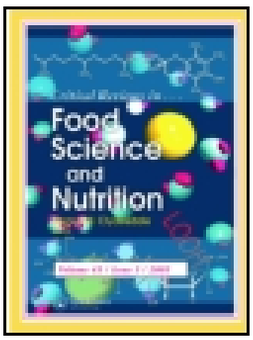

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Comparison of blood lipid-lowering effects of olive oil and other plant oils: A systematic review and meta−analysis of 27 randomized placebo−controlled clinical trials

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ABSTRACT

Objective: We aim to report a systematic review and meta-analysis of randomized controlled trials (RCTs) on effects of olive oil consumption compared with other plant oils on blood lipids.

Methods: PubMed, web of science, Scopus, ProQuest, and Embase were systematically searched until September 2017, with no age, language and design restrictions. Weighed mean difference (WMD) and 95% confidence interval (CI) were expressed as effect size. Sensitivity analyses and pre specified subgroup was conducted to evaluate potential heterogeneity. Meta-regression analyses were performed to investigate association between blood lipid-lowering effects of olive oil and duration of treatment.

Results: Twenty-seven trials, comprising 1089 participants met the eligibility criteria. Results of this study showed that compared to other plant oils, high-density lipoprotein level increased significantly more for OO (1.37 mg/dl: 95% CI: 0.4, 2.36). Also OO consumption reduced total cholesterol (TC) (6.27 mg/dl, 95% CI: 2.8, 10.6), Low-density lipoprotein (LDL-c) (4.2 mg/dl, 95% CI: 1.4, 7.01), and triglyceride (TG) (4.31 mg/dl, 95% CI: 0.5, 8.12) significantly less than other plant oils. There were no significant effects on Apo lipoprotein A1 and Apo lipoprotein B.

Conclusion: This meta-analysis suggested that OO consumption decreased serum TC, LDL-c, and TG less but increased HDL-c more than other plant oils.

KEYWORDS
Olive oil; Dyslipidemia; Low-density lipoprotein cholesterol; High-density lipoprotein cholesterol; Total cholesterol; Triacylglycerol

Introduction

Cardiovascular disease (CVD) continues to be the leading cause of death in the world (World Health Organisation 2013). Dyslipidemia and hypertension are the most important risk factors for CVD (Hohmann et al. 2015). Disability and death from CVD have undoubtedly multifactorial origin due to the interaction between genetic and environmental factors among which diet, particularly fatty acid composition, has probably the most important effects on CVD risk (Perez-Martinez et al. 2011). Having different fatty acid composition and un*saponifiable* components, edible fats and oils show different influences on serum lipid concentrations (Wagner, Tomasch, and Elmadfa 2001).

Mediterranean diet was shown to be effective in the primary and secondary prevention also treatment of CVD (Hohmann et al. 2015). Olive oil (OO) is the main source of fat in Mediterranean diet (Martínez-González, Dominguez, and Delgado-Rodríguez 2014). OO has a high content of monounsaturated fatty acids (MUFAs) specifically oleic acid and a low content of saturated fatty acids (SFAs) (Huang and Sumpio 2008). So that, fatty acids of OO are composed of 55 to 83% of oleic acid, 4 to 20% polyunsaturated fatty acids (PUFAs) and 8 to 14% SFAs also, contains almost 1 to 2% minor components such as phenolic compounds, tocopherols, triterpenes, pigments and sterols with biological properties (Covas, de la Torre, and Fito 2015). Some previous clinical studies found beneficial effects of MUFAs substituted for similar amount of SFAs on blood lipids (Gillingham, Harris-Janz, and Jones 2011). However, a recent meta-analysis of nine cohort studies reported that there was not any significant association between MUFAs intake and risk factors of CVD (Chowdhury et al. 2014).

Moreover, even though OO is the representative oil of the diet in Mediterranean countries, use of different types of vegetable oils like rapeseed oil (RO) and sunflower oil (SO) is popular in many other countries. There are several studies which compared the effects of olive oil rich diet with another type of vegetable oils on lipid profiles. Although some studies have demonstrated that there was no difference between lipid profile of OO rich diet consumption and other vegetable oils (Rozati

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et al. 2015; Nelson, Hokanson, and Hickey 2011; Cândido et al. 2017), other studies reported that consumption of OO resulted in less reduction of Low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) concentrations compared with diets rich in CO, SO or corn oil (Binkoski et al. 2005; Cicero et al. 2009; Maki et al. 2017).

Hence, it has remained unclear whether OO has more beneficial effects on lipid profile compared with other type of vegetable oils. The present systematic review and meta-analysis study has been designed to compare the effects of diets rich in OO with different types of vegetable oils on lipid profile including LDL-c, High-density lipoprotein cholesterol (HDL-c), triglyceride (TG), TC, Apo lipoprotein A1 (Apo A) and Apo lipoprotein B (Apo B).

Methods

Search strategy

We conducted a comprehensive and systematic search in the following electronic databases from inception through September 2017 without applying language and time restriction: PubMed, Scopus, Web of Science (ISI), ProQuest and EMBASE. We used the following search terms in title and abstract: ("Olive oil") AND ("lipid" OR "lipidemia" OR "hyperlipidemia" OR "dyslipidemia" OR "cholesterol" OR "hypercholesterolemia" OR "lipoprotein" OR "LDL" OR "low density lipoprotein" OR "HDL " OR "high density lipoprotein" OR "triglyceride" OR "hypertriglyceridemia" OR "Apolipoprotein A-I" OR "Apolipoprotein B" OR "Apo A1" OR "Apo B") AND ("Controlled Clinical Trial" OR "Randomized Controlled Trial" OR "intervention" OR "controlled trial" OR "randomized" OR "random" OR "randomly" OR "placebo" OR "assignment" OR "trial" OR "RCT" OR "Cross-over" OR "Parallel"). We identified only randomized controlled trials (RCTs) about the comparison of the effects of olive oil versus other edible plant oils on lipid profile. A manual search using the reference lists of all relevant studies and recent reviews were used to identify further eligible studies. Two studies did not report sufficient data and we contacted the corresponding authors for these values. But we received no response. This study was designed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA- checklist)(Moher et al. 2009).

Study selection

We applied the following criteria to include studies in the analysis: 1) Randomized controlled clinical trial in human with either crossover or parallel design. 2) Reporting the effect of olive oil and control groups on at least one of the lipid profile parameters (HDL-c, LDL-c, TC, TG, Apo A and Apo B) 3) Studies which used one of the plant oils as the control group for olive oil. 4) Studies involving adult participants (over 18 years old). 5) Intervention duration of at least two weeks. 6) Taking of at least 10 g/day olive oil. Animal studies, conferences abstracts, postprandial studies, non-clinical trial studies, studies on children and/or adolescents were not included. Moreover, studies which used olive oil combined with other oils or interventions such as EPA and DHA or olive oil enriched with polyphenol and plant sterols were excluded. Eligible studies were independently selected according to title and abstract by two authors (NG and AN) and discrepancies about the inclusion of studies were resolved by the third author (SF). Incomplete data of 2 studies were requested via sending emails by corresponding author (SF).

Data extraction and quality assessment

Data extraction, the risk of bias and quality assessment of included studies were done according to the Cochrane collaboration criteria independently by 2 authors (SG-NG) and disagreement was resolved by consultation. Following information was extracted from each article: first author's name, location of study, year of publication, study design, health status of participants, sample size, age and gender of participants, daily dose of olive oil, treatment duration and mean changes of blood lipids (HDL-c, LDL-c, TG, TC, Apo A and Apo B). Cochrane tool with 7 criteria was used to evaluate the quality of each article, including: selection bias (random sequence generation and allocation sequence concealment), performance and detection bias (blinding of participants and personnel and outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other probable sources of bias. The risk of bias in each included studies were rated as "low risk", "high risk" or "unclear risk".

Statistical analysis

Weighted mean differences (WMD) with 95% confidence interval (CI) for HDL-c, LDL-c, TG and TC levels were calculated for olive oil group and the controls. Mean changes of blood lipids were calculated by subtracting the end of study and baseline values. Standard deviations (SDs) of the net changes were calculated using following equation: $SD = \text{square root } [(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) = 0.5 (Higgins and Green 2011). To avoid data duplication, for studies with more than one measurement, only the end point values were used. If SD values were not available, they were calculated based on 95%CI or standard errors. Also, plot digitizer software was used to digitize and extract when the data was available only in the graphic form. Blood lipid levels were collated in mg/dl. Therefore, blood lipid values reported in mmol/L were converted to mg/dl. I^2 statistic and P value were used to analysis heterogeneity across the studies. A P value <0.1 or $I^2 > 50$ were considered as significant heterogeneity among the studies. The Random effect model was applied for all analysis. Sensitivity analysis was performed using a removed method by omitting one study or group of studies and repeating the analysis. Also, subgroup analyses were done for exploring the possible effects of olive oil versus other plant oils based on intervention duration (≤ 30 and > 30 days), age of participants (≤ 50 and > 50 years), comparison groups (omega3 rich oils (soya bean, rapeseed and flaxseed oil), omega6 rich oils (corn, sunflower and primrose oil), palm oil and Miscellaneous oils (argan, sesame, camellia, rice bran oil and mixture of soya bean and safflower

oil)), health status (Normolipidemic, hyperlipidemic and other disease) and type of olive oil (virgin, refined and not stated). Potential publication bias was assessed using visual inception of funnel plot asymmetry and further explored using Egger's and Begg's regression test. Duval and Tweedie's 'trim and fill' analysis was conducted to adjust any significant publication bias detected(Duval and Tweedie 2000). Random-effects meta-regression analysis were done using an unrestricted maximum likelihood method to explore the association between changes in blood lipid measurements, intervention duration of olive oil. All analyses were performed using STATA software version 13.0 (StataCorp, Texas, USA). A P value of < 0.05 was considered as statistically significant.

Results

Search results and study selection

Process of screening and study selection is presented in Figure 1. After removing duplicates, 2996 studies were identified through initial search of five databases. By reviewing title and abstract, 55 full-text articles were retrieved for further evaluation. In addition, one article was found through hand searching and reference checking. After that 29 articles were removed as follows; Seven articles because of the lack of any plant oils as a control group; five articles due to combining live oil with other intervention or supplements; three articles did not report blood lipid values; three studies were a duplicate report of another study; in five studies dose of olive oil was lower than 10 mg/day; in four studies duration of intervention was lower than two weeks; and two articles had not enough information about mean and SD of control and/or intervention group at baseline or endpoint of the intervention. Finally, 27 articles were included in the meta-analysis.

Study characteristics

Characteristics of eligible studies are summarized in Table 1. Thirteen of studies had crossover design and other studies were parallel. All studies were published between 1989 and 2017. Also, they were performed in European countries (n = 14), USA (n = 7), Asia (n = 2), Australia and Africa (each one 1 study). In total, 1089 subjects included in this meta-analysis and number of subjects for each study ranged from 12 to 145. More than half of the studies enrolled healthy subjects, nine studies were carried out on patients with hyperlipidemia and other studies included patients with non-alcoholic fatty liver disease (NAFLD), Metabolic syndrome, peripheral vascular disease and Rheumatoid arthritis. Among all studies, one study enrolled woman exclusively. Eight studies were conducted on men and eighteen studies were done on both sexes. Mean ages of participants were between 23 and 84 years approximately. Olive oil was compared with rapeseed oil (8 studies), sunflower oil (6 studies), corn oil (4 studies), palm oil (3 studies), soya bean oil (3 studies), Flaxseed oil (2 studies), or other plant oils including Soy bean/Safflower, Sesame, Primrose, Camellia, Peanut and Rice oil (each one 1 study). Virgin olive oil was used in 11 studies, refined olive oil in 6 studies and the remaining studies did not provide any information about the type of olive oil.

Most of the studies did not find significant differences in outcomes when olive oil was compared with other plant oils. In two studies, HDL-c increased significantly more in olive oil group

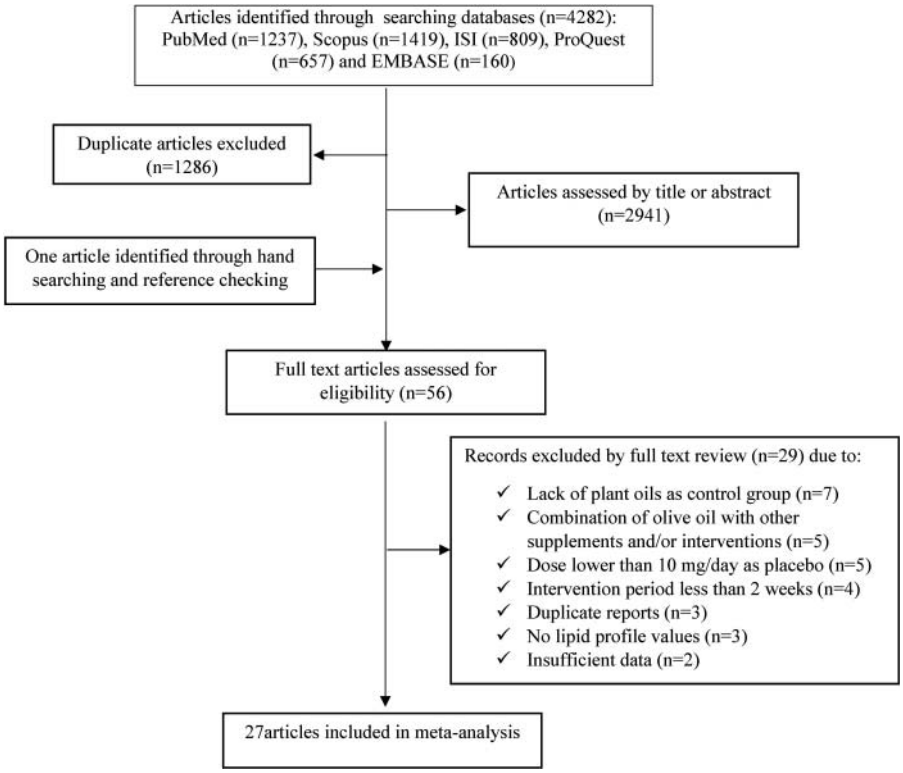

Figure 1. Flowchart of study procedure.

Table 1. Characteristics of 27 randomized controlled trials selected for Meta-analysis.

First author, country (year)	Sample size (sex)	Age (year)	Study design	Amount of olive oil intake	Intervention duration	Type of olive oil	Comparison group	Data presented	Health status	Results
Cândido et al. (2017)	41 (F)	27 ± 0.9	Parallel	25 ml/day	9 weeks	Virgin	Soybean oil	HDL, LDL, TG, TC	Overweight/ obese	No significant difference was found in outcomes when olive oil and soybean oil were compared.
Lucci et al. (2016)	145 (F & M)	63.2 ± 7.2	Parallel	25 ml/day	3 months	Virgin	Palm oil	HDL, LDL, TG, TC	Hyperlipidemia	No significant difference was found in outcomes when olive oil and palm oil were compared.
Rozati et al. (2015)	41 (F & M)	72 ± 1	Parallel	Not stated	3 months	Virgin	Soybean oil	HDL, LDL, TG	Overweight/ obese	No significant difference was found in outcomes when olive oil and soybean oil were compared.
Maki et al. USA (2016)	54 (F & M)	53.8 ± 1.3	Crossover	54 g/day	3 weeks	Virgin	Corn oil	HDL, LDL, TG, TC	Hyperlipidemia	LDL-c, TG and TC decreased significantly more in corn oil group compared to olive oil.
Kruse et al. (2015)	18 (M)	55 ± 7.3	Parallel	50 g/day	4 weeks	Refined	Rapeseed oil	HDL, LDL, TG, TC	Healthy	No significant difference was found in outcomes when olive oil and rapeseed oil were compared.
Nigam et al. (2014)	93 (M)	37.3 ± 6.4	Parallel	20 g/day	6 months	Not stated	Rapeseed oil (1) Soy bean/safflower oil (2)	HDL, TG	NAFLD	No significant difference was found in outcomes when olive oil and other oils were compared.
Namayandeh, Kaseb, and Lesan (2013)	48 (F & M)	41.7 ± 8.3	Parallel	60 g/day	1 month	Refined	Sesame oil	HDL, LDL, TG, TC	Hyperlipidemia	No significant difference was found in outcomes when olive oil and sesame oil were compared.
Kontogianni et al. (2013)	37 (F & M)	25.6 ± 5.9	Crossover	15 ml/day	6 weeks	Virgin	Flaxseed oil	HDL, LDL, TG, TC	Healthy	No significant difference was found in outcomes when olive oil and flaxseed oil were compared.
Tholstrup et al. Denmark (2012)	32 (M)	26.9 ± 10.3	Crossover	17% Energy of fat diet	3 weeks	Refined	palm oil	HDL, LDL, TG, TC	healthy	TG decreased significantly more in palm oil group compared to olive oil. But, TC and were significantly lower after the olive oil than palm oil.
Baxheinrich et al. (2012)	81 (F & M)	51.3 ± 10.2	Parallel	30 g/day	6 months	Refined	Rapeseed oil	HDL, LDL, TG, TC, Apo A, Apo B	Metabolic syndrome	TG decreased significantly more in Rapeseed oil group compared to olive oil.
Nelson, Hokanson, and Hickey (2011)	39 (F & M)	61.4 ± 7.4	Parallel	5/3% of total Energy	8 weeks	Not stated	Flaxseed oil	HDL, LDL, TG, TC	Healthy	No significant difference was found in outcomes when olive oil and flaxseed oil were compared.
Cicero et al. (2009)	22 (F & M)	50 ± 1	Parallel	Not stated exactly	45 days	Virgin	Corn oil	TC	Hyperlipidemia	TC decreased significantly more in Corn oil group compared to olive oil.
Derouiche et al. (2005)	60 (M)	23.4 ± 3.8	Parallel	25 gr/day	3 weeks	Virgin	Argan oil	HDL, LDL, TG, TC, Apo A, Apo B	Healthy	No significant difference was found in outcomes when olive oil and Argan oil were compared.
Binkoski et al. (2005)	31 (F & M)	46.2 ± 0.8	Crossover	half of the total fat diet	4 weeks	Not stated	Sunflower oil	HDL, LDL, TG, TC, Apo A, Apo B	Hyperlipidemia	LDL, APO A decreased significantly more in Sunflower oil group compared to olive oil.
Perona et al. (2004)	31 (F & M)	84 ± 7.4	Crossover	60 g/day	4 weeks	Virgin	Sunflower oil	HDL, LDL, TG, TC	hypertensive	LDL decreased significantly more in olive oil group compared to sunflower oil in healthy subjects but not in hypertensive.
Aguilera et al. Spain (2003)	20 (M)	65 ± 5.37	Parallel	Not stated exactly	4 months	Virgin	Sunflower oil	HDL, LDL, TG, TC, Apo A, Apo B	Healthy with peripheral vascular disease	No significant difference was found in outcomes when olive and sunflower oil were compared.
Karvonen et al. (2002)	68 (F & M)	51 ± 9	Parallel	30 g/day	6 weeks	Refined	Rapeseed oil (1) Camellia oil (2)	LDL, TC	Hyperlipidemia	No significant difference was found in outcomes when olive oil and other oils were compared.
Junker et al. (2001)	58 (F & M)	26 ± 5.3	Parallel	Not stated exactly	4 weeks	Refined	Rapeseed oil (1) Sunflower oil(2)	HDL, LDL, TC	Healthy	No significant difference was found in outcomes when olive oil and other oils were compared.
Pedersen et al. (2000)	18 (M)	24	Crossover	19% of total Energy	3 weeks	Virgin	Rapeseed oil (1) Sunflower oil(2)	HDL, TG, TC	Healthy	TG and TC decreased significantly more in Rapeseed oil and Sunflower oil groups compared to olive oil.
Castro et al. (2000)	22 (M)	23 ± 0.4	Crossover	40% Energy of fat diet	4 weeks	Not stated	Sunflower oil	HDL, LDL, TG, TC, Apo A, Apo B	Healthy	TC, LDL and Apo A increased significantly more in olive oil group compared to Sunflower oil.

Kris-Etherton et al. (1999)	22 (F & M)	34	Crossover	19% of total Energy	3 weeks	Not stated	Peanut oil	HDL, LDL, TG, TC, Apo A, Apo B	Healthy	No significant difference was found in outcomes when olive and Peanut oil were compared.
Nydahl et al. (1995)	22 (F & M)	54.2 ± 17.3	Crossover	30 g/day	3.5 weeks	Not stated	Rapeseed oil	HDL, LDL, TG, TC, Apo A, Apo B	Hyperlipidemia	No significant difference was found in outcomes when olive oil and Rapeseed oil were compared.
Choudhury, Tan, and Stewart Truswell (1995)	21 (F & M)	27.8 ± 8.4	Crossover	17% of total Energy	30 days	Virgin	Palm oil	HDL, LDL, TG, TC	Healthy	No significant difference was found in outcomes when olive oil and palm oil were compared.
Lichtenstein et al. (1994)	15 (F & M)	61 ± 13	Crossover	20% of total Energy	32 days	Not stated	Rice bran oil (1) Rapeseed oil (2) Corn oil (3)	HDL, LDL, TG, TC	Hyperlipidemia	LDL and TC decreased significantly more in Rapeseed, Rice bran and Sunflower oil groups compared to olive oil.
Kris-Etherton et al. (1993)	18 (M)	26	Crossover	81% of calories from fat	26 days	Virgin	Soybean oil	HDL, LDL, TG, TC, Apo A, Apo B	healthy	TG, TC and Apo B decreased significantly more in Soybean oil group compared to olive oil.
Sirtori et al. (1992)	12 (F & M)	47.4 ± 2.2	Crossover	Not stated exactly	6 weeks	Not stated	Corn oil	HDL, LDL, TG, TC, Apo A, Apo B	Hyperlipidemia	HDL increased significantly more in olive oil group compared to Corn oil.
Jantti et al. (1989)	20 (F & M)	44	Parallel	20 ml/day	12 weeks	Not stated	Primrose oil	HDL, TG, TC, Apo A, Apo B	Rheumatoid arthritis	HDL and Apo A increased significantly more in olive oil group compared to Primrose oil.

Abbreviations: F: female; M: male; HDL: high density lipoprotein-cholesterol; LDL: low density lipoprotein-cholesterol; TG: triglyceride; TC: total cholesterol; APO A: Apo lipoprotein A1; APO B: Apo lipoprotein B; RCT: randomized control trial; NAFLD: Non-alcoholic fatty liver disease

compared to corn and primrose oil (Jantti et al. 1989; Sirtori et al. 1992). TC in six studies (Castro et al. 2000; Cicero et al. 2009; Kris-Etherton et al. 1993; Lichtenstein et al. 1994; Maki et al. 2017; Pedersen et al. 2000), TG in five (Baxheinrich et al. 2012; Kris-Etherton et al. 1993; Maki et al. 2017; Pedersen et al. 2000; Tholstrup, Hjerpsted, and Raff 2011) and LDL-c in four studies (Binkoski et al. 2005; Castro et al. 2000; Lichtenstein et al. 1994; Maki et al. 2017) decreased significantly more in other plant oils group compared to olive oil. But, in two studies LDL-c and TC decreased significantly more in olive oil group compared to palm and sunflower oil (Perona et al. 2004; Tholstrup, Hjerpsted, and Raff 2011). In two studies Apo A increased significantly more in olive oil group compared to primrose and sunflower oil (Castro et al. 2000; Jantti et al. 1989). In one study, Apo B decreased significantly more in Soybean oil group compared to olive oil (Kris-Etherton et al. 1993). The study by Perona et al (Perona et al. 2004) evaluated effect of olive oil compared to sunflower oil on hypertensive and normotensive subject, separately. thus, we treated each intervention as a distinct trial. As a result, 2 effect sizes were extracted from this study for present meta-analysis. Assessment of the risk of bias in included studies was done based on standard methods recommended by Cochrane Collaboration (Table 2).

Effect of olive oil compared to other plant oils on blood lipids levels

Following olive oil consumption, serum TC decreased significantly less compared to other plant oils (WMD = 6.27 mg/dl: 95% CI: 2.8, 10.6; P = 0.001). As there was no heterogeneity in all included studies (I^2 = 46.4%, P = 0.05). Subgroup analyses indicated that when the studies were stratified according to different type of control groups, reduction of TC was significantly less for olive oil compared to W3 rich oils, W6 rich oils and miscellaneous oils but not for SFA rich oil. (Figure 2 & Table 3) In addition, TC significantly decreased less after olive oil consumption in subgroups of ≤ 50 years of age participants (WMD = 8.1 mg/dl: 95% CI: 4.6, 11.7) and ≤ 30 days intervention duration subgroup (WMD = 8.23 mg/dl: 95% CI: 4.13, 12.3) compared to other plant oils. In subgroup analysis for type of olive oil, refined not virgin olive oil decreased serum TC less (WMD = 5.21 mg/dl: 95% CI: 0.72, 9.7; P = 0.023). (Table 3)

Results of this meta-analysis showed that olive oil reduced LDL-c levels significantly less than other plant oil (WMD = 4.2 mg/dl: 95% CI: 1.4, 7.01; P = 0.003) with an insignificant heterogeneity (I^2 = 23%, P = 0.15). After stratification of control group according to different types of plant oils, reduction of serum LDL-c was significantly less in olive oil compared to miscellaneous oils (WMD = 6.43 mg/dl: 95% CI: 2, 11; P = 0.005). Furthermore, compared to other plant oils serum LDL-c significantly decreased less after olive oil consumption in the subgroup of ≤ 50 years of age participants (WMD = 7 mg/dl: 95% CI: 4.2, 9.76), after stratification of age as lower and higher than 50 years. Treatment with olive oil for ≤ 30 days, decreased LDL-c (WMD = 7 mg/dl: 95% CI: 3.8, 10.4) significantly less compared to other plant oils. (Figure 3 & Table 3) The analysis revealed a significant less reduction of LDL-c of olive oil

Table 2. Quality assessment of included studies based on the Cochrane guidelines.

study	ref	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Cândido et al. 2017		L	L	L	L	L	L	L
Lucci et al., 2015		L	U	H	H	L	L	L
Rozati et al. 2015		U	L	U	L	L	L	L
Maki et al., 2015		L	U	L	L	L	L	L
Kruse et al. 2015		L	U	U	U	L	L	L
Nigam et al. 2014		L	U	U	L	L	L	L
Namayandeh, Kaseb, and Lesan 2013		U	U	H	H	L	L	L
Kontogianni et al. 2013		U	L	L	L	L	L	L
Tholstrup et al., 2012		U	U	L	U	L	L	L
Baxheinrich et al. 2012		U	U	U	U	L	L	L
Nelson, Hokanson, and Hickey 2011		U	U	L	U	L	L	L
Cicero et al. 2009		L	U	H	H	L	L	L
Derouiche et al., 2004		U	U	U	U	L	L	L
Binkoski et al. 2005		U	U	L	U	L	L	L
Perona et al. 2004		U	U	H	U	L	L	L
Aguilera et al., 2004		U	U	H	H	L	L	L
Karvonen et al. 2002		U	U	U	U	L	L	L
Junker et al., 2002		U	U	H	U	L	L	L
Pedersen et al. 2000		U	U	L	U	L	L	L
Castro et al., 1999		L	U	L	L	L	L	L
Kris-etherton et al. 1999		U	U	U	U	L	L	L
Nydahl et al. 1995		U	U	U	U	L	L	L
Choudhury, Tan, and Stewart Truswell 1995		U	U	U	U	L	L	L
Lichtenstein et al. 1994		U	U	L	U	L	L	L
Kris-etherton et al. 1993		L	L	L	L	L	L	L
Sirtori et al. 1992		U	U	H	U	L	L	L
Jantti et al. 1989		U	L	L	U	L	L	L

L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

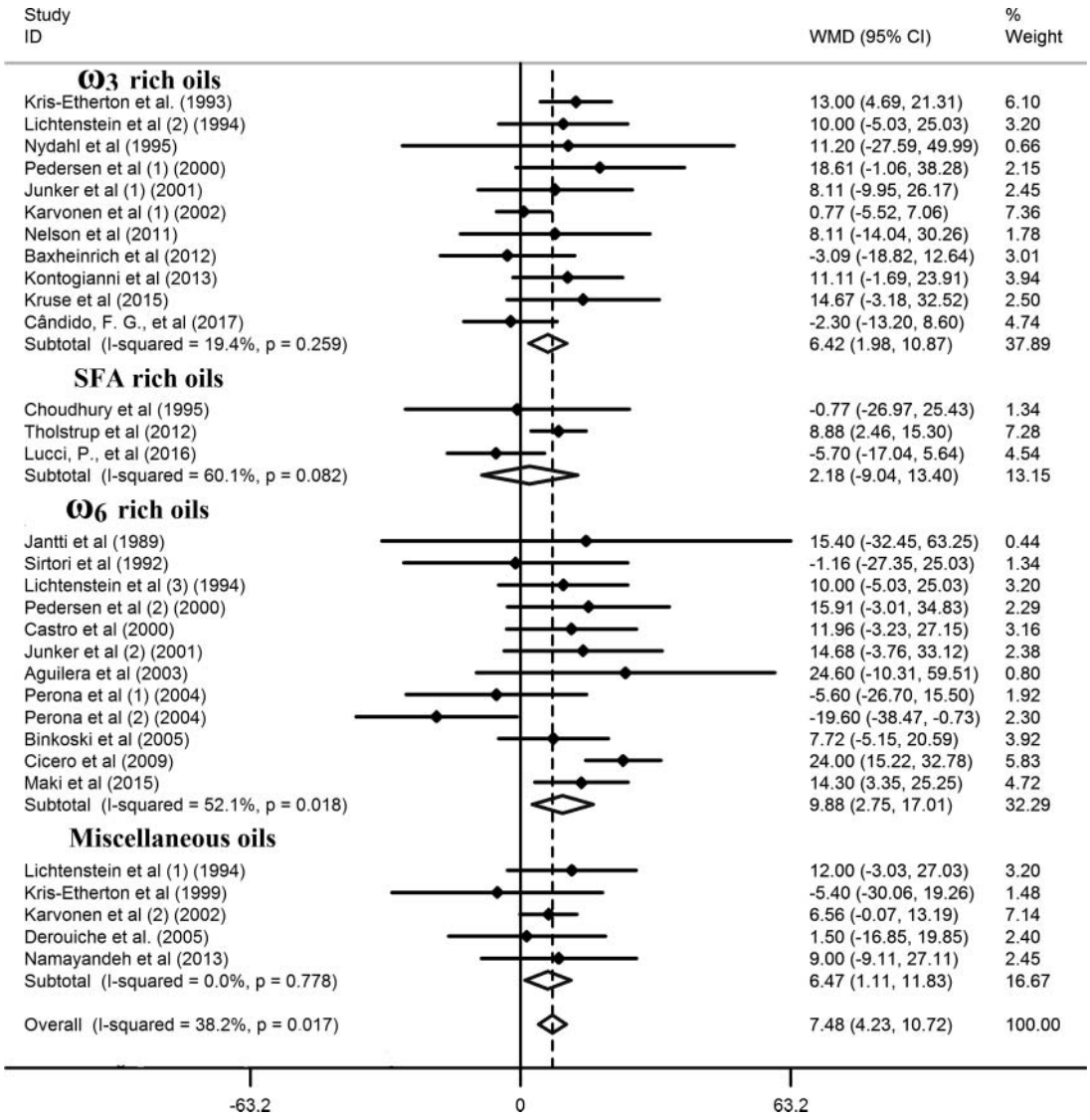

Figure 2. Random-effects meta-analysis comparing the effects of olive oil and other plant oils on net changes in Total cholesterol (TC) stratified by comparison groups.

consumers compared to other plant oils in normolipemic subgroup (WMD = 5.9 mg/dl: 95% CI: 2.65, 9.1). (Table 3)

Also, compared to other plant oils, HDL-c level increased significantly more for olive oil (WMD = 1.37 mg/dl: 95% CI: 0.4, 2.36; p = 0.007). Evidence of heterogeneity was also not identified between studies (I^2 = 0%, P = 0.81). After stratification of control group according to different types of plant oils, increase of serum HDL-c was significantly more in olive oil compared to W3 rich oils (WMD = 1.9 mg/dl: 95% CI: 0.5, 3.25; P = 0.008) and Miscellaneous oils (WMD = 4.11 mg/dl: 95% CI: 0.95, 7.3; P = 0.01). There were no significant differences in plasma HDL-c levels between different type of olive oil such as virgin and refine olive oil. However, subgroup analyses indicated that in > 30 days intervention duration (WMD = 1.77 mg/dl: 95% CI: 0.28, 3.27; P = 0.02), ≤ 50 years of age participants (WMD = 1.55 mg/dl: 95% CI: 0.4, 2.7; P = 0.01) (Figure 4 & Table 3) and normolipemic (WMD = 1.53 mg/dl: 95% CI: 0.17, 3; P = 0.03) subgroups, HDL-c significantly increased more after olive oil consumption compared to other plant oils. (Table 3)

Results of this meta-analysis found a borderline significant less decrease in TG serum levels after olive oil consumption compared with other plant oils (WMD = 4.31 mg/dl: 95% CI: 0.5, 8.12; P = 0.03). Heterogeneity between studies was not significant (I^2 = 0%, p = 0.7). In comparison of other plant oils, pooled effects size showed that olive oil decreased serum TG less than W3 rich oils (WMD = 8.32 mg/dl: 95% CI: 2.66, 14; P = 0.004). Also, in subgroup analysis for type of olive oil, virgin not refined olive oil decreased serum TG less (WMD = 7.75 mg/dl: 95% CI: 2.77, 12.7; P = 0.002). (Figure 5 & Table 3) But, there was no difference between serum TG changes in olive oil and other plant oil group, even after adjusting for intervention duration, age and health status of subjects. (Table 3)

As shown in Table 3, Apo A1 and B did not significantly change following olive oil consumption compared with other

Table 3. Comparison of Olive oil and other vegetables oil on serum lipids by, intervention duration, age, comparison groups, health status and Type of Olive oil.

	Subgroups	No[†]	WMD (95% CI)[*]	*P* value	I^2 (%) [§]	*P* for heterogeneity
TC	Overall	26	6.72 (2.8, 10.6)	0.001	46.4	0.05
	Intervention duration					
	≤ 30 day	14	8.23 (4.13, 12.3)	0.001	14.7	0.29
	> 30 day	11	5.9 (−1.32, 13.2)	0.11	65.3	0.001
	Age					
	≤ 50 years	14	8.1 (4.6, 11.7)	0.001	0	0.76
	> 50 years	12	5.6 (−2.12, 13.31)	0.15	70.3	0.001
	Comparison groups					
	ω_3 rich oils	11	6.4 (2, 10.87)	0.005	19.4	0.25
	ω_6 rich oils	12	9.9 (2.75, 17)	0.007	52.1	0.02
	SFA rich oils	3	2.2 (−9.04, 13.4)	0.7	60	0.08
	Miscellaneous oils	5	6.5 (1.11, 11.8)	0.02	0	0.8
	Health status					
	Normolipemic	14	6.9 (2.27, 11.5)	0.003	25	0.18
	Hyperlipidemia	9	8.1 (0.44, 15.7)	0.038	68.3	0.001
	Other disease	3	−0.21 (−13.4, 13)	0.97	13.5	0.32
	Type of Olive oil					
	Virgin	12	6.36 (−1.16, 13.9)	0.1	70.4	0.001
	Refine	6	5.21 (0.72, 9.7)	0.023	10.4	0.3
	Not stated	8	7.7 (0.84, 14.6)	0.03	0	0.95
LDL	Overall	24	4.2 (1.4, 7.01)	0.003	23	0.15
	Intervention duration					
	≤ 30 day	15	7.1 (3.8, 10.4)	0.001	11.6	0.32
	> 30 day	10	0.03 (−3.5, 3.56)	0.98	0	0.84
	Age					
	≤ 50 years	13	6.95 (4.2, 9.7)	0.001	0	0.66
	> 50 years	12	0.95 (−3.6, 5.48)	0.68	21.9	0.12
	Comparison groups					
	ω_3 rich oils	12	3.3 (−0.2, 6.7)	0.06	4.2	0.4
	ω_6 rich oils	10	5.23 (−0.2, 10.5)	0.051	22.6	0.23
	SFA rich oils	3	3.8 (−5.78, 13.4)	0.43	50.3	0.13
	Miscellaneous oils	5	6.43 (2, 11)	0.005	0	0.5
	Health status					
	Normolipemic	14	5.9 (2.65, 9.1)	0.001	9	0.35
	Hyperlipidemia	8	3.66 (−1.55, 8.87)	0.17	34.4	0.15
	Other disease	3	−2.3 (−11.82, 7.22)	0.64	0	0.42
	Type of Olive oil					
	Virgin	12	3.36 (−1.33, 8.05)	0.16	34	0.12
	Refine	6	5.04 (−0.96, 11.1)	0.1	57.3	0.04
	Not stated	7	4.84 (−1.32, 11)	0.12	0	0.87
HDL	Overall	26	1.37 (0.4, 2.36)	0.007	0	0.81
	Intervention duration					
	≤ 30 day	15	1.05 (−0.27, 2.4)	0.12	0	0.5
	> 30 day	11	1.77 (0.28, 3.27)	0.02	0	0.9
	Age					
	≤ 50 years	15	1.55 (0.4, 2.7)	0.01	0	0.9
	> 50 years	11	0.71 (−1.56, 3.01)	0.54	24.4	0.21
	Comparison groups					
	ω_3 rich oils	12	1.9 (0.5, 3.25)	0.008	0	0.84
	ω_6 rich oils	11	0.75 (−1.4, 2.9)	0.5	0	0.52
	SFA rich oil	3	0.76 (−1.2, 2.7)	0.44	0	0.65
	Miscellaneous oils	5	4.11 (0.95, 7.3)	0.011	49.1	0.097
	Health status					
	Normolipemic	15	1.5 (0.17, 2.8)	0.03	2	0.43
	Hyperlipidemia	7	1.24 (−0.96, 3.44)	0.27	0	0.9
	Other disease	4	0.42 (−2.68, 3.52)	0.8	21.2	0.28
	Type of Olive oil					
	Virgin	12	1.02 (−0.6, 2.64)	0.22	4.4	0.4
	Refine	5	1.02 (−0.9, 2.9)	0.3	6.6	0.37
	Not stated	9	2.3 (0.4, 4.2)	0.02	0	0.98
TG	Overall	25	4.31 (0.5, 8.12)	0.03	0	0.7
	Intervention duration					
	≤ 30 day	14	3.8 (−1.14, 8.7)	0.13	9.3	0.35
	> 30 day	11	5.7 (−1.9, 13.24)	0.15	0	0.81
	Age					
	≤ 50 years	14	3.35 (−1.23, 7.9)	0.15	7	0.37
	> 50 years	11	7.9 (−0.8, 16.54)	0.07	0	0.88
	Comparison groups					
	ω_3 rich oils	11	8.32 (2.66, 13.9)	0.004	0	0.9
	ω_6 rich oils	10	5.51 (−1.2, 12.2)	0.11	0	0.86
	SFA rich oils	3	−8.3 (−17.4, 0.8)	0.07	0	0.87
	Miscellaneous oils	5	3.9 (−7.7, 15.6)	0.5	0	0.9

(*Continued on next page*)

Table 3. (*Continued*)

	Subgroups	No[†]	WMD (95% CI)[*]	*P* value	I^2 (%) [§]	*P* for heterogeneity
	Health status					
	Normolipemic	14	3.9 (−0.84, 8.65)	0.1	12.2	0.32
	Hyperlipidemia	7	4.3 (−7.5, 16.1)	0.71	0	0.89
	Other disease	4	8.5 (−6.62, 23.6)	0.27	0	0.5
	Type of Olive oil					
	Virgin	12	7.75 (2.77, 12.7)	0.002	0	0.8
	Refine	4	−1.22 (−17.8, 15.4)	0.9	24.2	0.27
	Not stated	9	3.32 (−4.4, 11)	0.4	0	0.9
Apo A1	Overall	10	4.3 (−0.43, 9.01)	0.075	36.4	0.12
Apo B	Overall	10	4.05 (−0.64, 8.75)	0.09	38.6	0.1

[†]Number of records included the meta-analysis,
[*]Mean differences and 95% confidence intervals,
[§]I-squared (percentage of heterogeneity),
TC; total cholesterol, LDL; low density lipoprotein, HDL; high density lipoprotein, TG; triglyceride, Apo A1; apolipoprotein A1, and Apo B; apolipoprotein B.

plant oils. Since the Apo A1, and Apo B were reported by few trials, the subgroup analysis was not applicable for them.

Publication bias and sensitivity analysis

Potential publication bias was assessed by visual scanning of the funnel plots and Egger's regression test. Funnel plots had symmetric distribution and Egger's tests showed no sign of publication bias in current meta-analysis of HDL-c, LDL-c, TC and TG levels (P = 0.45, 0.47, 0.64, 0.9 respectively) (Figure 6 A-D). Sensitivity analysis showed that systematic removal of each studies did not significantly alter the overall effect of olive oil compared to other plant oils on HDL-c, LDL-c and TC. (Data not shown) However, excluding two studies done by Kris-Etherton et al. (1993) (Kris-Etherton et al. 1993) and Kontogianni et al. (2013) (Kontogianni et al. 2013) can apparently

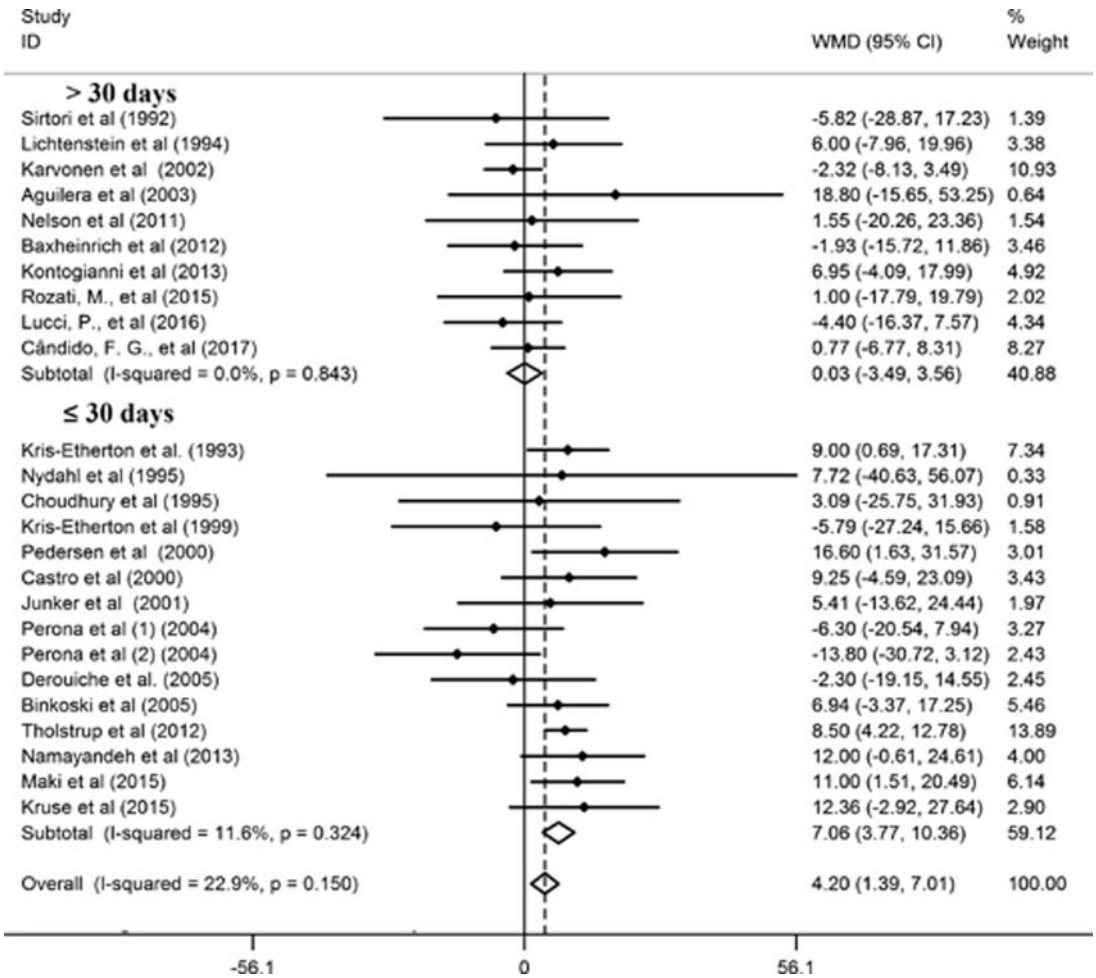

Figure 3. Random-effects meta-analysis comparing the effects of olive oil and other plant oils on net changes in Low-density cholesterol (LDL-c) stratified by intervention duration.

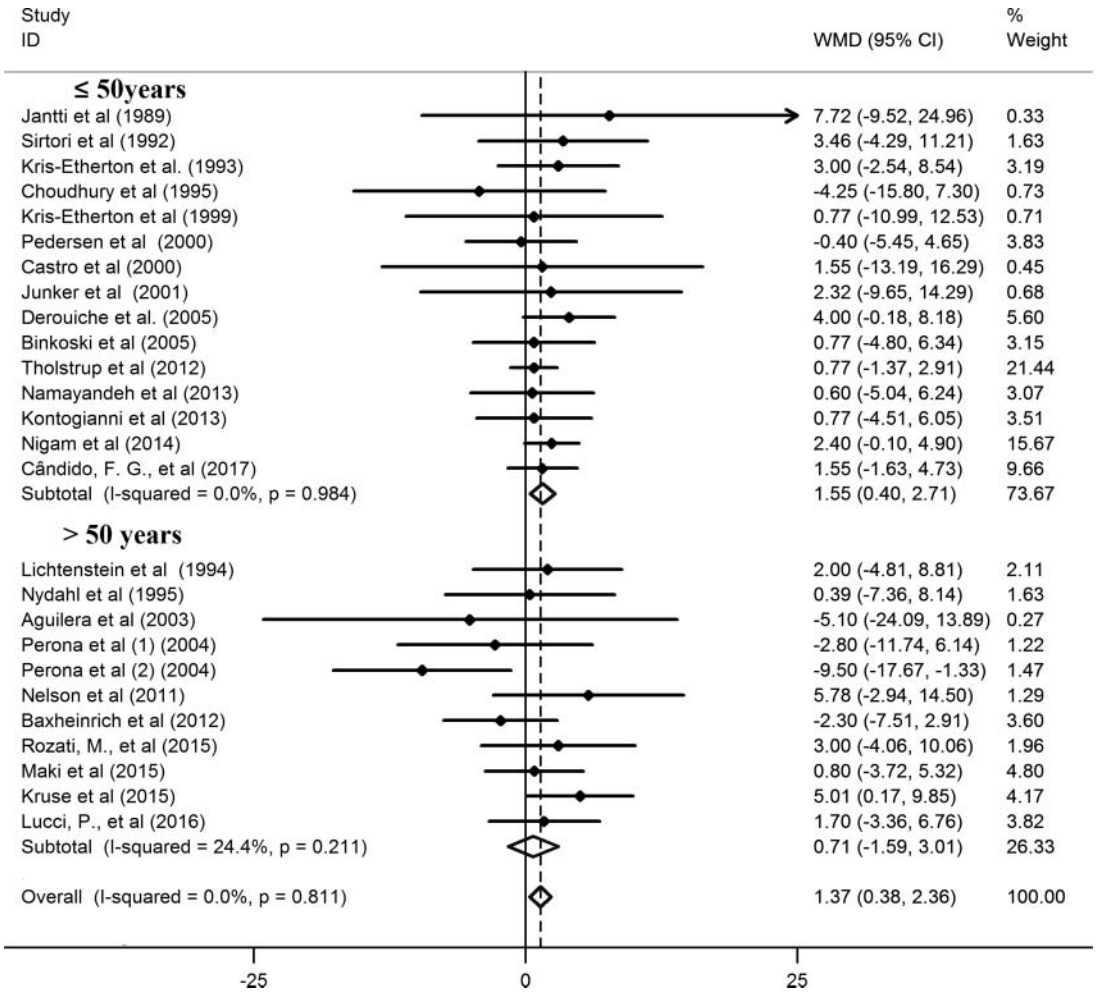

Figure 4. Random-effects meta-analysis comparing the effects of olive oil and other plant oils on net changes in High-density cholesterol (HDL-c) stratified by age groups.

change the effect of olive oil compared to other plant oils on TG to no significant result. (WMD = 2.5 mg/dl: 95% CI: −1.75, 6.8 and WMD = 3.75 mg/dl: 95% CI: −0.24, 7.75, respectively).

Meta-regression

We used univariate meta-regression analysis to assess the association of lipid profile levels changes and treatment duration (weeks). The results showed an inverse association of the changes in LDL-c and TC with duration of intervention (slope −0.7; 95% CI, −1.26, −0.14; P = 0.01 and slope −0.58; 95% CI, −1.4, −0.08;P = 0.03). However, Changes in HDL-c and TG had no association with treatment duration. (Figure 7 A-D)

Discussion

This meta-analysis showed that OO consumption could decrease TC, LDL-C, and TG concentration in lesser extent than other vegetable oils and increased HDL-C in much more extent. However, OO had no significant effects on Apo AI and Apo B.

Lower decreasing effects of OO on total and LDL-c may be due to its FA composition. The predominant FA of OO is Oleic acid (69%), and SFAs (13%), LA (8%), and ALA (1%) comprise the rest of it (Karvonen et al. 2002). It has been proposed that substitution of SFAs by both PUFAs and MUFAs could decrease serum cholesterol levels (Kralova Lesna et al. 2008, Mensink and Katan 1989, Trautwein et al. 1999). Furthermore, the most studies demonstrated n-3 and n-6 enriched oils effectively decreased TC, LDL-C, and HDL-C (Lichtenstein et al. 1994; Pedersen et al. 2000), whereas oleic acid was not as comparable as PUFAs in lowering total and LDL-cholesterol concentration (Sirtori et al. 1992). Consistently, Binkoski et al. reported that despite of having less SFAs content, OO rich diet changed serum lipoprotein levels the same as American diet. (Binkoski et al. 2005). Thereby, it could be attributed to low amount of PUFAs in OO rich diet. Moreover, Etherton et al. concluded that linoleic acid decreased cholesterol concentration more effective than oleic acid in normolipidemic young men (Kris-Etherton et al. 1993). N-3 PUFAs regulate gene expression and could affect lipid metabolism thorough induction of β-oxidation and inhibition of lipogenesis (Baltzell, Wooten, and Otto 1991). Other than FA composition, vegetable oils contain varieties of antioxidant and phytoesterols that may decrease serum cholesterol in different ways. Tocotrienols may inhibit hydroxy-methylglutaryl-coenzyme A reductase activity and cholesterol synthesis. Gama-orisanol enhances

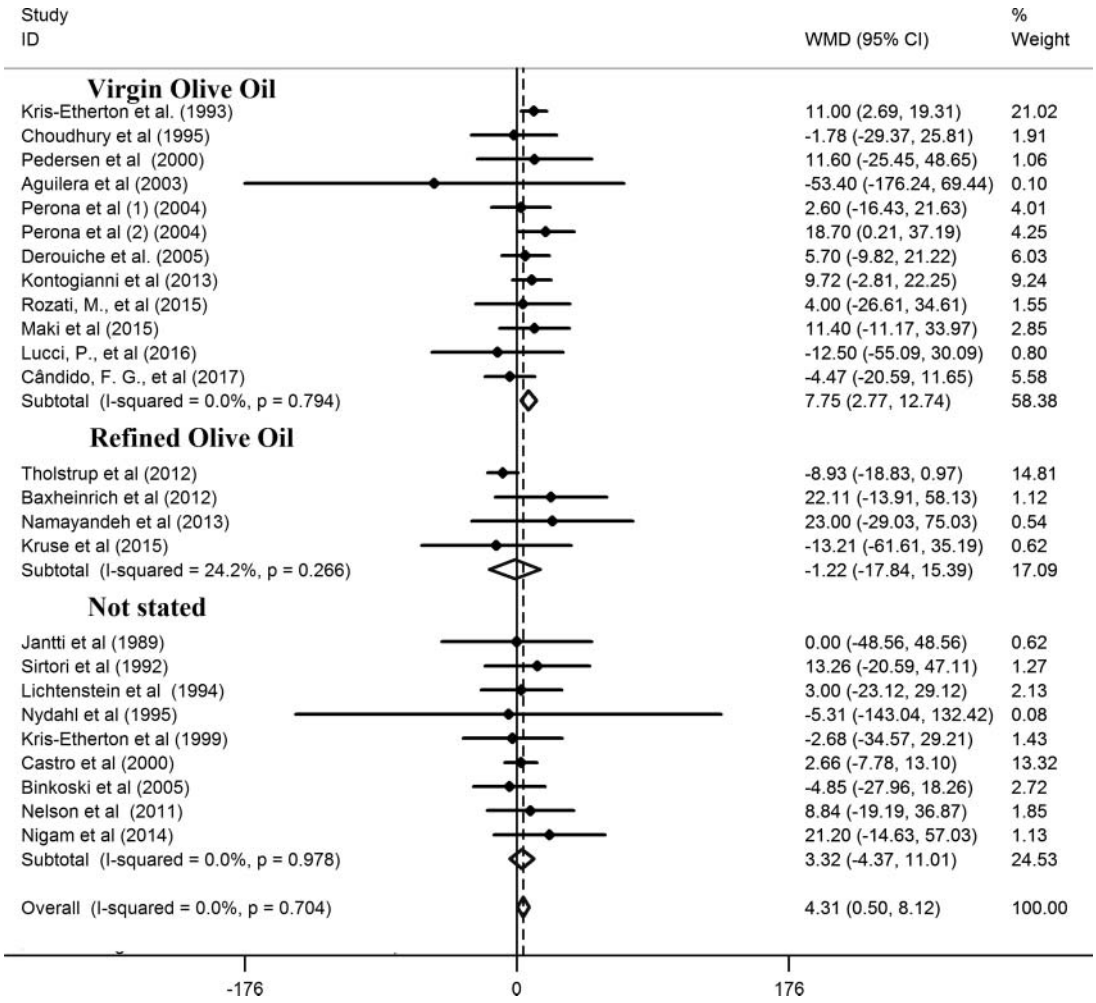

Figure 5. Random-effects meta-analysis comparing the effects of olive oil and other plant oils on net changes in triglyceride (TG) stratified by type of olive oil.

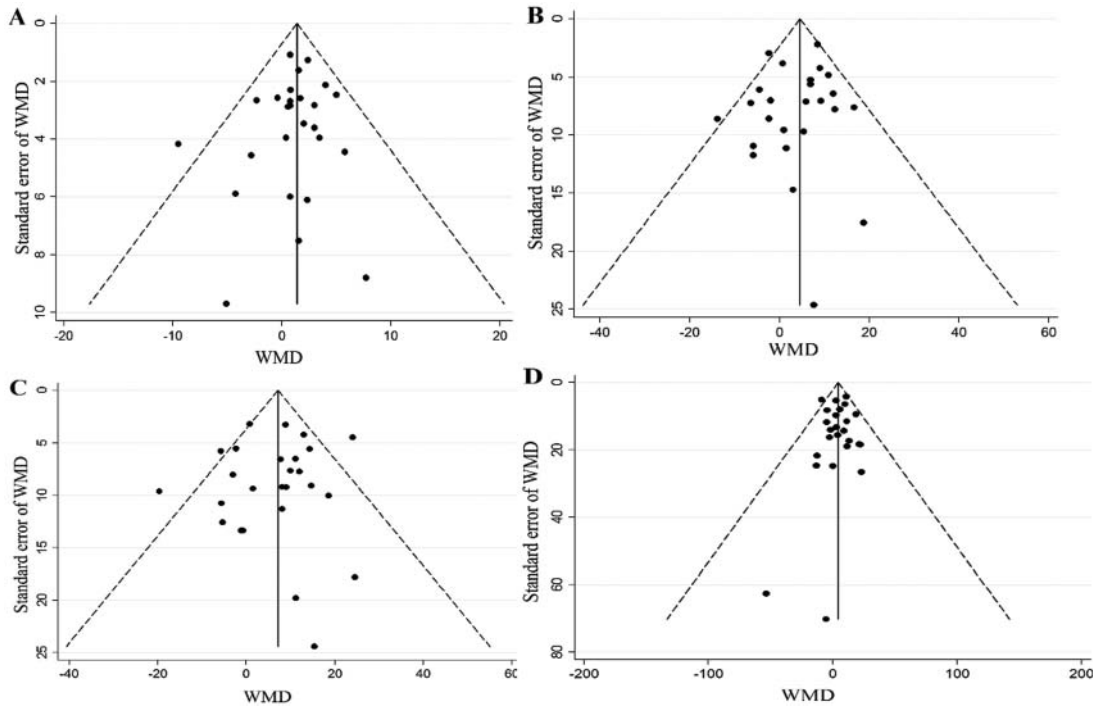

Figure 6. Funnel plots detailing publication bias in the studies selected for the analysis of olive oil's effects on high density lipoprotein (A), low density lipoprotein (B), total cholesterol (C) and triglyceride (D) comprised to other plant oils.

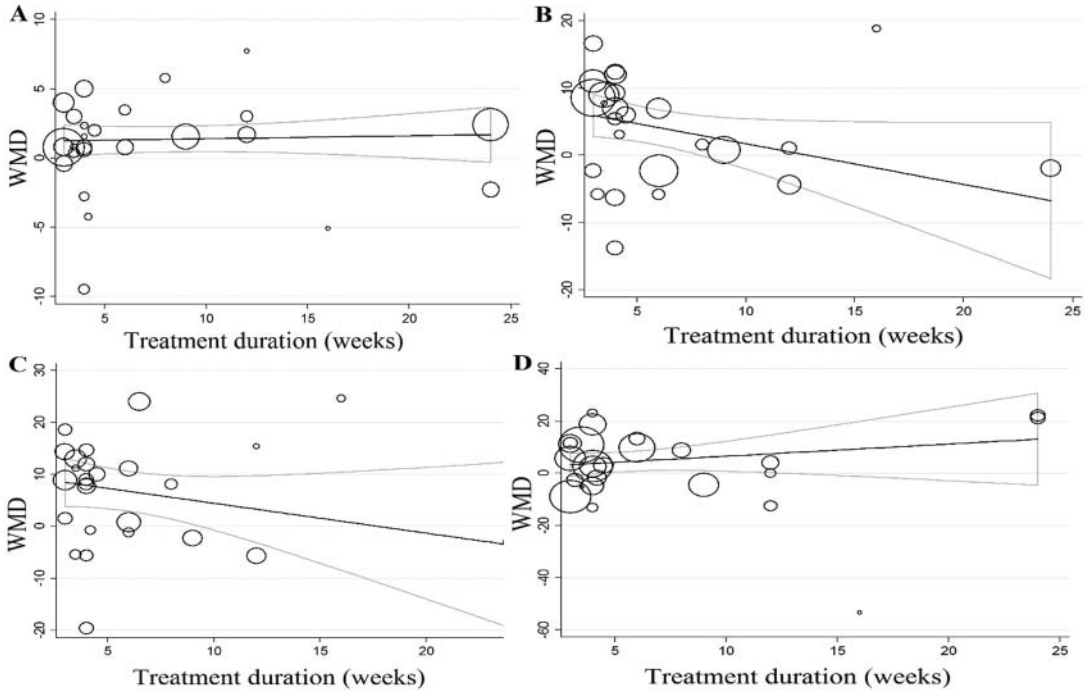

Figure 7. Meta-regression plots of the association between mean changes in high density lipoprotein (A), low density lipoprotein (B), total cholesterol, (C) and triglyceride (D) with treatment duration (weeks) of olive oil consumption comprised to other plant oils.

fecal excretion of cholesterol by reducing its intestinal reabsorption (Cicero and Gaddi 2001; Tanasescu et al. 2004). Furthermore, plant sterols have the same structure as cholesterol which reduce intestinal absorption of cholesterol molecules (Plat and Mensink2001). They also decrease cholesterol esterification by inhibition of cholesterol esterase, that attenuated cholesterol storage and LDL-C formation (Ostlund, Racette, and Stenson2002).

Similarly, results of subgroup analysis of this meta-analysis indicated n-3 and n-6 enriched oils were more potent than OO in decreasing TC. Besides, lowering effect of OO on LDL-C level was statistically significant compared to miscellaneous group which comprised of the oils rich in PUFAs, but in mixture amount of both fatty acids which were lower than oils placed in subgroup of n-3 or n-6 enriched group.

We found no significant differences between OO and Palm oil, as only SFA rich oil. However, as we mentioned above, when unsaturated FAs are substituted for SFAs, total and LDL-cholesterol will decrease. This controversy may be due to other components of palm oil as a vegetable oil. For instance, palm oil contains sterol that have hypo-cholesterolemic effect (Lucci et al. 2016). On the other hand, despite of its high amount of SFA, palm oil contains considerable amount of oleic acid (45% of total FAs) which may have lowering effect on cholesterol concentration, (Truswell 2000).

Furthermore, current study showed OO significantly enhanced HDL-C compared to control oils. Similarly, Mata et al. pointed out HDL-C was lowered followed by PUFA consumption vs. high MUFA diet (Mata et al. 1992). This finding was confirmed by some other studies (Berglund et al. 2007; Griffin et al. 1996; Thomsen et al. 2003). Also we found that compared to n-3 rich and miscellaneous groups, OO intake increased HDL-C which was consistent with mentioned evidences.

Moreover, we found a lesser lowering effect of OO on TC and LDL-C compared to control oils just in studies with intervention duration of lower than 30 days. On the other hand, OO increased HDL-C in higher than 30 days intervention subgroup. Therefore it is assumed that compared to short duration, long-term consumption of OO may result in more desirable lipid profiles.

Analysis conducted on age categories demonstrated OO significantly decreased TC and LDL-C and also increased HDL-C compared to control oils, just in under 50 years of age subgroup. Elderly people are more prone to dyslipidemia and need hypocholesterolemic drug treatment (Shanmugasundaram, Rough, and Alpert 2010). Taking hypo-cholesterolemic drugs may change serum cholesterol parameters more strong than diet modification, therefore different effects of experimental oils were not evident. In this regard, Wang et al. reported that combination of whole-grains and statins resulted in lower non-HDL-C concentrations and TC:HDL-C ratio compared to the group who did not use statins (Wang et al. 2014). On the other hand, the impact of OO consumption on LDL-C or HDL-C was only significant in normo-lipidemic subgroup that may be due to probable use of hypo-cholesterolemic drugs in hyperlipidemic patients. Moreover, disease were categorized in other diseases subgroup included metabolic disorders, inflammatory diseases and the like. Therefore, lipid profile may be affected by pathological causes of insulin resistance associated with dyslipidemia in metabolic syndrome (Drew et al. 2009; Roehrich et al. 2003). Furthermore, lower TC concentrations has been reported in patients with active rheumatoid arthritis (Jantti et al. 1989).

Despite of significant differences seen in TC, LDL-C, and HDL-C concentration, changes of serum Apo-AI and Apo-B were not different between studied groups. This controversy may be due to relatively low number of studies which assessed

apoproteins. Since Apo-B is an appropriate representer of atherogenic particles including chylomicrons, chylomicron remnants, VLDL, IDL and LDL, it could be more accurate than LDL-C alone to predict atherogenic properties of interventions (Klop, Elte, and Cabezas 2013). It is suggested that future studies measure apoproteins in addition to TC, LDL-C, and HDL-C.

Results of this meta-analysis showed that OO decreased TG level less than other vegetable oils, and subgroup analysis demonstrated more lowering effect of n-3 rich oils on TG. Similar results were reported by Tzang et al. that cotton seed oil decreased TG and cholesterol compared to butter and coconut oil (Tzang et al. 2009). Also, Fish oil as a rich source of n-3 FAs decreased serum TG level and change lipoprotein sub fractions (Baumstark et al. 1992).It is suggested that ALA could decrease serum TG levels by decreasing the activity of lipogenic enzymes such as FA synthetize, acyl coA carboxylase, and malic enzyme (Umesha and Naidu 2012). It also enhance β-oxidation and LpL activity in endothelium (Xu et al. 2013). N-3 PUFAs are the ligand of PPARs, inhibit SREBP, and decrease FA synthase (Poudyal et al. 2011). Moreover inhibit VLDL-C synthesis and apo-B100, thereby could decrease serum TG (Asadi, Shahriari, and Chahardah-Cheric 2010). On the other hand, some mechanisms were proposed for MUFA to lower serum TG level. MUFAs may have hypo-triacylglycerolemic properties by affecting enzymes and proteins involved in VLDL metabolism (McNamara 1992). Another well-known mechanism is involvement of cholesteryl ester transfer protein, which decrease TAG value as HDL concentration enhanced (Tall et al. 1987). However, we observed more potent impact of n-3 rich oils in decreasing serum TAG concentration compared to OO as a MUFA rich oil.

We found that subgroup of virgin OO lowered TC the same as other oils while refined OO was less effective. Higher antioxidant and phytochemical compounds in virgin OO may reflected this superiority compared to refined OO (Covas, de la Torre, and Fito 2015). Inconsistently, refined OO decreased TG the same as control groups. However, sensitivity analysis revealed that removing studies performed by Kris-Etherton et al. (1993) and Kontogianni et al. (2013) which assessed virgin OO, considerably changed the effect of OO on serum TG to nonsignificant. So, the interpretation of our results must be done with caution. Furthermore, as nine studies did not report the type of OO, which were categorized in "not stated" subgroup, the effect of OO on lipid parameters may be interpreted imprecisely.

Squalene is a hydrocarbon with hypercholesterolemic properties (Pedersen et al. 2000). OO contain extremely high amount of squalene compared to rapeseed oil and sunflower oil (Pedersen et al. 2000). Although Perona et al. did not find any relation between squalene and serum cholesterol levels, Madigan et al. showed the hypercholesterolemic properties of squalene in VOO (Perona et al. 2004; Madigan et al. 2000). Beside the high value of squalene, OO contains lower sterol compared to some other vegetable oils (Pedersen et al. 2000). Thus, it can be speculated that OO is not as effective as other vegetable oils in decreasing total and LDL- cholesterol.

Our meta-analysis had some limitations as follow: The doses of CO were reported in different units and different type of diets that we could not analyze them in subgroups; diets were consumed during intervention were not constant among all interventions, and included studies did not report energy and macronutrients composition. Thereby, we propose more accurate randomized clinical trials in future studies. Although we did not restricted our searches based on language, just studies from English databases were included and missed non-English articles may affect the final results. Finally, as this meta-analysis was based on published articles, potential publication bias could affect the results.

Conclusion

We concluded that OO was less potent than other vegetable oils in lowering TC, LDL-C, and TAG. This effect was more evident for PUFAs- rich oils, especially n-3 rich ones. However, the different impact of OO on TC, LDL-C, and TAG compared to control oils were disappeared in intervention duration higher than 30 days. Moreover, the impact of OO on serum lipoprotein levels was the same as plant sources of SFA. In addition, HDL-C increasing effect of OO was higher than other oils, just in higher than 30 days intervention duration.

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