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Effects of high phenolic olive oil on cardiovascular risk factors: A systematic review and meta-analysis

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Introduction

Cardiovascular diseases (CVDs) are still the leading causes of death in the world (WorldHealthOrganisation 2013). Risk factors like dyslipidaemias and hypertension are of significant importance for the pathophysiology of CVD (Foody 2006). The Mediterranean diet was found to be effective in the prevention and treatment of CVD (Finks et al. 2012). Olive oil as its primary source of fat is seen as a key factor of this diet (Bullo et al. 2011). The focus of research was set on fatty acids during the last decades. But besides the favourable high content in monounsaturated fatty acids (MUFA), olive oil contains a notable amount of active micro compounds. Among them the phenols oleuropein and (hydroxy-) thyrosol were identified as the most important active substances. These phenols are able to modulate cardiovascular pathogenesis specifically referring to its inflammative aspects (Cicerale et al. 2010; Urpi-Sarda et al. 2012).

Generally, there is clear evidence for the positive effects of MUFA as well as the negative effects of saturated fatty acids on the serum lipoprotein profile (Mensink and Katan 1992; Michas et al. 2014). Positive effects on serum lipids have also been found for olive oil in some studies without specific consideration of micro compounds (Williams 2001; Violante et al. 2009). Only high quality olive oils, sold as virgin or extra virgin olive oil, contain sufficient amounts of phenols. To preserve the phenols these oils must not be processed or refined e.g. filtered or washed (Covas et al. 2009). The bioavailability of the

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Table 1
Complete search strategy for PubMed.

Concept	Search strategy
Olive oil	"olive"[Title/Abstract] AND "oil"[Title/Abstract]
	AND
Cardiovascular risk factors	"Blood pressure"[Mesh] OR "Blood pressure"[Title/Abstract] OR "BP"[Title/Abstract] OR "RR"[Title/Abstract] OR "Lipoproteins"[Mesh] OR "HDL"[Title/Abstract] OR "LDL"[Title/Abstract] OR "Triglyceride*"[Title/Abstract] OR "oxidized LDL"[Title/Abstract] OR "oxLDL"[Title/Abstract] OR "ox-LDL"[Title/Abstract] OR "dimethylarginine" [Title/Abstract] OR "malondialdehyde"[mesh] OR "malondialdehyde" [Title/Abstract] OR "MDA" [Title/Abstract]
	AND
Cardiovascular or metabolic diseases or healthy subjects	"Cardiomyopathies"[MeSH] OR "Coronary Disease"[MeSH] OR "heart failure"[MeSH] OR "hypertension"[MeSH] OR "prehypertension"[MeSH] OR "Myocardial Ischemia"[MeSH] OR "Coronary Artery Disease"[Mesh] OR "peripheral arterial disease"[mesh] OR "CHD"[Title/Abstract] OR "Cardiomyopathy"[Title/Abstract] OR "Coronary Disease"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "hypertension"[Title/Abstract] OR "prehypertension"[Title/Abstract] OR "Myocardial Ischemia"[Title/Abstract] OR "CAD"[Title/Abstract] OR "Coronary Heart Disease"[Title/Abstract] OR "Coronary Artery Disease"[Title/Abstract] OR "peripheral arterial disease"[Title/abstract] OR "gene*"[Title/Abstract] OR "Metabolic Syndrome X"[Mesh] OR "Metabolic Syndrome"[Title/Abstract] OR "MetS"[Title/Abstract] OR "dyslipidemias"[Mesh] OR "dyslipidemia"[Title/Abstract] OR "hyperglycemia"[Mesh] OR "hyperglycemia"[Title/Abstract] OR "healthy subjects"[Title/Abstract] OR "Metabolic Syndrome X"[Mesh] OR "Metabolic Syndrome"[Title/Abstract] OR "MetS"[Title/Abstract] OR "insulin resistance"[Mesh] OR "insulin resistance"[Title/Abstract] OR "healthy subjects"[Title/Abstract]"

phenols is high after ingestion (Cicerale et al. 2010). It has been shown that the mentioned phenols affect the plasmatic oxidative status and several inflammative pathways. Investigated outcomes include NF-κB, MCP-1, TNF-α, oxidized LDL (oxLDL), malondialdehyde (MDA), asymmetric dimethylarginase (ADMA), IL-2 and 6 (Covas et al. 2009; Cicerale et al. 2010). Clinical trials found promising results like increase of the anti-inflammatory activities of PON1. More recently, inflammation related nutrigenomic effects turned into focus like lower postprandial expression of p65 or MCP-1 (Camargo et al. 2012).

To date several narrative reviews about olive oil and cardiovascular effects exist (Covas et al. 2009; Badimon et al. 2010; Bullo et al. 2011; Rees et al. 2013). All of them deliver an extensive overview about the topic, but none of them are systematic or include a meta-analysis. Hence the aim of this review and meta-analysis is to systematically assess and to summarize the state of knowledge about the effects of high phenolic olive oil on cardiovascular risk factors either in healthy human beings or in patients suffering from CVDs by analysing randomised controlled and cross over studies that compared the ingestion of low/no phenolic olive oil to HPOO.

Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009) and the recommendations of the Cochrane Collaboration (Furlan et al. 2011) were followed. A systematic review protocol was developed a priori and not modified after beginning of the review process. The review was not registered and provides therefore no registration number.

Eligibility criteria

Types of studies

Randomized controlled trials (RCTs) and randomized crossover studies were eligible. No language restrictions were applied.

Types of participants

Either healthy adults or adult patients with

- heart diseases namely heart failure, myocardial ischemia, cardiomyopathy and coronary (arterial) disease,
- peripheral vascular disease
- hypertension or prehypertension
- metabolic disorders namely metabolic syndrome, dyslipidaemia, hyperglycaemia

were eligible. No restrictions were made in sex, participants had to be at least 18.

Types of interventions

Studies that compared mid-term, semi long-term or long-term interventions with HPOO vs. low phenolic olive oil (LPOO) were included. Mid term was defined as $\geq$3 to $<$6 weeks, semi-long term as $\geq$6 weeks to $<$3 months and long term as $\geq$3 months. Low phenolic was defined as $\leq$5 mg/kg and high phenolic as $\geq$150 mg/kg.

Types of outcome measures

For inclusion, RCTs had to assess at least one primary outcome, i.e. blood pressure, lipids (total cholesterol, HDL, LDL, TG) or serum markers of oxidative status (e.g. oxLDL, malondialdehyde). Safety was defined as secondary outcome and assessed as adverse events or other reported items e.g. laboratory parameters.

Search methods

The following electronic databases were searched from their inception through July 23, 2014:

Medline/PubMed, EMBase, the Cochrane Library, CAMbase and CAM-QUEST. Search terms for cardiovascular and metabolic diseases or diagnoses were combined with search terms for cardiovascular risk factors (e.g. plasma lipoproteins) and search terms for olive oil. Table 1 shows the complete search strategy for PubMed.

The search strategy was adapted for each database as necessary. Reference lists of identified original articles or reviews were searched manually. Two review authors independently screened abstracts identified during the literature review and potentially eligible articles were read in full to determine whether they met the eligibility criteria.

Data extraction and management

Two authors independently extracted data on patients (e.g. age, gender, diagnosis), methods (e.g. randomization, allocation concealment), interventions (e.g. HPOO/LPOO, frequency, and duration), control interventions (e.g. phenols, frequency, duration), outcomes (e.g. outcome measures, assessment time points), and results. An a priori developed data extraction form was used. Discrepancies were discussed with a third review author until consensus was reached. If necessary, the study authors were contacted for additional information.

Risk of bias in individual studies

Risk of bias was assessed by two authors independently using the Cochrane risk of bias tool (Higgins et al. 2008). This tool assesses risk of

bias within the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Discrepancies were rechecked with a third reviewer and consensus achieved by discussion.

Data analysis

Studies that compared mid-term or long-term interventions with HPOO vs. LPOO content were analysed. Mid-term was defined as ≥3; <6 weeks, semi-long-term ≥6 weeks; <3 months and long-term as ≥3 months, LPOO as ≤5 mg/kg and HPOO as ≥150 mg/kg.

Assessment of overall effect size

Meta-analyses were conducted using Review Manager 5 software (Version 5.2, The Nordic Cochrane Centre, Copenhagen) if at least two studies assessing this specific outcome were available. As only randomized cross over studies were included in the analysis the generic inverse variance method was used with a random effects model (Higgins et al. 2008).

For continuous outcomes, standardized mean differences (SMD) with 95% confidence intervals (CIs) were calculated as the difference in means between groups divided by the pooled standard deviation. Thus differently scaled outcomes of the same kind could be compared by group differences. Where no standard deviations were available, they were calculated from standard errors, CIs or *t*-values, or attempts were made to obtain the missing data from the trial authors by email. SMD was calculated as Hedge's *g* using a standardized LibreOffice-Calc® spread sheet. For randomized cross over trials the calculation was adapted for intercorrelations between groups. Where no correlation was reported it was assumed as 0.7 (Cooper et al. 2009).

A negative SMD was defined to indicate beneficial effects of high phenolic olive oil compared to the low phenolic olive oil intervention for all outcomes (e.g. decreased BP) except for HDL where a positive SMD was defined to indicate beneficial effects. If necessary, scores were inverted by subtracting the mean of the maximum score from zero (Higgins et al. 2008).

Cohen's categories were used to evaluate the magnitude of the overall effect size with (1) SMD = 0.2–0.5: small; (2) SMD = 0.5–0.8: medium, and (3) SMD > 0.8: large effect sizes (Cohen 1988).

Assessment of heterogeneity

I^2 statistics, a measure of how much variance between studies can be attributed to differences between studies rather than chance, was used to analyse statistical heterogeneity between studies. The magnitude of heterogeneity was categorized as (1) I^2 = 0–24%: low heterogeneity; I^2 = 25–49%: moderate heterogeneity; I^2 = 50–74%: substantial heterogeneity; and I^2 = 75–100%: considerable heterogeneity (Higgins et al. 2003). The χ^2 test was used to assess whether differences in results were compatible with chance alone. Given the low power of this test when only few studies or studies with low sample size are included in a meta-analysis, a *p*-value ≤0.10 was regarded to indicate significant heterogeneity (Higgins et al. 2008).

Subgroup and sensitivity analyses

Besides overall effect assessment, subgroup analyses were conducted for types of participants (healthy patients or such with cardiovascular diseases). Another analysis was conducted for duration of the intervention. Interventions using mid-term or semi-long-term interventions where compared. The third subgroup analysis compared interventions with high DIP (daily intake of phenols) (>5 mg) against low DIP (<5 mg).

The robustness of significant results was tested with sensitivity analyses for studies with high vs. low or unclear risk of bias for the following domains: selection bias, performance bias, and detection bias. If statistical heterogeneity was detected in the respective meta-analysis, subgroup and sensitivity analyses were also used to explore possible reasons for heterogeneity.

Risk of bias across studies

If at least 10 studies were included in a meta-analysis, assessment of risk of publication was originally planned by visual analysis of funnel plots (Egger et al. 1997).

Results

Literature research

1238 results were retrieved through the literature search, one additional article was retrieved from reference lists of identified original articles (Fig. 1). After exclusion of duplicates 308 abstracts were screened. Out of them 289 did not match the inclusion criteria. We accessed 19 full texts for eligibility. Seven were excluded because the control group did not receive an olive oil with no phenolic content but another oil (e.g. sunflower or corn oil) (Sirtori et al. 1992; Choudhury et al. 1995; Perez-Jimenez et al. 1995; Ruiz-Gutierrez et al. 1996; Aguilera et al. 2004; Damasceno et al. 2011; Labraimi et al. 2011), three were excluded because they referred to the same main study (Machowetz et al. 2008; de la Torre-Carbot et al. 2010; Castaner et al. 2012) and one because it compared to a control group without olive oil ingestion (Oliveras-Lopez et al. 2013). One study did not provide raw data of outcome measures but the data could be retrieved from trial authors (Covas et al. 2006). Finally eight studies were included in the meta-analysis.

Study characteristics

Characteristics of the sample, interventions, outcome assessment and results are shown in Table 2.

Setting and participant characteristics

All of the eight included RCTs originated from Europe (five from Spain (Ramirez-Tortosa et al. 1999; Marrugat et al. 2004; Fito et al. 2005; Covas et al. 2006; Moreno-Luna et al. 2012), two from the Netherlands (Vissers et al. 2001; Moschandreas et al. 2002) and one from Italy (Visioli et al. 2005)). Patients were recruited from department outpatient clinics (Ramirez-Tortosa et al. 1999; Visioli et al. 2005; Moreno-Luna et al. 2012), local newspapers (Vissers et al. 2001), universities and connected facilities (Vissers et al. 2001; Moschandreas et al. 2002) as well as male religious centre (Marrugat et al. 2004).

One study did not report from where patients were recruited from (Fito et al. 2005). Three studies included healthy subjects (Vissers et al. 2001; Visioli et al. 2005; Covas et al. 2006), one each included healthy males (Marrugat et al. 2004), healthy smokers (Moschandreas et al. 2002), mild-hypertensive women (Moreno-Luna et al. 2012), patients with stable coronary heart disease (Fito et al. 2005), and men with peripheral vascular disease (Ramirez-Tortosa et al. 1999).

Patient's mean age ranged from 26 to 69.9 years with a median age of 57.5 years. Between 0 and 100% of the subjects were female (median 54.5%). Race was not reported in any trial.

Intervention characteristics

All studies used a cross over design and compared olive oils with differing amounts of phenolic compounds. Participants were advised to use the oil for all prepared meals. Five studies were two armed and compared HPOO vs. low phenolic olive oil (LPOO) (Ramirez-Tortosa et al. 1999; Vissers et al. 2001; Moschandreas et al. 2002; Visioli et al. 2005; Moreno-Luna et al. 2012) and three studies (Marrugat et al. 2004; Fito et al. 2005; Covas et al. 2006) were three armed with HPOO, medium phenolic olive oil and LPOO. Of the latter only results for the HPOO and LPOO groups were included for the calculation. All gave an exact figure for the phenolic content of the oil (mg/kg; where mg/l

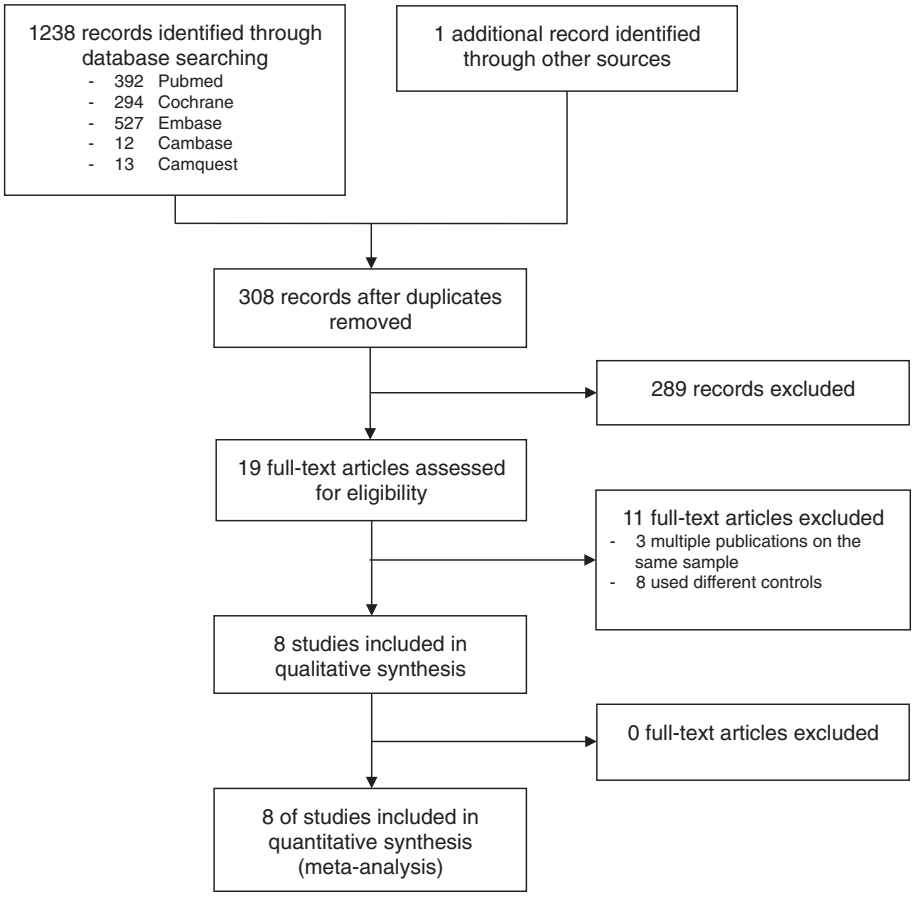

Fig. 1. Flow chart of study procedure.

was declared figures were transformed using a mean ρ of 0.915 kg/l olive oil). All but one (Visioli et al. 2005) gave an exact amount of oil that was consumed daily. For better comparability we calculated the daily intake of phenols (DIP). DIP in control interventions ranged from 0 to 4.3 mg (median 0.01 mg) and for the interventions group between 3.4 to 31 mg (median: 14.5 mg). The daily given volume of oil differed between 25 and 76 ml (median: 50). The periods ranged from 3 weeks up to 3 months with a median of 3 weeks. Five studies used mid-term (Vissers et al. 2001; Moschandreas et al. 2002; Marrugat et al. 2004; Fito et al. 2005; Covas et al. 2006), and three semi-long-term interventions (Ramirez-Tortosa et al. 1999; Visioli et al. 2005; Moreno-Luna et al. 2012). Four studies described no co-interventions (Moschandreas et al. 2002; Marrugat et al. 2004; Visioli et al. 2005; Moreno-Luna et al. 2012), one each announced: co-medication (Fito et al. 2005), dietary assistance including the recommendation to quit smoking and for walking 1 km/d (Ramirez-Tortosa et al. 1999), and a diet low in tocopherols (Vissers et al. 2001). Three studies reported markers of dietary adherence (measurement of phenol metabolics in urine) (Marrugat et al. 2004; Fito et al. 2005; Covas et al. 2006). All studies were conducted in clinical outpatient centres and all patients were examined and assessed after by a physician. All studies used mid- or semi-long-term interventions (3 weeks up to 2 months).

Outcome measures

Two studies assessed blood pressure (each systolic and diastolic) (Fito et al. 2005; Moreno-Luna et al. 2012), four oxidized LDL (Marrugat et al. 2004; Fito et al. 2005; Covas et al. 2006; Moreno-Luna et al. 2012), and six each total cholesterol HDL, LDL and TG (Ramirez-Tortosa et al. 1999; Vissers et al. 2001; Marrugat et al. 2004; Fito et al. 2005; Visioli et al. 2005; Covas et al. 2006). Two studies reported data about malondialdehyde (Vissers et al. 2001; Moschandreas et al. 2002).

Only one study that met the inclusion criteria reported nutrigenomic effects. Due to no other data on the particular outcome (CD-40 ligand expression) it could not be included in the quantitative analysis. Safety data was reported in two studies, but no adverse events or critical results were mentioned (Vissers et al. 2001; Covas et al. 2006).

Risk of bias in individual studies

We used the Cochrane risk of bias tool (Higgins et al. 2008) to assess all studies for their risk of bias within the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. By using this method we estimated the methodological quality of the trials. Table 3 provides an overview of the risk of bias assessment. All but one study had an unclear risk of bias. For the mentioned study a low risk of bias was detected (Covas et al. 2006). The random sequence generation was adequate where reported (Vissers et al. 2001; Moschandreas et al. 2002; Visioli et al. 2005; Covas et al. 2006; Moreno-Luna et al. 2012). Data about allocation concealment was only reported for one study (Covas et al. 2006). Participant blinding was described in two studies, one indicated a high (Moreno-Luna et al. 2012) and one low risk of bias (Covas et al. 2006). The blinding of outcome assessment was reported for only one study (Vissers et al. 2001) and classified as low risk. Three studies reported data and showed a low risk for attrition bias (Vissers et al. 2001; Moschandreas et al. 2002; Covas et al. 2006). All studies had a low risk for selective reporting bias. No other kinds of bias were detected. In summary we could not identify enough reported items most of the studies to clearly access risk of bias.

Table 2
Study characteristics.

Reference	Design	Participants- condition- sample- size mean- age gender	Treatment group: intervention	Control group: intervention	Co-interventions	Outcomes (selection of plasmatic parameters)	Results (treatment group)
Covas 2006	3-period cross-over RCT, 2 w wash-out period where ROO was used	200 healthy men, mean age 33.2 y	VOO 25 ml/d for 3 w, PC 366 mg/kg, DIP 8.4 mg	ROO 25 ml/d for 3 w, PC 2.7 mg/kg; DIP 0.6 mg	Dietary assistance	Total cholesterol, HDL, LDL, TG, oxidized LDL	oxLDL decrease, HDL increase
Fito 2005	3-period cross-over RCT, 2 w wash-out period where ROO was used	46 males with stable CHD, mean age 67.7 y	VOO 50 ml/d, for 3 w PC 161.0 mg/kg, DIP 7.4 mg	ROO 50 ml/d for 3 w PC 14.7 mg/kg; DIP 0.8 mg	Standard medication	BP, glucose, LDL, HDL, TG, Lipoprotein (a), oxLDL (U/l), glutathione peroxidase, total antioxidant status, tyrosol	Reduction D-BP
Marrrugat 2004	3-period cross-over RCT, 2 w washout	30 healthy males mean age 57.5 y	VOO 25 ml/d for 3 w, PC 150 mg/kg, DIP 3.4 mg	ROO 25 ml/d for 3 w, PC 0 mg/kg; DIP 0 mg	Not described	Total cholesterol, HDL, LDL, TG, oxidized LDL, antibodies against LDL	oxLDL decrease, HDL increase
Moreno-Luna 2013	2-period cross-over RCT, 2m run in, 2 w wash out	24 mild hypertensive young women, mean age 26 y	VOO 60 ml/d for 2 m, PC 564 mg/kg DIP 31.0 mg	ROO 60 ml/d for 2 m, PC 0 mg/kg; DIP 0 mg	Not described	BP, Nitrite/Nitrate, ADMA, oxLDL, CRP	Reduction of S- and D-BP and ADMA levels
Moschandreas 2002	2-period cross-over RCT, 2 w run-in, 2 wash out	25 healthy subjects, all smokers, 14 f, 11 m, mean age 30 y	VOO 76 ml/d for 3 w, PC 308 mg/kg DIP 21.6 mg	ROO 76 ml/d for 3 w, PC 43 mg/kg DIP 3.0 mg	Not described	Total cholesterol, LDL, HDL, TG, oxidisability of LDL and HDL, malondialdehyde	No significant group differences
Ramirez-Tortosa 1999	2-period cross-over RCT, 3 m wash out	24 males with PVD, mean age 69.9 y	VOO, no exact amount given, for 3 m, PC 800 mg/kg DIP n.e.	ROO, no exact amount given, for 3 m, PC 0 mg/kg	Dietary assistance, recomm. to quit smoking, walk 1 km/d	LDL, HDL, TG, oxidisability of LDL, oxLDL uptake by macrophages	Higher TG and lower LDL levels, lower oxLDL uptake by macrophages
Visioli 2005	2-period cross over RCT 3 w run-in, 4 w wash out	22 healthy subjects, 10 f, 12 m, age 18–65 y	VOO 40 ml/d for 7 w PC 181 mg/kg DIP 6.7 mg	ROO 40 ml/d for 7 w PC 2 mg/kg DIP < 0.01 ml	Not described	Total cholesterol, LDL, HDL, TG, plasma antioxidant capacity	Increased plasma antioxidant capacity
Vissers 2001	2-period cross-over RCT, 2 w run-in resp. wash out	46 healthy subjects, 32 f, 14 m, age 18–58 y	VOO 69 ml/d for 3 w, PC 308 mg/kg, DIP 19.5 mg	ROO 69 ml/d for 3 w, PC 43 mg/kg DIP 4.3 mg	Diet low in vitamin E	Total cholesterol, LDL, HDL, TG, oxidisability of LDL and HDL, malondialdehyde	No affection on plasma lipids and markers of oxidation

VOO: virgin olive oil (=HPOO); ROO: refined olive oil without/with reduced phenolic content (=LPOO) DIP daily intake of phenols; PC: phenol content; S-/D-BP: systolic/diastolic blood pressure; TG: plasma triglycerides; ADMA: asymmetric dimethylarginine; PVD: peripheral vascular disease; CHD: coronary heart disease.

Table 3
Risk of bias.

Author, year	Bias						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Covas, 2006	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Fito, 2005	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Marrugat, 2004	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Moreno-Luna, 2012	Low risk	Unclear risk	High risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Moschandreas, 2002	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Ramirez-Tortoza, 1999	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Visioli, 2005	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk
Vissers, 2001	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk

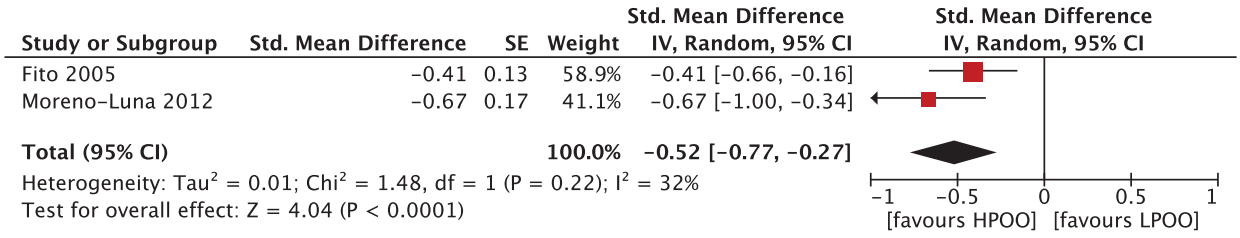

Fig. 2. Effects of HPOO vs. LPOO on systolic blood pressure.

Analysis of overall-effects

Blood pressure: Evidence for a medium effect lowering systolic blood pressure was revealed by meta-analysis ($n = 69$; SMD −0.52 CI −0.77/−0.27; $p < 0.01$; see Fig. 2). No effect was found for diastolic blood pressure ($n = 69$; SMD −0.20; CI −1.01/0.62; $p = 0.64$; see Fig. 3).

oxLDL: Small effects were found on decreasing the oxLDL-level ($n = 300$; SMD −0.25; CI [−0.50/0.00]; $p = 005$; see Fig. 4).

Malondialdehyde: No effect was found on malondialdehyde ($n = 71$; SMD −0.02; CI [−0.20/0.15]; $p = 0.79$; see Fig. 5).

Total cholesterol: No effect was found on total cholesterol ($n = 400$; SMD −0.05; CI [−0.16/0.05]; $p = 0.33$; see Fig. 6).

HDL: No effect was found on HDL ($n = 400$; SMD −0.03; CI [−0.14/0.08]; $p = 0.62$; see Fig. 7).

LDL: No effect was found on LDL ($n = 400$; SMD −0.03; CI [−0.15/0.09]; $p = 0.61$; see Fig. 8).

TG: No effect was found on TG ($n = 360$; SMD 0.02; CI [−0.22/0.25]; $p = 0.90$; see Fig. 9).

Safety

Data about adverse events was only reported in two studies (Vissers et al. 2001; Covas et al. 2006). Both of them did not mention adverse events. Vissers et al. (2001) assessed furthermore serum liver enzyme levels (AST/ALT) to see whether the pharmacologic properties of phenols which presumably affect the liver function may where harmful. They detected no increase of the mentioned enzyme levels.

Sub group analysis

Type of participants

We found no substantial changes for all but one outcome between studies with healthy participants compared to such with CVD patients included. The oxLDL decreasing effect was not detected in healthy patients ($n = 230$; SMD −0.07; CI [−0.17/0.02]; $p = 0.12$) but in CVD patients ($n = 70$; SMD −0.47; CI [−1.04/0.09]; $p = 0.1$); see Fig. 4.

Duration of intervention

This subgroup analysis was applicable for total cholesterol, HDL, LDL and TG. We did not find substantial changes for any of those outcomes between studies with mid-term (<2 w; >6 w) and semi-long-term (<6 w; >3 m) interventions.

Results for total cholesterol: mid-term interventions (Vissers et al. 2001; Marrugat et al. 2004; Fito et al. 2005; Covas et al. 2006): ($n = 322$; SMD −0.02; CI [−0.14/0.10]; $p = 0.79$); semi long-term interventions (Ramirez-Tortosa et al. 1999; Visioli et al. 2005): ($n = 46$; SMD −0.26; CI [−0.54/0.02]; $p = 0.06$).

Results for HDL: mid-term interventions: ($n = 322$; SMD −0.06; CI [−0.15/0.02]; $p = 0.17$); semi long-term interventions ($n = 46$; SMD 0.16; CI [−0.50/0.82]; $p = 0.63$).

Results for LDL: in mid-term interventions: ($n = 322$; SMD −0.01; CI [−0.15/0.12]; $p = 0.83$); semi-long-term interventions ($n = 46$; SMD 0.10; CI [−0.44/0.82]; $p = 0.63$).

Daily intake of phenols

Only one study (Marrugat et al. 2004) provided a low DIP (3.4 mg/d) in the HPOO group thusly no subgroup analysis could be performed.

Sensitivity analyses

Studies with a low risk of selection bias had no effect for oxLDL as the only affected value. Other correlations between risk of bias (performance, detection) and altered results could not be detected.

Risk of bias across studies

As less than 10 studies were included in each meta-analysis, analysis of risk of publication bias was not possible.

Assessment of heterogeneity

We detected a low to moderate heterogeneity for SBP, malondialdehyde, total cholesterol, HDL and LDL (see Figs. 2, 5, 6–8). A considerable heterogeneity was found for DBP, oxLDL and TG (see Figs. 3, 4 and 9).

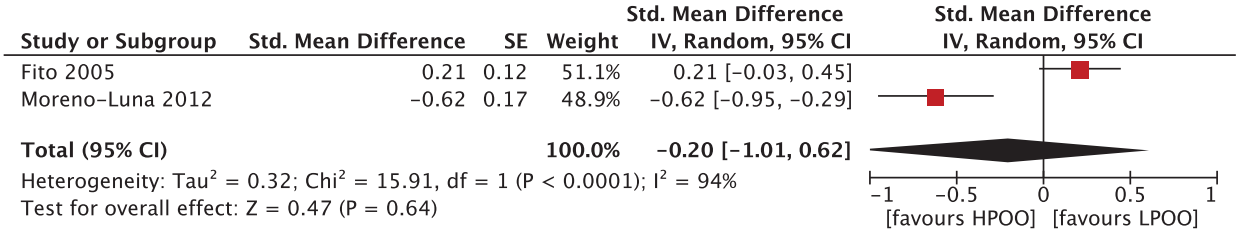

Fig. 3. Effects of HPOO vs. LPOO on diastolic blood pressure.

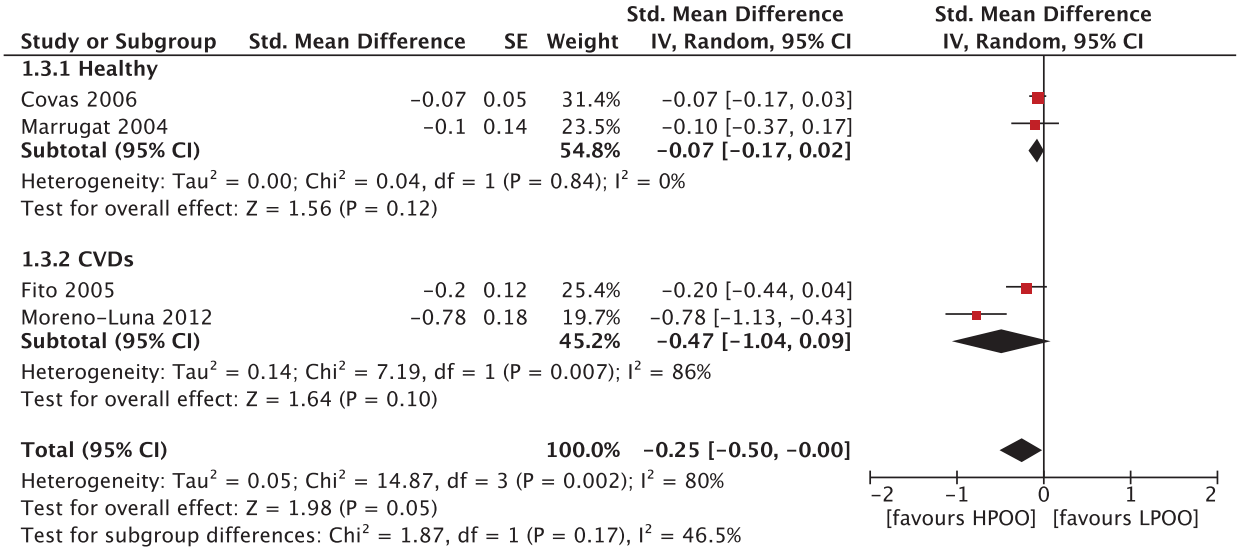

Fig. 4. Effects of HPOO vs. LPOO on oxLDL.

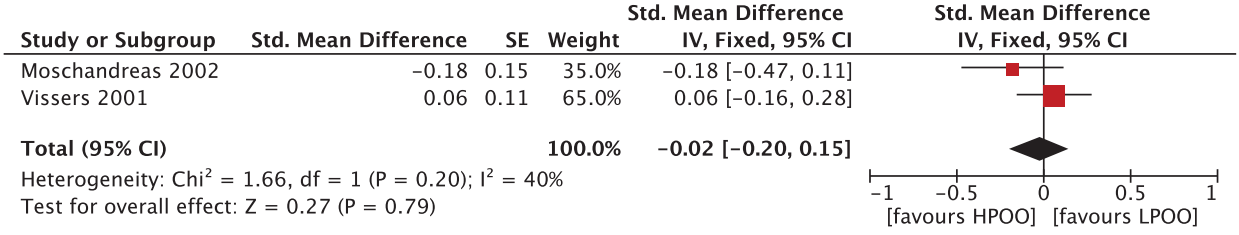

Fig. 5. Effects of HPOO vs. LPOO on malondialdehyde.

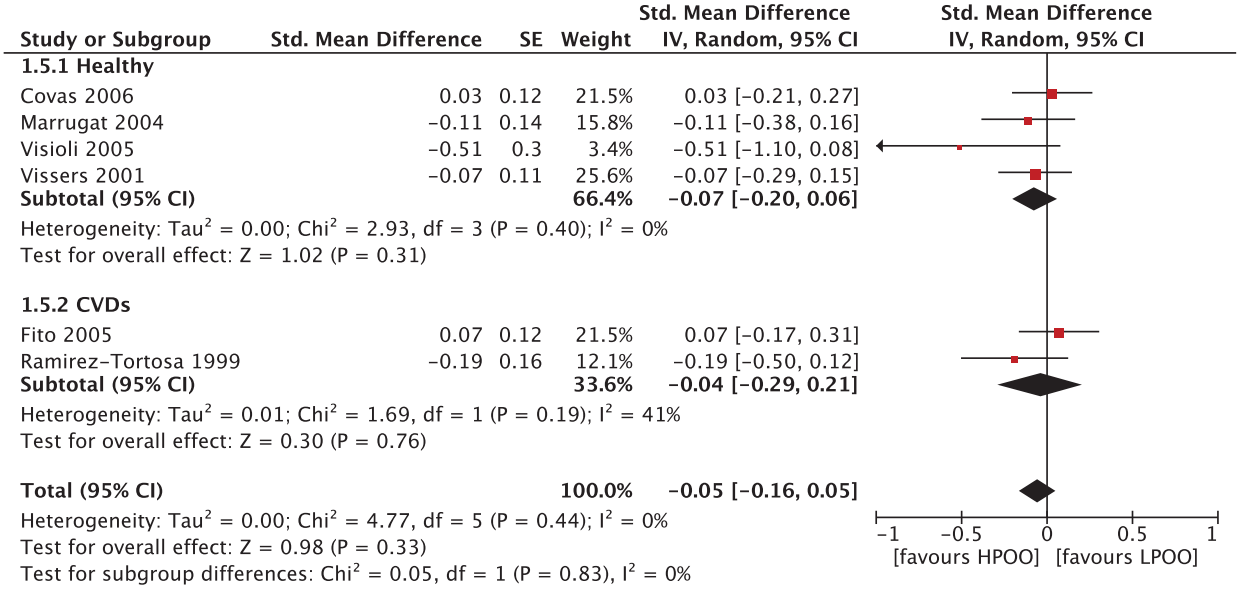

Fig. 6. Effects of HPOO vs. LPOO on total cholesterol.

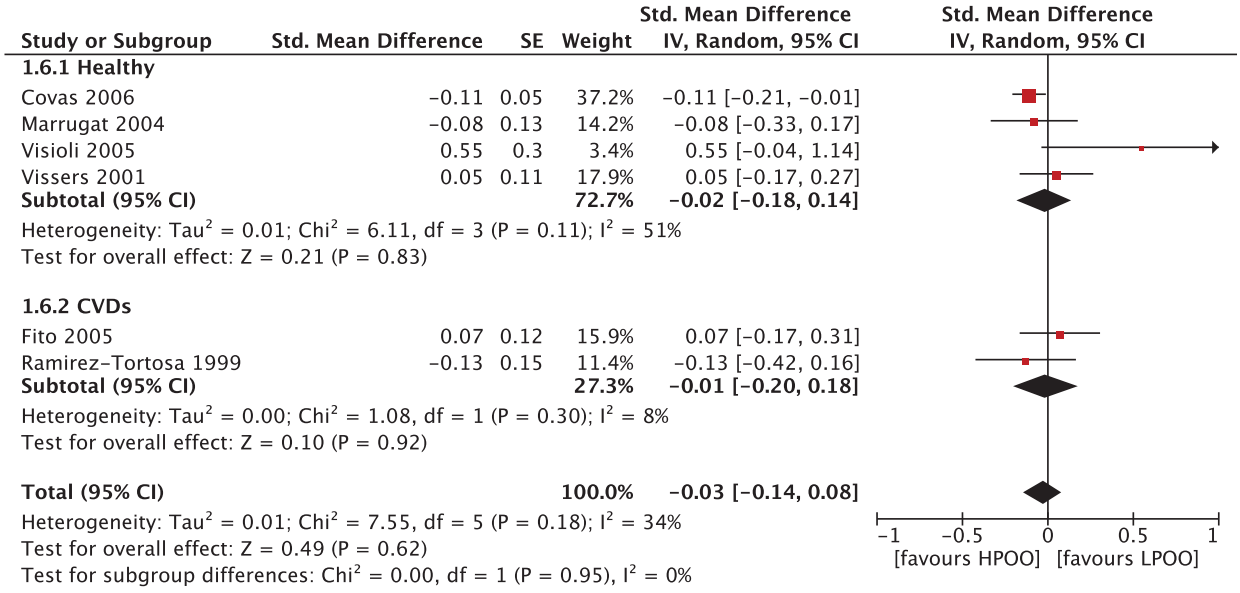

Fig. 7. Effects of HPOO vs. LPOO on HDL.

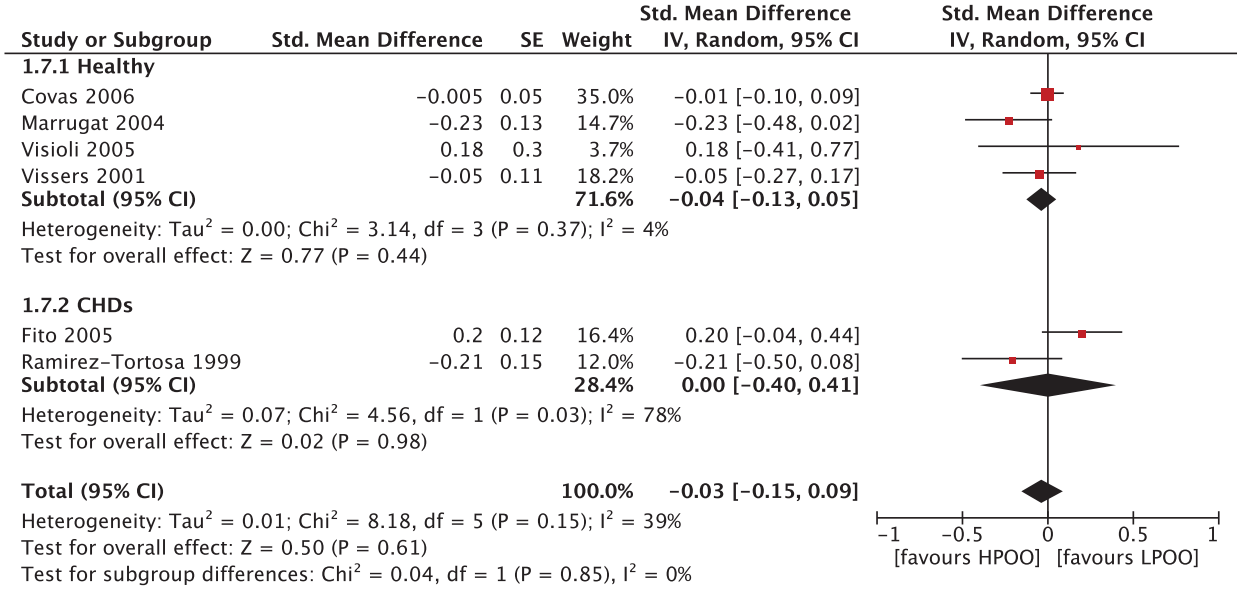

Fig. 8. Effects of HPOO vs. LPOO on LDL.

Discussion

Summary of evidence

High phenolic olive oils provide small beneficial effects on distinct cardiovascular risk factors such as systolic blood pressure and oxLDL while diastolic blood pressure, lipoproteins and malondialdehyde are not affected. The presently available data are too small for drawing a solid conclusion. The included trials can only hint towards the role of HPOO with respect to the effects of the Mediterranean diet. Seeing a traditional diet as a part of the individual lifestyle it is hardly possible to exclude many confounding factors.

Furthermore we found reasonable heterogeneity within groups/subgroups hinting that the studies might have been underpowered. The subgroup analyses revealed a bigger effect on oxLDL in the CVDs group. As a marker of oxidative stress an association exists between cardiovascular diseases and plasmatic oxLDL levels (Ho et al. 2013). Due to the use of differing units and measurement methods and a lack of standards we could not directly compare or classify the baseline oxLDL levels. In regard to the heterogeneous results one could draw two successive assumptions: CVD patients had higher baseline oxLDL levels. The anti-oxidative effect of polyphenols is bigger on high levels of oxLDL than on low.

For TG we could include 360 patients. Based on this reasonable number of participants the heterogeneous results may indicate that olive oil ingestion in general does not affect TGs. Conversely the small number of participants ($n = 69$) may reason the heterogenic findings for DBP.

Agreements with prior systematic reviews

The results of this review are in line with prior narrative qualitative reviews. The first review from 2007 (Fito et al. 2007) summarized that olive oil phenols improve the antioxidant capacity in general and especially the LDL resistance to oxidation. The most recent review confirmed this conclusion and added a nutrigenomic effect as decrease

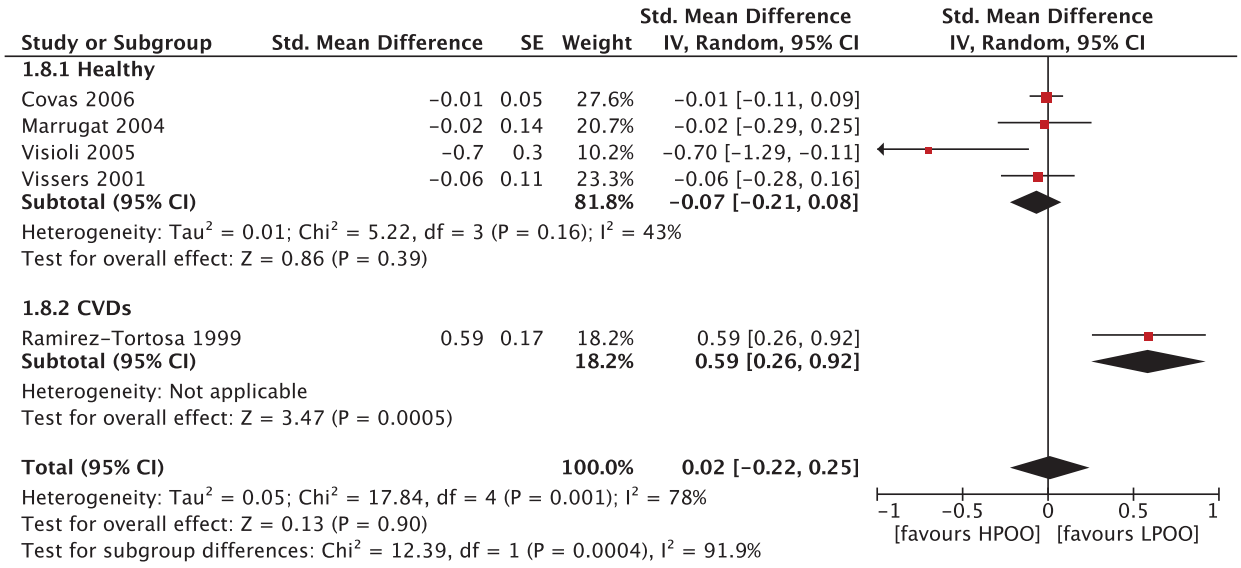

Fig. 9. Effects of HPOO vs. LPOO on TG.

of DNA oxidative damage and down-regulation of inflammatory and thrombogenic genes (Covas et al. 2009). To date no systematic review or meta-analysis about the topic exists.

External and internal validity

As HPOO has small effects on systolic blood pressure it could be advised as a dietary fat in the primary prevention of CVDs. Using it in secondary prevention could be considered because CVD patients gain at least little effects on their oxLDL levels and thusly HPOO could slow down the disease development.

Six of the eight included studies were conducted in Mediterranean countries. To achieve the same high level of daily oil consumption (respectively phenol intake) like in the trials HPOO has to be used as the primary source of fat. Only in Mediterranean countries olive oil is traditionally the primary source of fat. Thus it remains unclear if it would be feasible to establish a new primary source of fat into the everyday diet in non-Mediterranean countries. Therefore, the results of this meta-analysis are only partly applicable to patients who live outside the Mediterranean region and are using other traditional diets.

Due to the lack of reporting we could not assess the risk of bias completely. The assessable risks were mostly low and did not considerably influence the results in the sensitivity analysis.

Strength and weaknesses

This publication is the first systematic review and meta-analysis available on high phenolic olive oil and cardiovascular risk factors. Another strength is that we did apply no language restrictions.

The small number of included studies limits this review in first line. For some outcomes only two studies could be included. Unfortunately we could analyse only a small number of participants (n = 69) for the two improving risk factors (SBP, oxLDL). Due to the small numbers some outcomes are of considerable heterogeneity. Since the effect sizes were found to be small, the results should not be over interpreted. We could not clearly assess the risk of bias because it was incompletely reported.

Implications for further research

As the results indicate the effectiveness of HPOO this should be further evaluated in better powered trials and in intervention with longer observation periods. The study of Covas et al. (Covas et al. 2006) points to a putative dose-to-effect relationship. Therefore, dose-finding trials should also be considered. Furthermore, newer laboratory parameters assessing cardiovascular risk or estimating chronic inflammations, e.g. functional immunoassays, should be implemented in future studies assuming they could add to a deeper understanding of the protective mechanisms of HPOO in CVD. Clearly, these studies should follow more closely the guidelines of the CONSORT statement (Schulz et al. 2010) with regard to the reporting of methods.

Implications for clinical practice

This meta-analysis only delivers small evidence for the positive effects of HPOO on cardiovascular risk factors. But the results hint once more (Urpi-Sarda et al. 2012) that HPOO is one of the key features in the Mediterranean diet. Clinicians who implement the Mediterranean diet in their treatments should recommend the usage of HPOO to support the cardiovascular protecting effects. Regarding the good evidence for the Mediterranean diet (Rees et al. 2013) it can be further advised to use HPOO in this particular diet. As oxidative stress and blood pressure harm the cardiovascular system in long-term conditions, olive oil phenols should not be seen as short term pharmaceutical but high phenolic olive oils should be considered as a permanent nutraceutical.

Conflict of interest

None of the authors declare a conflict of interest.

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