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SYSTEMATIC REVIEWS AND META-ANALYSES

Impact of different types of olive oil on cardiovascular risk factors: A systematic review and network meta-analysis

Lukas Schwingshackl [a,*], Marc Krause [a], Christine Schmucker [a], Georg Hoffmann [b], Gerta Rücker [c], Joerg J. Meerpohl [a]

[a] *Institute for Evidence in Medicine, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany*
[b] *Department of Nutritional Sciences, Faculty of Life Sciences, University of Vienna, Austria*
[c] *Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center - University of Freiburg, Freiburg, Germany*

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Abstract *Background and aim:* This network meta-analysis (NMA) compares the effects of different types of olive oil (OO) on cardiovascular risk factors.
Methods and results: Literature search was conducted on three electronic databases (Medline, Web of Science, and Cochrane Central). Inclusion criteria: Randomized controlled trials (RCTs) (≥3 weeks duration of intervention) comparing at least two of the following types of OO: refined OO (ROO), mixed OO (MOO), low phenolic (extra) virgin OO (LP(E)VOO), and high phenolic (extra) virgin OO (HP(E)VOO). Random-effects NMA was performed for seven outcomes; and surface under the cumulative ranking curve (SUCRA) was estimated, using an analytical approach (P-score). Thirteen RCTs (16 reports) with 611 mainly healthy participants (mean age: 26–70 years) were identified. No differences for total cholesterol, HDL-cholesterol, triacylglycerols, and diastolic blood pressure were observed comparing ROO, MOO, LP(E)VOO and HP(E)VOO. HP(E)VOO slightly reduce LDL-cholesterol (LDL-C) compared to LP(E)VOO (mean difference [MD]: −0.14 mmol/L, 95%−CI: −0.28, −0.01). Both, HP(E)VOO and LP(E)VOO reduces SBP compared to ROO (range of MD: −2.99 to −2.87 mmHg), and HP(E)VOO may improve oxidized LDL-cholesterol (oxLDL-C) compared to ROO (standardized MD: −0.68, 95%−CI: −1.31, −0.04). In secondary analyses, EVOO may reduce oxLDL-C compared to ROO, and a dose-response relationship between higher intakes of phenolic compounds from OO and lower SBP and oxLDL-C values was detected. HP(E)VOO was ranked as best treatment for LDL-C (P-score: 0.83), oxLDL-C (0.88), and SBP (0.75).
Conclusions: HP(E)VOO may improve some cardiovascular risk factors, however, public health implications are limited by overall low or moderate certainty of evidence.

* Corresponding author. Breisacher Straße 153, 79110, Freiburg, Germany.
E-mail address: schwingshackl@ifem.uni-freiburg.de (L. Schwingshackl).

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Background

Cardiovascular disease (CVD) is the leading cause of mortality, and accounted for 21% of deaths worldwide in 2017 [1]. High blood pressure and dyslipidemia are among the most important modifiable risk factors for the development of CVD [2]. The Seven Countries Study observed half a century ago a lower mortality from CVD in countries around the Mediterranean sea [3]. This observation was attributed to the traditional Mediterranean diet, which is characterized by the high consumption of extra virgin olive oil (EVOO), fruits, vegetables, nuts and seeds, legumes, in conjunction with low intakes of red meat and dairy products [3,4].

EVOO is often considered the core characteristic of the Mediterranean diet, and recent meta-analyses supports its cardio-protective effect. For example, a large meta-analysis of 32 prospective observational studies has shown that the top versus bottom third of olive oil (OO) consumption was inversely associated with risk of stroke and coronary heart disease (CHD) [5]. In other meta-analyses, OO consumption has been associated with lower diabetes risk and improvements in metabolic and inflammatory biomarkers [6,7]. Moreover, two recent pairwise meta-analyses compared the effects of high phenolic olive oil (HPOO) vs. low phenolic olive oil (LPOO) [8,9]. Whereas one meta-analysis showed a beneficial effect of HPOO on oxidized LDL-cholesterol (oxLDL-C), total-cholesterol (TC), HDL-cholesterol (HDL-C), and malondialdehyde [8], whereas the second meta-analysis found beneficial effects on cardiovascular risk factors only with respect to oxLDL-C and systolic blood pressure (SBP) [9].

The above mentioned pairwise meta-analyses did not distinguish between the different types of olive oil: e.g. refined OO (ROO), mixed OO (ROO + virgin OO), virgin OO, EVOO, LPVOO, and HPVOO. Compared to the above described pairwise meta-analyses, the methodological approach of network meta-analysis (NMA) offers the possibility to combine direct (i.e., from trials comparing directly two interventions: e.g. ROO vs. MOO) and indirect (i.e., from a connected root via one more intermediate comparators) evidence in a network of trials. In this way, it enables inference about every possible comparison between a pair of olive oil interventions in the network even when some comparisons have never been evaluated in a trial [10,11]. To the best of our knowledge, no systematic review has been conducted to date that simultaneously compared the effects of different types of olive oil on cardiovascular risk factors. Therefore, the aim of the present research was to include all possible comparisons of the various types of OO, combine the direct and indirect evidence, and rank the different types of olive oil for effects on blood lipids (TC, LDL-cholesterol, oxLDL-C, HDL-C, and triacylglycerols) and blood pressure using a NMA methodology.

Methods and design

This NMA was registered in PROSPERO (International Prospective Register of Systematic Reviews; www.crd.york.ac.uk/prospero/index.asp, identifier 42019122776), and was reported in adherence to PRISMA standards of quality for reporting NMAs [12,13].

Search strategy

The literature search was performed in the electronic databases Medline, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) until 17th December 2018 with no restriction of language and calendar date using a pre-defined search strategy (Supplementary Appendix 1).

The reference lists from eligible studies were screened to identify additional relevant research. Screening and study selection was conducted by two authors independently (LS, MK).

Selection of studies

Studies were included in the NMA if they met the following criteria:

i) Randomized controlled trials (RCTs; with a parallel or cross-over design) examining diets varying in the composition of at least two of the following types of OO:

a. ROO: According to the definition by the International olive council (IOC) ROO is the OO obtained from VOO by refining methods, which do not lead to alterations in the initial glyceridic structure. The refining process allows the elimination of color, odor, or flavor of those oils that are unacceptable to consumers or to remove chemical compounds that might be toxic or have bad influence on the olive oil stability [14]. However most bioactive and antioxidant compounds, such as polyphenols and tocopherols are removed during the refining process [15]. It has a free acidity, expressed as oleic acid, of not more than 0.3 g per 100 g and its other characteristics correspond to those fixed for this category in the IOC standard.
b. Mixed OO: blend of ROO and VOO.
c. (E)VOO: obtained from the fruit of the olive tree solely by mechanical or other physical means under conditions, particularly thermal conditions that do not lead to alterations in the OO. VOO which has a free acidity, expressed as oleic acid, of not more than 2 g/100 g (0.8 g/100 for EVOO):
   i) LP(E)VOO (<200 mg/kg phenolic content)
   ii) HP(E)VOO (≥200 mg/kg phenolic content).

ii) Comparison of iso-caloric exchange of the different OO within a RCT.

iii) Minimum duration of the intervention: 3 weeks.

iv) Participants with a mean age ≥18 years.

The following studies were excluded:

i) RCTs of acute (single meal) post-prandial effects only.

ii) RCTs using encapsulated oil supplements.
iii) RCTs using fish oils or MCT oils, or omega-3 fatty enriched oils/solid fats.
iv) RCTs based on liquid/formula diets.
v) Co-intervention (e.g. drug, diet, or exercise) not applied in all intervention arms.

Data extraction

For included studies, two reviewers independently (LS, MK) extracted the following characteristics: name of first author, year of publication, study origin (country), study design (RCT: parallel or cross-over, duration of washout period), specification of OO, dose of OO, phenolic content of OO, daily dose of phenols from OO, number of participants, disease status (i.e. healthy, hypercholesterolemia, peripheral disease), mean age, mean Body Mass Index (BMI), % type 2 diabetics, % female, duration of intervention (weeks), outcome data, and conflict of interest. The preferred outcome data (LDL-cholesterol (LDL-C), oxLDL-C, SBP, TC, HDL-C, triacylglycerols (TG), and diastolic blood pressure (DBP)) were change scores adjusted for baseline measurements with corresponding standard deviations, followed by post-intervention values and change scores not adjusted for baseline measurements.

Risk of bias assessment

Risk of bias was assessed by two authors independently (LS, MK) according to the method described in the Cochrane Handbook for Systematic Reviews of Interventions [16]. The following domains were considered: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (carry over effect in cross-over RCTs).

We intended to perform sensitivity analyses including only RCTs at low risk of bias in the domains of random sequence generation, allocation concealment and incomplete outcome data; however, these analyses were not feasible owing to poor reporting (excluding a thorough bias assessment for these aspect) in the included RCTs.

Data synthesis

Statistical analysis

Available direct comparisons between types of OO were illustrated using a network plot [17] for the following outcomes: LDL-cholesterol (LDL-C), oxLDL-C, systolic blood pressure (SBP) (these outcomes are defined as primary outcomes in the present NMA); TC, HDL-C, triacylglycerols (TG), and diastolic blood pressure (DBP) (these outcomes are defined as secondary outcomes). Of note, in NMA the size of the nodes is proportional to the sample size of each dietary intervention and the thickness of the lines proportional to the number of studies available. For all outcomes mean differences (MDs) were calculated, with the exception of oxLDL-C, where we used both MDs and standardized mean differences (SMDs) (due to different measurement methods used across included RCTs).

We performed NMAs in a contrast-based framework using the R package netmeta, Version 1.0–1 [18]. Treatments were ranked by P-scores that are a frequentist version of the Surface Under the Cumulative Ranking curve (SUCRA) [19,20]. P-scores are values between 0 and 1, where a value of 1 means that a treatment ranks always best and a value of 0 means that a treatment ranks always worst.

Assessment of transitivity

To evaluate the assumption of transitivity [11], we compared the similarity of the included populations and study settings in terms of age, BMI, disease status and study length for the available direct comparisons.

Assessment of inconsistency

We assessed potential inconsistency by splitting the effect estimate for each comparison into the contribution of direct and indirect evidence and testing whether they differed. We also applied a full treatment–design interaction model which separates effects within and between different designs, visualized by the net heat plot [21]. In the context of NMA, a design is defined as the subset of treatments that are compared in a trial. This plot is a “heat map” where the colors on the diagonal represent the inconsistency contribution of the corresponding design and the colors on the off-diagonal are associated with the change in inconsistency between direct and indirect evidence in a network estimate in the row after relaxing the consistency assumption for the effect of a design in the column (Supplementary Fig. 6). A blue colored element indicates that the evidence of the design in the column supports the evidence in the row; a red colored element indicates that the evidence of the design in the column contrasts to the evidence in the row.

Secondary analyses and sensitivity analyses

Secondary analyses were conducted comparing ROO, MOO, VOO and EVOO, irrespective of the phenolic content, and by comparing OO solely categorized according to the daily dose of phenolic compounds ($<$1 mg/d vs. 1 to $<$5 mg/d vs. $\geq$5 mg/d). Although we planned a-priori to conduct sensitivity analyses for low risk of bias studies, due to the low number of available RCTs this was not possible.

Dissemination bias

In order to evaluate dissemination bias, a funnel plot was created for each direct pairwise comparison, and Egger test was conducted to investigate small study effects [22].

Grading of recommendations assessment, development, and evaluation (certainty of the evidence)

We followed the GRADE approach to rate the certainty of evidence derived from NMA. For each primary outcome, two authors independently (LS, CS) rated the certainty of evidence in each of the direct, indirect and network estimates [23]. Direct estimates were evaluated with the following GRADE criteria: risk of bias, indirectness, inconsistency and publication bias. As suggested recently by the GRADE working group, consideration of imprecision is not necessary when rating the direct and indirect estimates to inform the rating of NMA estimates [23]. The indirect estimate assessments were based on the direct estimate certainty and were rated down if intransitivity was judged as serious (i.e. disease status). The NMA certainty estimates were based on the direct and indirect estimates certainty (specifically, the higher of the certainty between direct and indirect, was chosen as the certainty of the NMA estimate), and rating down if incoherence or imprecision were present [23].

Results

Out of 1154 records identified by the literature search, 28 records were assessed as full texts in detail (Fig. 1). Overall, 13 RCTs (16 reports) [24–39] with a total of 611 participants published between 1999 and 2018 were included in the systematic review, of which 11 RCTs (14 reports) were included in the NMA. Two RCTs were not considered for the NMA due to missing outcome data [33,39].

Nine RCTs [24–35,38,39] were conducted in Spain and the study length ranged between 3 and 12 weeks; the mean age of the participants was between 26 and 70 years, their BMI between 22.7 and 27.5 kg/m^2. Daily dose of OO ranged between 20 ml/d (approximately 18.5 g/d given a density of olive oil at ~0.92 g/ml) and 75 ml/d (~69 g/d). The daily phenolic intake from OO ranged between 0 mg/d and 21.6 mg/d. In six RCTs, only healthy participants were included, and two RCTs included participants with CHD or peripheral vascular disease [27,34], respectively. Study and participant characteristics are summarized in Table 1 and Supplementary Table 1, respectively.

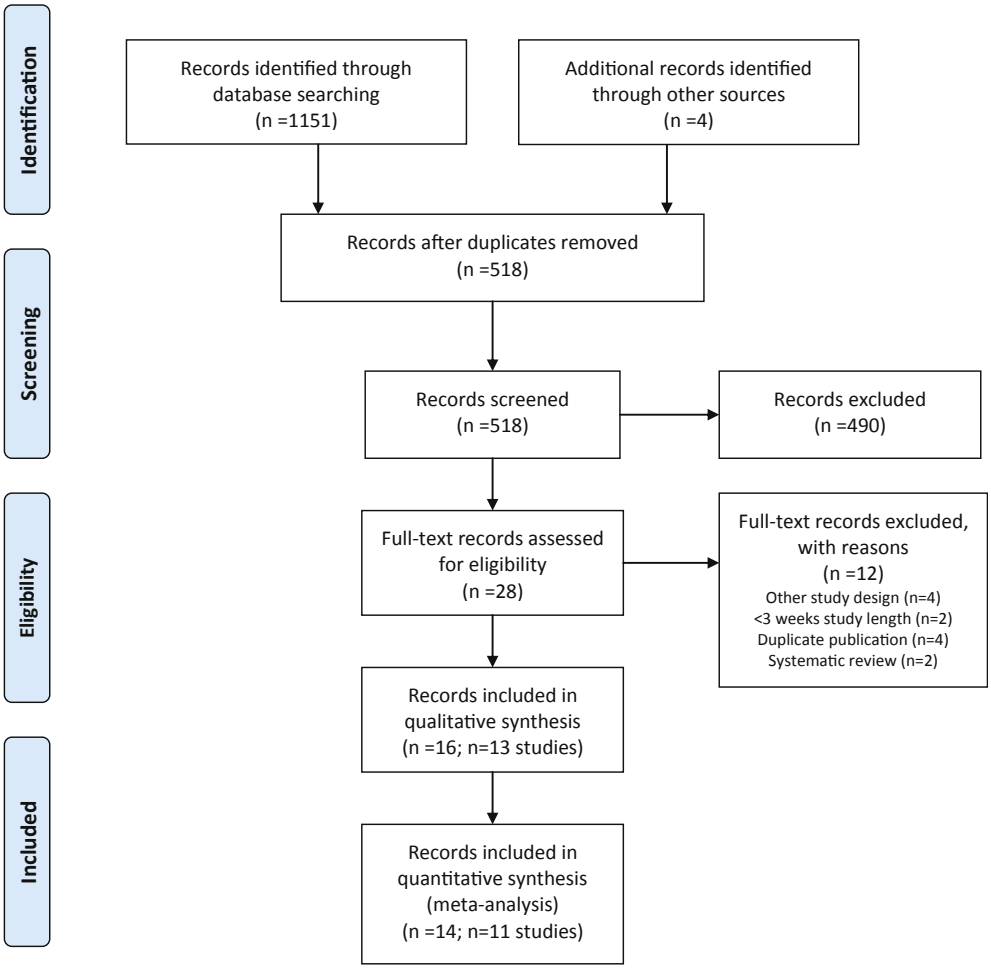

Figure 1 Flow diagram showing study selection process.

Table 1 Study characteristics of the included randomized controlled trials.

Reference	Country	Study design	Comparison	Sample size Disease status	Mean age	Mean baseline BMI (k/m^2)	Type 2 diabetes (%)	Female (%)	Duration, weeks	Outcomes	Conflict of interest
Covas, 2006 [24]	5 European countries (Denmark, Germany, Finland, Italy, Spain)	RCT, cross-over (washout: 2 weeks)	ROO vs. MOO vs. HPVOO	200, Healthy	33.2	23.8	0%	0%	3	TC, LDL-C, HDL-C, TG, oxLDL	No conflict of interest
Fernandez-Castillejo, 2016 [25] Martín-Peláez, 2016 [26]	Spain	RCT, cross-over (washout: 2 weeks)	LPEVOO vs. HPEVOO	33, Hyper-cholesterolemic	55.2	26.6	0%	42%	3	LDL-C, HDL-C, oxLDL	No conflict of interest
Fito, 2005 [27]	Spain	RCT, cross-over (washout: 2 weeks)	ROO vs. LPVOO	46, Stable coronary heart disease	67.5	27.5	22.5%	0%	3	TC, LDL-C, HDL-C, TG, oxLDL, SBP, DBP	Not reported
Konstantinidou, 2010 [28]	Spain	RCT, parallel	ROO vs. HPVOO	60, Healthy	45	25	0%	75%	12	TC, LDL-C, HDL-C, TG, oxLDL, SBP, DBP	No conflict of interest
Marrugat, 2004 [29] Gimeno, 2007 [30] Perona, 2011 [31]	Spain	RCT, cross-over (washout: 2 weeks)	ROO vs. MOO vs. LPVOO	30, Healthy	57.5	22.7	0%	0%	3	TC, LDL-C, HDL-C, TG, oxLDL	Not reported
Moreno-Luna, 2012 [32]	Spain	RCT, cross-over (washout: 4 weeks)	ROO vs. HPVOO	40, High-normal BP or stage 1 essential hypertension	26	25.4	0%	100%	8	oxLDL, SBP, DBP	No conflict of interest
Moschandreas, 2002 [33]	Greece	RCT, cross-over (washout: 2 weeks)	ROO vs. HPEVOO	28, Smokers	30	25	0%	56%	3	–	Unilever
Ramirez-Tortosa, 1999 [34]	Spain	RCT, cross-over (washout: 12 weeks)	ROO vs. HPEVOO	24, Peripheral vascular disease	69.9	24.8	0%	0%	12	TC, LDL-C, HDL-C, TG, oxLDL	Not reported
Rus, 2017 [39]	Spain	RCT, parallel	ROO vs. EVOO	23, Fibromyalgia	50.9	27	0%	100%	3	SBP, DBP	No conflict of interest
Sanchez-Rodriguez, 2018 [38]	Spain	RCT, cross-over (washout: 2 weeks)	LPEVOO vs. HPEVOO	39, Healthy	30.5	24	0%	44%	3	TC, LDL-C, HDL-C, TG, SBP, DBP	No conflict of interest Funding: Acer Campestres S.L., San Francisco de asis Coop and Agroinsur S.L.

Silva, 2015 [35]	Spain	RCT, parallel	ROO vs. HPEVOO	69, Healthy	30.9	24.1	0%	57%	6	TC, LDL-C, HDL-C, TG, oxLDL, SBP, DBP	Two authors: Mosaiques Diagnostics
Visoli, 2005 [36]	Italy	RCT, cross-over (washout: 3 weeks)	ROO vs. LPEVOO	22, Mild dyslipidemia	18–65	<25	NR	45%	7	TC, LDL-C, HDL-C, TG	Carapelli
Vissers, 2001 [37]	Netherlands	RCT, cross-over (washout: 2 weeks)	LPEVOO vs. HPEVOO	49, Healthy	18–58	NR	0%	NR	3	TC, LDL-C, HDL-C, TG	International Olive Oil Council

BMI: Body Mass Index; DBP: diastolic blood pressure; EVOO: extra-virgin olive oil; HDL-C: high-density lipoprotein cholesterol; HPVOO: high-phenolic virgin olive oil; LDL-C: low-density lipoprotein cholesterol; LPVOO: low-phenolic virgin olive oil; MOO: mixed olive oil; oxLDL: oxidized low-density lipoprotein cholesterol; RCT: randomized controlled trial; ROO: refined olive oil; SBP: systolic blood pressure; TG: triacylglycerol's; TC: total cholesterol.

Risk of bias

The results of the risk of bias assessment are provided in Supplementary Fig. 1. Four studies were judged to have a low risk of selection bias [24–26,35,38], six RCTs (46%) adequately performed blinding of participants and personnel [25,26,29–32,35,39], no RCT (0%) was judged as low risk of bias for blinding of outcome assessment, and nine RCTs (69%) were judged as low risk of bias for incomplete data outcome [24–26,28–31,33,35,36,38,39]. Four RCTs (31%) were judged to have a low risk of bias for selective reporting [27,28,35,38], and none RCTs showed a high risk of other bias (Supplementary Fig. 1). Two RCTs were rated with a high risk of bias, due to attrition bias, and conducted only per-protocol analysis (those RCTs excluded participants (n = 12) not adhering to dietary intervention from the statistical analysis) [27,32].

Fig. 2 shows the network diagrams for LDL-C (A), oxLDL-C (B), SBP and DBP (C), TC and HDL-C (D), and TG (E). For the comparison ROO versus HP(E)VOO most trials could be considered (n = 5).

The effect estimates for the comparison of different types of OO on LDL-C, oxLDL-C, SBP, TC, HDL-C, TG, DBP are shown in Fig. 3 and Supplementary Figs. 2–5.

Primary outcomes

Compared to ROO, all other types of OO (MOO, LP(E)VOO and HP(E)VOO) may make no difference in reducing LDL-C, but HP(E)VOO slightly reduce LDL-C compared to LP(E)VOO (MD: −0.14 mmol/L, 95% CI: −0.28, −0.01; high certainty of evidence) (Fig. 3, Supplementary Table 2). Additionally, HP(E)VOO may reduce oxLDL-C compared to ROO (SMD: −0.68, 95% CI: −1.31, −0.04, low certainty of evidence; MD: −4.18, 95% CI: −7.06, −1.31 U/L). No differences were observed between the intake of LP(E)VOO, MOO, and ROO (Fig. 3, Supplementary Table 4). Both, LP(E)VOO in comparison to ROO (MD: −2.87 mmHg, 95% CI: −5.39, −0.35; moderate certainty of evidence) and HP(E)VOO in comparison to ROO (MD: −2.99 mmHg, 95%: −6.12, 0.15; low certainty of evidence) may improve SBP (Fig. 3, Supplementary Table 3).

Secondary outcomes

Comparing ROO, MOO, LP(E)VOO and HP(E)VOO against each other no differences in reducing TC, TG or DBP, or increasing HDL-C was observed (Supplementary Figs. 2–5).

P score and rankings HP(E)VOO was ranked as the best treatment for the primary outcomes LDL-C (P-score: 0.83), oxLDL-C (0.88), and SBP (0.75), whereas ROO was ranked worst treatment for oxLDL-C (0.23) and SBP (0.02) (Fig. 3).

Inconsistency The net heat plots are shown in Supplementary Figs. 6–10. Overall no important inconsistency was observed considering all comparisons. Similarly also the design-by-treatment model showed no significant inconsistency for all outcomes.

Secondary analysis No differences in the two secondary analyses comparing ROO, MOO, VOO and EVOO, and comparing different daily doses of phenolic compound intake from OO (<1 ml/d, 1 to<5 ml/d, and ≥5 ml/d) were

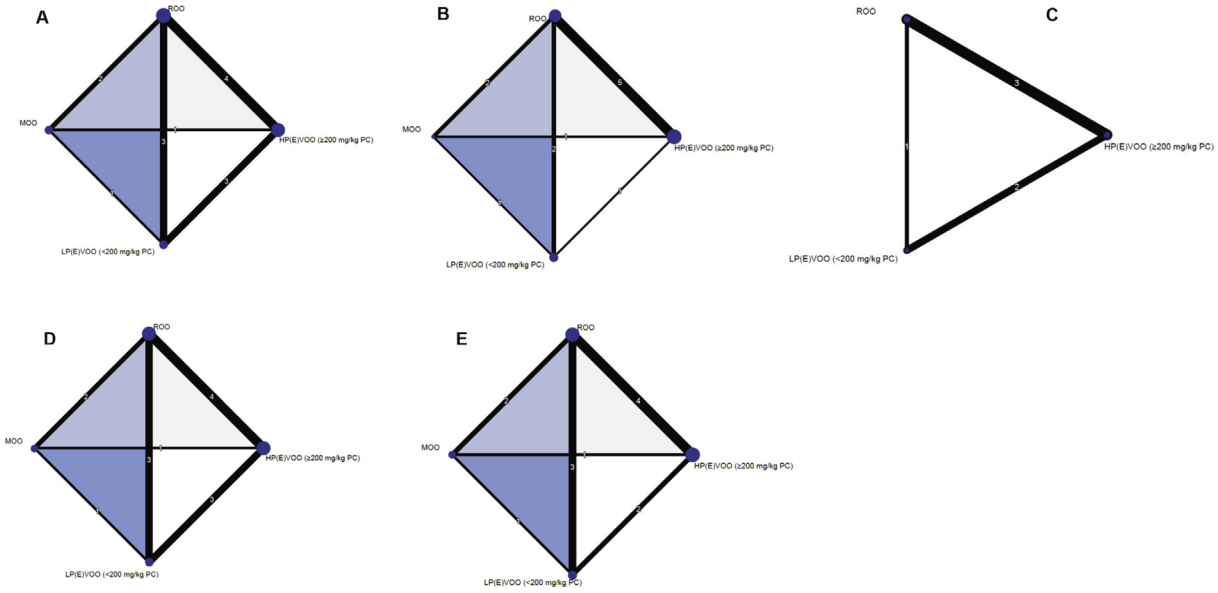

Figure 2 Network diagrams for LDL-C (A), oxLDL-C (B), SBP and DBP (C), TC and HDL-C (D), and TG (E): The size of the nodes is proportional to the total number of participants allocated to intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison.

observed for TC, LDL-C, HDL-C, TG and DBP (data not shown). However, VOO may improve SBP compared to ROO (MD: −3.28 mmHg, 95% CI: −5.53, −1.03) (Supplementary Fig. 11), and a dose ≥5 ml/d of phenolic compounds from OO may reduce SBP compared to a daily dose <1 ml/d (MD: −2.91 mmHg, 95% CI: −5.04, −0.79) (Supplementary Fig. 12). Regarding oxLDL-C reduction, EVOO was more effective compared to ROO (SMD: −1.25, 95% CI: −2.32, −0.19) (Supplementary Fig. 13), and a dose ≥5 ml/d of phenolic compounds from OO may improve oxLDL-C compared to ROO (SMD: −0.60, 95% CI: −1.18, −0.03) (Supplementary Fig. 14), and (MD: −4.21 U/L, 95% CI: −7.08, −1.33).

In further analyses, EVOO was ranked best treatment for LDL-C (0.70) and oxLDL-C (0.96), whereas VOO was ranked best treatment for SBP (0.92). Moreover, interventions with the highest daily dose of phenolic compound from OO (≥5 ml/d) were ranked best treatment for LDL-C (0.82) and oxLDL-C (0.90) (Supplementary Figs. 11 and 16).

Small study effects For none of the outcomes, the funnel plots appeared asymmetric, and the Egger test showed no evidence for small study effects (Supplementary Figs. 17–23).

Discussion

This NMA synthesized direct and indirect evidence on the effects of different types of OO on cardiovascular risk factors such as blood lipids (TC, LDL-C, oxLDL-C, HDL-C, and TG) and blood pressure.

In summary, for TC, HDL, TG and DBP, no differences between the different types of OO were observed, respectively. However, HP(E)VOO slightly reduced LDL-C compared to LP(E)VOO, and SBP and oxLDL-C compared to ROO, and was ranked best treatment for all primary outcomes including LDL-C, oxLDL-C and SBP. The certainty of our findings was rated mainly low or moderate.

Comparison with other systematic reviews

In recent NMA and pairwise MA of RCTs, OO in comparison with other oils and solid fats, it was found that n-3 and n-6 rich oils were more effective in reducing TC and LDL-C compared to OO [40,41], whereas a 10% iso-caloric replacement of butter by OO was more effective in reducing LDL-C (by −0.25 mmol/L) [41].

Regarding the effects of different types of OO, in line with findings from the present NMA, a recent pairwise MA of RCTs has shown that HPOO was more effective in reducing oxLDL-C compared to LPOO. In contrast to our findings, the authors observed also improvement of TC and HDL-C. These differences might be explained by the inclusion of both RCTs and non-RCTs and the distinction between only two major types of OO (OO low or high in phenolic compounds) in the pairwise MA [8]. In another pairwise meta-analysis comparing these two major types of OO, similar findings to our NMA have been reported. Compared to LPOO, HPOO showed improvements in SBP and (albeit only slightly) in oxLDL-C [9]. In line with our findings, in a subgroup analysis of another recent pairwise meta-analysis, no differences between VOO and ROO were found for blood lipids [40].

Focusing on patient-relevant endpoints, in a meta-analysis of prospective observational studies, the top versus bottom third of OO consumption was inversely associated with risk of stroke and CHD [5]. However, likewise to other meta-analyses of observational studies

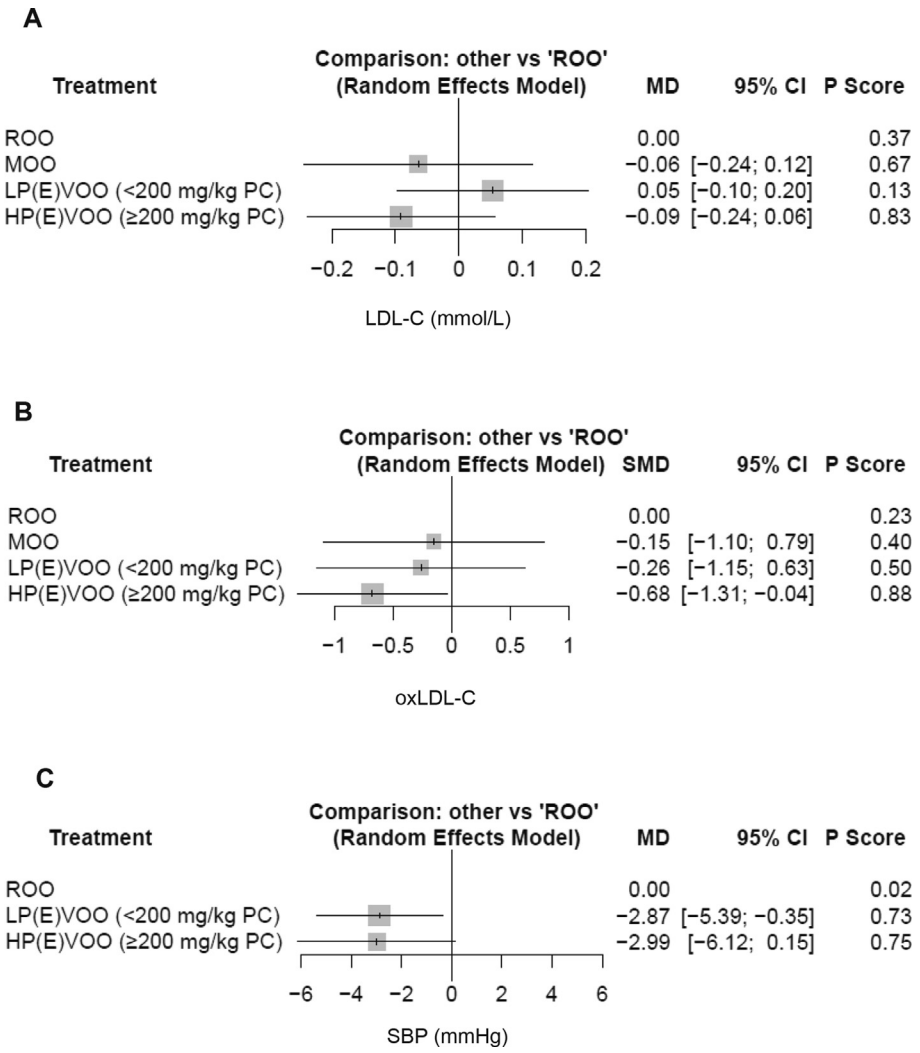

Figure 3 Summary effect estimates for the comparison of different types of olive oil on LDL-C (A), oxLDL-C (B), and SBP (C). Refined olive oil is defined as the reference treatment. P-scores are defined such that they are between 0 and 1, where 0 means that a treatment is always worst and 1 means that a treatment is always best compared to the other treatments in the network. For example, HP(E)VOO (P-score: 0.88) was ranked best to improve oxLDL-C, followed by LP(E)VOO (0.50) mixed olive oil (0.40), and refined olive oil (0.23). HP(E)VOO: high-phenolic (extra) virgin olive oil; LP(E)VOO: low-phenolic (extra) virgin olive oil; MD: mean difference; MOO: mixed olive oil; ROO: refined olive oil; SMD: standardized mean difference.

focusing on various other outcomes, the authors were not able to distinguish between different types of OO, due to missing dietary assessment information [5,7,42,43].

In addition to these observational data, a large RCT investigated the effects of EVOO on risk of CVD. The PREDIMED (Prevencion con Dieta Mediterranea) trial compared a Mediterranean diet with an additional provision of either EVOO (50 g/d) or tree nuts (30 g/d) against a low-fat regimen. The incidence of combined cardiovascular events was lower among those assigned to a Mediterranean diet supplemented with EVOO or nuts than among those assigned to a lower-fat diet [44].

Relevance of our findings

LDL-C is an established risk factor for the development of CVD. For instance, a meta-analysis of 26 trials reported that every 1 mmol/L reduction in LDL-C plasma levels was associated with a corresponding 20% risk reduction in CHD mortality [45]. The reduction in LDL-C (−0.14 mmol/L) of HP(E)VOO compared with LP(E)VOO observed in the present NMA was clinically not relevant.

Increased concentrations of oxLDL-C are associated with obesity, dyslipidemia and insulin resistance [46] and are widely accepted as an established risk factor for the development of cardiovascular disease [47]. Thus, a recent meta-analysis of 12 observational studies showed that increased circulating oxLDL-C was associated with a 79% increased risk of atherosclerotic cardiovascular disease [48].

According to the Global Burden of Disease study, in 2017 SBP was ranked as the most important modifiable risk factor for disability worldwide [2]. A recent meta-analysis of 123 trials of approximately 600.000 participants showed that a 10 mmHg reduction in SBP was inversely associated with risk of CVD events by 20%, CHD by 17%, stroke by 27%, heart failure by 28% and all-cause mortality by 13% [49], and another meta-analysis stressed the fact

that even a small decline in SBP of about 2 mmHg will be accompanied by a 10% lower risk of death due to stroke or 7% due to ischemic heart disease [50]. Thus, the significantly more pronounced decrease in oxLDL-C and SBP following intake of HP(E)VOO as compared to ROO demonstrated in the present NMA seems to be important in regard of the prevention of CVD. Additional benefits of HP(E)VOO on CVD can be accrued through additional mechanisms, including improved insulin sensitivity [51], reductions in inflammatory biomarkers [6] and benefits on the functional properties of HDL [52].

Strength & limitations

Our systematic review and NMA has several strengths and limitations that need to be considered. Amongst the strengths are the application of the NMA methodology, the breadth in scope with consideration of seven important cardiovascular risk factors (TC, LDL-C, oxLDL-C, HDL-C, TG, SBP, and DBP), the a-priori published protocol, the well-connected network for most outcomes, the risk of bias assessment, sensitivity analyses, and the GRADE certainty of evidence judgment.

The main limitation of the present NMA is that no data could be found for patient-relevant outcomes such as CHD or stroke, since all of the identified RCTs had a too short duration ($\leq$12 weeks). Therefore, the present NMA takes only intermediate disease markers for CVD risk into account, and − as previously shown for HDL-C − a causal link could not be confirmed [53]. Moreover, limitations of the present systematic review and NMA include the overall low number of RCTs included in the quantitative synthesis (n = 11), the modest similarity across the included RCTs (health status of participants differed between trials), and the possibly limited generalizability (since most trials were conducted in Spain). The certainty of evidence was rated mainly low or moderate for most outcomes. This implies that further research will likely provide important additional data to impact on the certainty of the evidence, and will likely change the effect estimate. Finally, in several RCTs [24,27−32] based on the available reports, we were not able to distinguish between VOO and EVOO since this information was not provided.

Conclusion

HP(E)VOO may improve some cardiovascular risk factors, however, public health implications are limited by overall low to moderate certainty of evidence. Well conducted, longer-term RCTs evaluating not only intermediate disease markers, but also patient-relevant outcomes are needed. Moreover, there is a need for observational studies that fully take into account different types of OO given the available evidence to support a beneficial effect of OO on CHD.

Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.07.001.

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