control diet = low-fat diet (reduced all types of fat)	MedDiet + EVOO MedDiet + nuts Control diet	4.1 yrs	MedDiet + EVOO: 80 Control diet: 101	**Incident T2D:** Control diet: 1.00 Ref. MedDiet + EVOO: 0.60 (0.43–0.85)	Sex, age, BMI, smoking status, fasting glucose level, prevalence of dyslipidemia, and hypertension, total energy intake, adherence to Med Diet, physical activity, educational level, alcohol intake. Stratified by recruitment center.	NA
All cause-mortality										
Estruch PREDIMED group [8],	PREDIMED Study, main results, Spain (b)	7447 55–80 years	All-cause mortality	FFQ (137 items)	MedDiet + EVOO = Mediterranean diet supplemented with extra-virgin olive oil Control diet = low-fat diet (reduced all types of fat)	MedDiet + EVOO Control diet	4.8 yrs	MedDiet + EVOO: 118 Control: 114	***All-cause mortality:*** Control diet: 1.00 Ref MedDiet + EVOO: 0.90 (0.69–1.18)	Age, smoking status, family history of premature coronary heart disease, BMI, waist-to-height ratio, physical activity, hypertension at baseline, dyslipidemia at baseline, diabetes at baseline, and propensity scores to estimate the probability assignment to each of the intervention groups, stratified according to sex, recruiting site, and educational level.	NA

Abbreviations: PREDIMED, PREvención con DIeta MEDiterránea; FFQ, food frequency questionnaire; AF, atrial fibrillation; CVD, cardiovascular disease; BMI, body mass index; MedDiet, Mediterranean diet; EVOO, extra-virgin olive oil; T2DM, type 2 diabetes mellitus.

[a] These studies were excluded from the meta-analyses because they were part of the PREDIMED TRIAL. Also, in the Diabetes meta-analysis, the PREDIMED Reus results [54] were excluded because results of the PREDIMED trial [11] included those participants.

Table 3
Risk of bias scores of cohort studies for the association of olive oil with the risk of cardiovascular disease, cancer, type 2 diabetes mellitus or all-cause mortality, according to the Newcastle–Ottawa Scale.

Author, Publication year	Study	Outcome	Selection (maximum = 4)	Comparability (maximum = 2)	Outcome (maximum = 3)	Total score (maximum = 9)
Samieri C, 2011 [26]	3C study, France	Stroke	4	1	3	8
Bendinelli B, 2011 [27]	EPICOR Study, Italy	CHD	3	2	3	8
Misirli G, 2012 [28]	EPIC Study, Greece	Stroke and mortality	3	2	3	8
Buckland G, 2012 (a) [29]	EPIC study, Spain	CVD mortality All-cause mortality Cancer mortality	3	2	3	8
Dilis V, 2012 [30]	EPIC study, Greece	CHD event and mortality	3	1	3	7
Buckland G, 2012 (b) [31]	EPIC study, Spain	CHD	3	2	3	8
Guasch-Ferre M, 2014 [32]	PREDIMED observational study, Spain	CVD event and mortality All-cause mortality Cancer mortality	4	2	3	9
Atkins JL, 2014 [33]	British Regional Heart Study, United Kingdom	CVD event and mortality CHD All-cause mortality	3	2	3	8
Stefler D, 2017 [34]	HAPIEE, Czech Republic, Poland and Russian Federation	CVD CHD Stroke All-cause mortality	3	1	3	7
Bazal P, 2019 [35]	SUN Cohort, Spain	Atrial fibrillation	2	2	3	7
Kouli G-M, 2019 [36]	ATTICA Study, Greece	CVD	4	1	3	8
Guasch- Ferre M, 2020 [14]	NHS and HPFUS, USA	CVD CHD Stroke	2	2	3	7
Sadeghi M, 2021 [37]	ICS study, Iran	CVD Stroke Myocardial infarction Ischemic heart disease All-cause mortality	4	1	3	8
Zhang, 2021 [15]	NIH-AARP Diet and Health Study, USA	CVD mortality Heart disease Stroke All cause-mortality Cancer mortality Diabetes mortality	3	2	3	8
Donat-Vargas C, 2021 (a, b) [16]	EPIC, SUN, Spain	CVD	2	2	3	7
Guasch-Ferre M, 2021 [38]	NHS and HPFUS, USA	CVD mortality All-cause mortality Cancer mortality	2	2	3	7
Donat-Vargas C, 2021 (c) [39]	ENRICA study, Spain	CVD mortality Cancer mortality All-cause mortality	4	2	3	9
Trichopoulou, 2010 [40]	EPIC Study, Greece	Breast cancer	3	2	3	8
Buckland G, 2010 [41]	EPIC Study, United Kingdom, France, Denmark, Sweden, Germany, Italy, Spain, the Netherlands, Norway, and Greece.	Gastric adenocarcinoma	2	2	3	7
Buckland G, 2012 (c) [42]	EPIC study, Spain, Greece and Italy	Breast cancer	3	2	3	8
Agnoli C, 2013 [43]	EPIC Study, Italy	Colorectal cancer	2	2	3	7
Gnagnarella P, 2013 [44]	COSMOS Study, Italy	Lung cancer	1	1	2	4
Mahamat-Saleh Y, 2019 [45]	E3N study, France	Skin cancer	2	2	3	7
Marí-Sanchis A, 2011 [46]	SUN study, Spain	T2D	2	2	3	7
Guasch- Ferre M, 2015 [47]	NHS I– II, USA	T2D	2	2	3	7
Trichopoulou, 2003 (48)	EPIC Study, Greece	All cause-mortality	3	2	3	8
Masala, 2007 (49)	EPIC study, Italy	All cause-mortality	2	2	3	7
Barzi F, 2013 [50]	GISSI-Prevenzione study, Italy	All cause-mortality	3	2	3	8
Chrysohoou C, 2016 [51]	Ikara Blue Zones, Greece	All cause-mortality	4	2	3	9
Letois F, 2016 [52]	Three-City study, France	All cause-mortality	4	2	3	9

Abbreviations: 3C study, Three-city study; EPICOR, European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts in Italy, EPIC, European Prospective Investigation into Cancer and Nutrition; PREDIMED, PREvención con DIeta MEDiterránea; HAPIEE, Health Alcohol and Psychosocial factors in Eastern Europe; COSMOS; Continuous Observation of Smoking Subjects; SUN, Seguimiento Universidad de Navarra; NHS: Nurses' Health Study; HPFUS: Health Professionals Follow-up Study; ICS, Isfahan Cohort Study; NIH-AARP, National Institutes of Health–American Association of Retired Persons; ENRICA, Estudio de Nutrición y Riesgo Cardiovascular; COSMOS, Continuous Observation of Smoking Subjects; E3N; Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education National; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; CHD, coronary heart disease; CVD, cardiovascular disease; T2D, type 2 diabetes.
Buckland (a) and (b): EPIC, Spain, (c), EPIC (10 countries); Donat-Vargas (a): SUN study, (b): EPIC, Spain, (c): ENRICA Study.

Table 4
Quality assessment scores of RCT assessing the effect of olive oil on cardiovascular disease, cancer, type 2 diabetes mellitus or all-cause mortality, according to Cochrane Risk of Bias tool (RoB 2).

Author, Publication year	Study	Outcome	Randomization process	Deviations from the intended	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Martínez-González MA, 2014 [9]	PREDIMED study, Spain	Atrial fibrillation	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Estruch (PREDIMED), 2018 [8]	PREDIMED study, Spain (main results)	Stroke Myocardial infarction CVD mortality All cause-mortality	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Papadaki A, 2019 [53]	PREDIMED study, Spain	Heart failure event	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Toledo E, 2015 [12]	PREDIMED study, Spain	Breast cancer	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Salas-Salvadó J, 2011 [54]	PREDIMED-Reus, Spain	T2D	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Salas-Salvadó J, 2014 [11]	PREDIMED study, Spain	T2D	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Abbreviations: RCT, randomized control trial; PREDIMED, PREvención con Dieta MEDiterránea; CVD, cardiovascular disease; T2D, type 2 diabetes.
*As nutritional intervention studies with a dietary pattern cannot be double-blind (the participant will always know what he or she is eating), the blinding was only applied to the ascertainment of the outcome.

exclusion of the PREDIMED trial did not change this estimate. There was no evidence of publication bias (p = 0.277 in the Egger's test) (Supplemental Fig. S3).

3.2.1.5. Heterogeneity, subgroup and sensitivity analyses of main outcomes. For all outcomes included in the meta-analysis with the exception of T2D, there was obvious heterogeneity (I^2 >50%). Therefore, subgroup analyses considering study location, number of participants, years of follow-up and other characteristics were conducted to try to identify potential sources of heterogeneity. In most cases, heterogeneity remained within subgroups when stratified analyses were conducted (Supplemental Tables S4–S7). However, the results of the meta-regression analyses suggested that between-group differences were not statistically significant. The subgroup analysis for the risk of CVD showed moderate to high degree of heterogeneity (Supplemental Table S4). However, within the group of studies with shorter follow-up (<10 years, five estimates) lower heterogeneity (I^2 = 44.6%; P = 0.125) and a stronger inverse association were observed. This finding could be related to the difficulties of capturing changes in diet during longer follow-up periods, because with a single exception [13] all other studies with longer follow-up (a total of 10 estimates) assessed olive oil consumption only at baseline, leaving room for measurement error and potential misclassification of olive oil intake, due to changes in consumption during follow-up. Interestingly, the point estimate (RR = 0.73) from the single study with long follow-up and repeated measurements of diet [14] was almost identical to the pooled point estimate for the 5 studies with shorter follow-up (RR = 0.72). The association of olive oil consumption with cancer (incidence or mortality) was not significant within any of the subgroups. Heterogeneity remained within several subgroups, including studies conducted in non-Mediterranean countries (I^2 = 89.6%; P = 0.002) and those which had less than 10,000 participants (I^2 = 77.9%; P = 0.033), but it was only marginally significant within the subgroup of studies with shorter follow-up (I^2 = 56.6%; P = 0.056) (Supplemental Table S5). For T2D, the stratified analysis revealed no heterogeneity within any subgroup (Supplemental Table S6).

With respect to studies assessing the association of olive oil consumption with all-cause mortality, higher heterogeneity was found in studies conducted in non-Mediterranean countries (I^2 = 81.2%; P < 0.001) than in Mediterranean countries. Heterogeneity was also greater among studies including more than 10,000 participants (I^2 = 75.6%; P = 0.001), those with longer follow up (I^2 = 72.4%; P = 0.003), and within the subgroup of studies that reported <12 g/d of mean/median intake of olive oil (I^2 = 92.0%; P < 0.001) (Supplemental Table S7).

In a sensitivity analyses omitting one study at a time, the random-effects models showed that summary RRs for all outcomes remained stable (Supplemental Tables S8–S11), suggesting that the results were not influenced by any single study.

4. Discussion

In this outcome-wide systematic review and meta-analysis of the association between olive oil and hard clinical events of chronic disease, we found evidence for a protective association against CVD, T2D, and all-cause mortality, but not for cancer. In line with our results, a previous meta-analysis reported that olive oil intake was associated with reduced risk of all-cause mortality and combined CVD events when comparing the highest versus the lowest tertile [55]. That study included five original studies for all-cause mortality and seven studies for combined CVD events [55]. Our meta-analysis found similar results after including new original studies (in total, eleven studies for all-cause mortality and thirteen for CVD

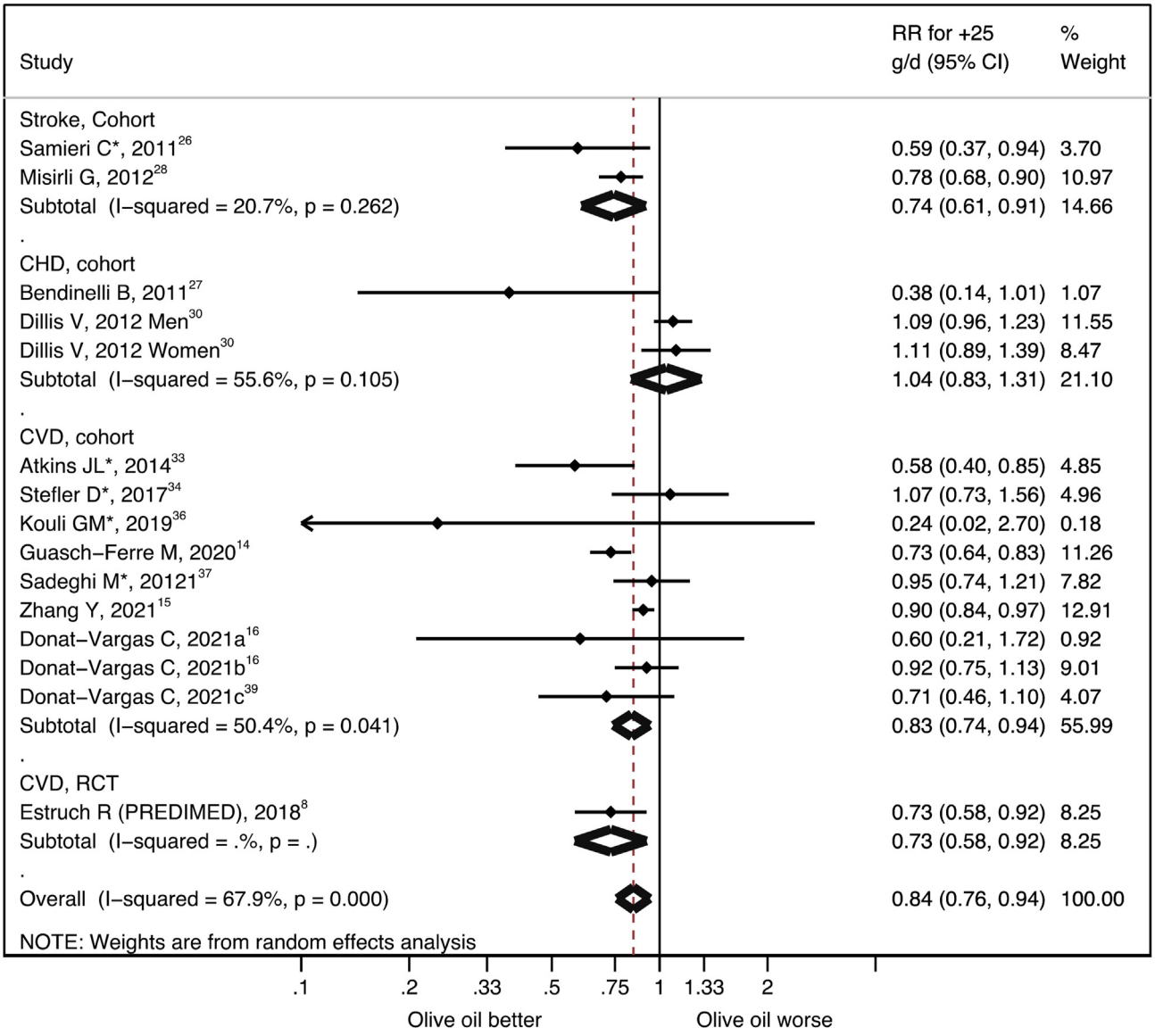

Fig. 2. RR and 95% CI of fatal and non-fatal cardiovascular disease associated with 25 g/d increase in olive oil consumption. Abbreviations: RR, relative risk; CI, confidence interval; CHD: coronary heart disease; CVD: cardiovascular disease; RCT: randomized controlled trial; PREDIMED: Prevención con Dieta Mediterránea. Donat-Vargas C, 2021: SUN Study = a, EPIC study = b; Donat-Vargas C, 2021: ENRICA Study = c. *These 5 studies did not quantify the consumption of olive oil in g/d and we assumed 25 g/d as the difference between assessed extreme categories. When these 4 studies were removed, the RR for the subgroup of cohort studies assessing CVD was 0.83 (0.73–0.94) and the overall RR did not change.

events). On the other hand, our results were consistent with those of the main RCT for CVD [8] and T2D [11]. For all-cause mortality, the inverse association reported by the RCT after 4.8 years median follow-up did not reach statistical significance, probably because longer follow-up may be needed to assess the impact of extra-virgin olive oil on total mortality. However, the reported multivariable-adjusted hazard ratio for all-cause death (HR = 0.90) in the original report of PREDIMED [8] was close to our current pooled estimate (HR = 0.89). The wider confidence intervals in PREDIMED were expected given the number of observed fatalities (n = 232) and the total sample within each comparison group (n = 2543 in the extra-virgin olive oil group and n = 2450 in the control group).

No association between olive oil consumption and the risk of cancer was found. Previous meta-analyses reported inconsistent results for cancer [56–58]. The most recent systematic review and meta-analysis that evaluated the association of olive oil and all forms of cancer reported that a higher intake of olive oil was associated with a reduced risk (RR = 0.69, 95%CI: 0.62, 0.77). Nonetheless, these pooled results should be interpreted carefully, considering that they incorporated different cancer types with heterogenous prognosis and also included a large number of case–control studies, which are prone to issues of recall bias or selection bias [59].

Our funnel plots results raised the issue of a potential need for delving deeper into a possible publication bias for studies on olive oil and CVD, given the suggestive funnel plot. Notwithstanding, the Egger test was not statistically significant, thus supporting our overall results on the effect of dietary olive oil consumption and the risk of major chronic disease.

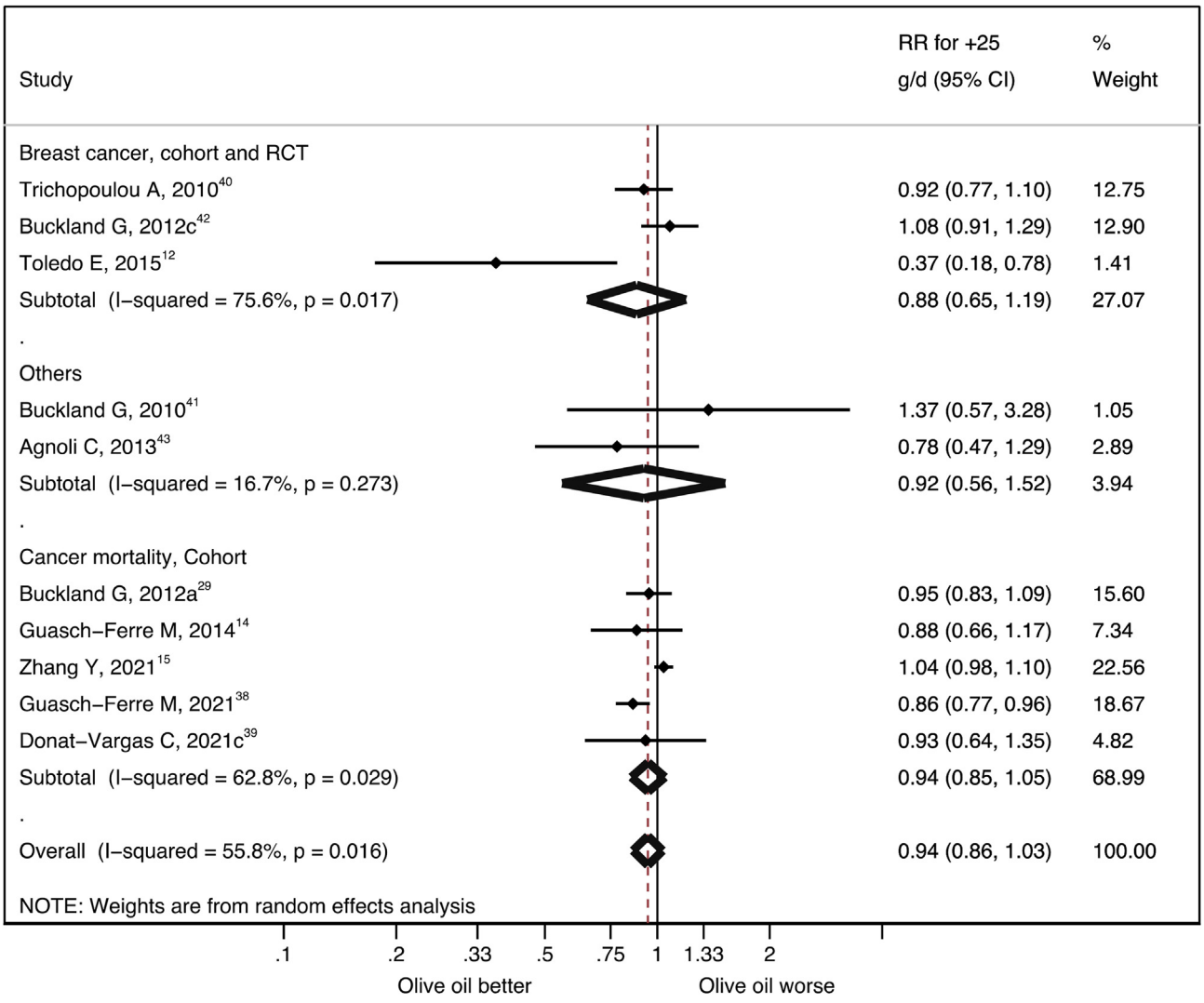

Fig. 3. RR and 95% CI of cancer (incidence or mortality) associated with 25 g/d increase in olive oil consumption. Abbreviations: RR, relative risk; CI, confidence interval; RCT: randomized controlled trial. Buckland G, 2012: Cancer mortality = a; breast cancer = c. Donat-Vargas C, 2021: ENRICA Study = c.

A recent report from three Spanish cohorts, where customarily there is a high consumption of olive oil and, consequently, a wide variability in intake, consistently showed a protection against CVD [16]; and, according to that report, the highest benefit could be potentially obtained with consumptions between 20 and 30 g/day, as observed in the largest of these 3 cohorts, the EPIC-Spain study.

In the largest cohorts, which included both fatal and non-fatal cases of CVD and used repeated measurements of diet during a long follow-up period (up to 24 years), a relative reduction of 14% (95% CI: 6%–21%) in CVD risk was found for a consumption of only >0.5 tablespoon/day or >7 g/day as compared to no consumption [14]. This reduction would be translated into a relative risk of 0.73 for a difference in intake of 25 g/d. However, the assumption of a linear dose–response trend was not consistent with the results of the EPIC-Spain study. In the SUN study, only after including probable cases of CVD, the inverse linear trend did become apparent [16]. Interestingly, in the studies conducted by Guasch-Ferre et al. in large American cohorts, substitution of saturated fats or margarines for olive oil was associated with significant benefits [14,38,47].

A considerable advantage of our review is that a large RCT (PREDIMED) using hard end-points, previously reported favorable effects of olive oil against CVD [5,8] and against T2D [11]. Moreover, a previous systematic review and meta-analysis performed by Schwingshackl et al. reported that high olive oil intake was inversely associated with lower risk of T2D (RR = 0.84, 95% CI: 0.77,0.92) [60], which is consistent with our present meta-analysis of observational studies.

All studies included in previous meta-analyses [13,55–60] are shown in Supplementary Table S12. Those studies which were reviewed applying our selection criteria, but were ultimately not included in our analysis for various reasons (case–control, other exposures different than olive oil, results from a same study, oral communication, and studies which included non-healthy participants at baseline).

All these results taken together provide scientific support to the hypothesis that regular olive oil consumption is associated with a clinically meaningful reduction in the risk of CVD, T2D and all-cause death, without any observed harmful effects at higher intakes.

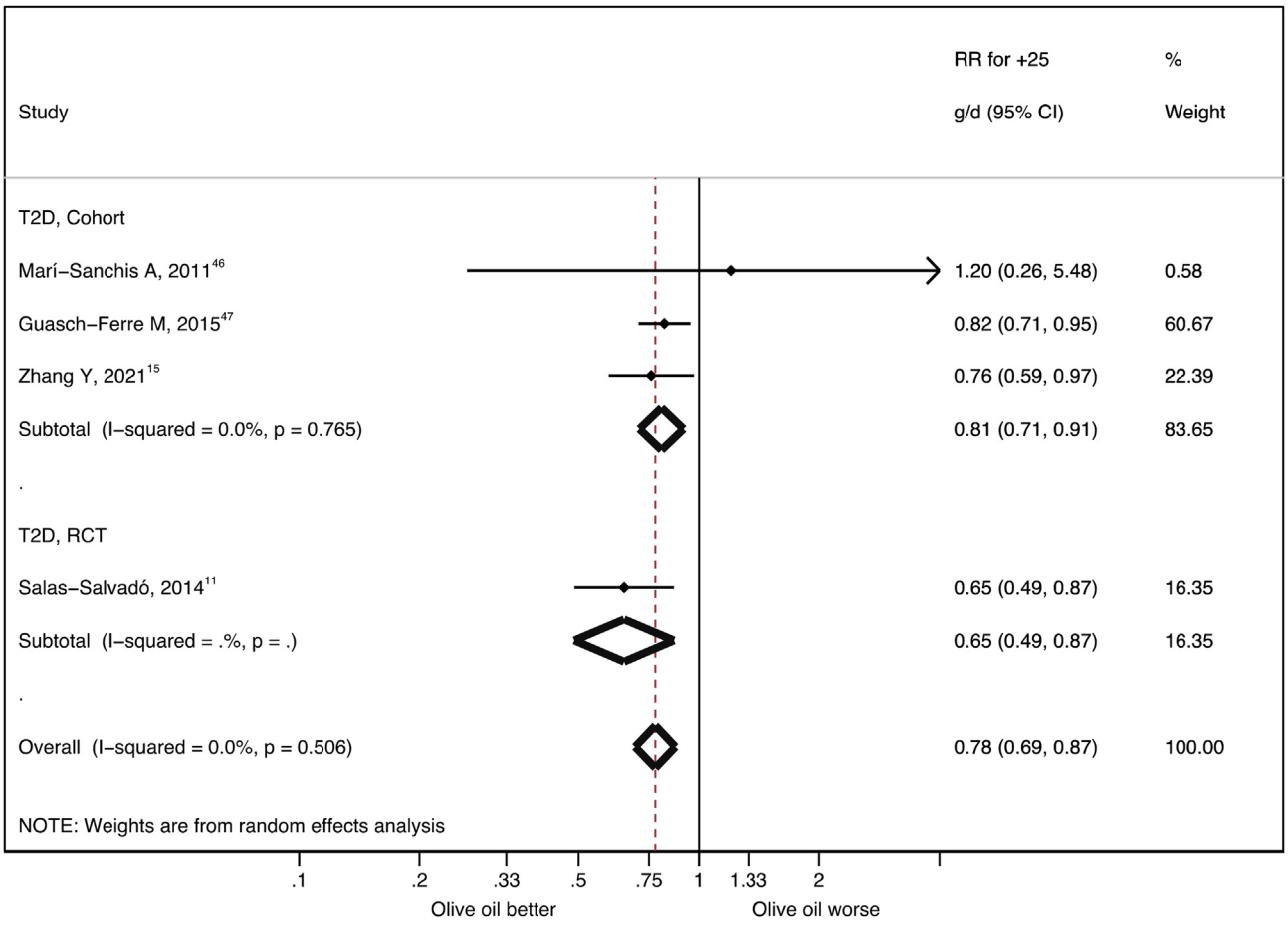

Fig. 4. RR and 95% CI of type 2 diabetes associated with 25 g/d increase in olive oil consumption. Abbreviations: RR, relative risk; CI, confidence interval; T2D, type 2 diabetes mellitus; RCT: randomized controlled trial.

Notwithstanding, as much of the available evidence is observational, the possibility of residual confounding cannot be definitively excluded.

In any case, there are enough studies with appropriate temporal sequence, sufficient experimental evidence, consistency, strength of the association and a high biological plausibility. In addition, many small mechanistic trials supporting beneficial effects of olive oil on blood lipids (and their functionality), inflammatory pathways and oxidative stress [55,61–66], several case–control studies on olive oil and CVD not included in our systematic review and meta-analysis, also reported beneficial results [67,68]. Additionally, some of the observed benefits of the PREDIMED randomized trial were only seen in the group which specifically received a substantial provision of olive oil. This was the case for T2D [11], breast cancer [12] and atrial fibrillation [9], but not in the group which also received intensive intervention for behavior modification to foster the same adherence to the MedDiet but did not receive olive oil (i.e., the group randomized to MedDiet + nuts). Given the importance of randomization for causal inference, the results of the PREDIMED trial in the context of the present meta-analysis reinforce the case for supporting a truly causal association.

The results that we report here for primary prevention are also in agreement with the results reported in May 2022 by the Spanish CORDIOPREV trial for secondary cardiovascular prevention. CORDIOPREV was a large RCT that compared the effects of Mediterranean diet (with free provision of EVOO) versus low-fat diet in secondary prevention of CVD and reported an adjusted HR = 0.72 (0.51–0.96) for the primary end-point (a composite outcome of mayor CV events, including myocardial infarction, revascularization, ischemic stroke, peripheral artery disease and CV death) [69].

In addition, an important case-cohort study not included in our systematic review and meta-analysis reported a protection by the MedDiet against T2D; interestingly, moderate alcohol intake, low meat, and high olive oil were the dietary components that accounted for most of the observed benefits of the MedDiet in that case-cohort study [70]. Considering these results and that olive oil is the hallmark of the MedDiet, the available epidemiological evidence consistently reflects the innate benefits of the MedDiet against CVD [6] and T2D [60], Of note, many of the original studies were conducted in Mediterranean countries where olive oil consumption is both highly correlated with adherence to the MedDiet, but olive oil also represented a sizable proportion of total energy intake, further supporting the relationship.

A potential limitation of our meta-analysis is that we were not able to differentiate between the common (and less expensive) variety of olive oil, which is rich in monounsaturated fatty acids but not in bioactive polyphenols, and the extra-virgin variety (extra-virgin/virgin olive oil or EVOO/VOO) which is the juice of the ripe fruit of the olive tree obtained only by cold pressing. The

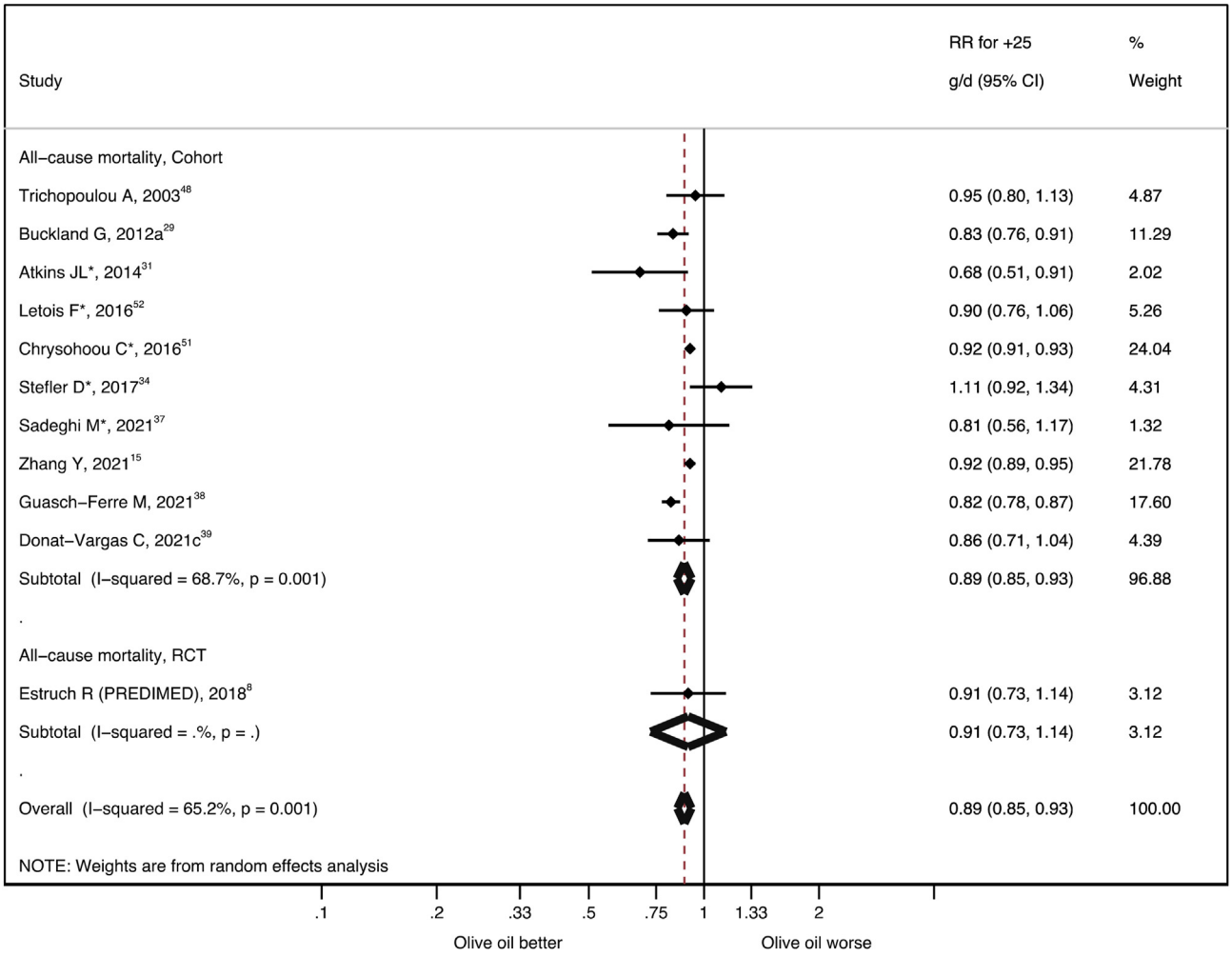

Fig. 5. RR and 95% CI of all cause-mortality associated with 25 g/d increase in olive oil consumption. Abbreviations: RR, relative risk; CI, confidence interval; RCT: randomized controlled trial. Buckland G, 2012: Cancer mortality = a. Donat-Vargas C, 2021: ENRICA Study = c. *These 5 studies did not quantify the consumption of olive oil in g/d and we assumed 25 g/d as the difference between extreme categories. When these 5 studies were removed, the RR for the subgroup of cohort studies assessing all-cause mortality was 0.87 (0.81–0.93) and the overall RR was 0.87 (0.82–0.93).

result of this process is that EVOO and VOO are very rich in phenolic components with substantial evidence of protection against inflammatory and oxidative mechanisms [6,61–64,66]. Both of these mechanisms have been involved in the pathophysiology of CVD and T2D. The inability to differentiate between types of olive oil in many cohort studies and the relative consumption of each variety of olive oil in the assessed studies might be a potential explanation for the observed heterogeneity in some pooled estimates and may also have contributed to the lack of significance for the association between olive oil and cancer risk. In fact, a recent case–control study reported that the virgin variety of olive oil was a key characteristic to afford protection against breast cancer [71]. Another limitation of this study was that when studying the risk of T2D we were not able to assess publication bias using funnel plots, and meta-regression analysis due to the small number of studies included.

A potential source of heterogeneity could be related to the degree of measurement error in the different dietary assessment tools, with diverse degrees of validity across studies. Indirectly, we were able to suggest this possibility by the reduction in heterogeneity observed when studies with follow-up duration shorter than 10 years or which used repeated dietary measurement were separately assessed. Seldom of the included studies provided assessments of the effects of iso-calorically substituting other fats or oils for olive oil. The laudable exceptions are the studies conducted by Guasch-Ferré et al. Future studies should assess these effects.

Our outcome-wide approach represents a strength of this systematic review and meta-analysis because it provides a comprehensive picture of the overall health effects of olive oil. This approach is especially important for exposures, such as olive oil, that may benefit some end-points but are sometimes thought to be harmful for others. Outcome-wide systematic reviews and meta-analysis can also be helpful in prioritizing public health recommendations [17]. The prospective design, high quality, large sample size and ability to control for a wide array of potential confounders in the individual studies included in our meta-analysis are additional praiseworthy methodological strengths of the available evidence and reinforce our pooled estimates from cohort studies and randomized trials.

In conclusion, despite some degree of heterogeneity and the inherent limitations of observational studies, we found that regular consumption of olive oil –as the main added fat in the context of a healthy diet– was inversely associated with all-cause mortality, type 2 diabetes and cardiovascular disease. These observed reductions were clinically meaningful. No association with cancer was identified. However, there was scarce prospective investigation

on olive oil consumption and cancer risk. Future studies should explore these associations in further depth and try to identify major sources of heterogeneity.

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Author disclosures

Authors report no conflicts of interest.

Authors contribution

M.A.M.-G, M.B.-R, C.S.-O, V.B.-V: study concept and design; C.S.-O., V.B.-V: data collection; M.A.M.-G, C.S.-O, V.B.-V, M.B.-R: statistical analysis; M.A.M.-G; M.B.-R, C.S.-O, V.B.-V, F.R.-A, M.G.-S, M.J.Y.-B: interpretation of data: M.A.M.-G, C.S.-O, V.B.-V, M.B.-R, F.R.-A, M.G.-S, M.J.Y.-B: drafting of the manuscript. All authors: have critically revised and approved the final version.

Data availability

Data described in the manuscript will be made available upon request, pending application and approval.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.10.001.

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