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MASTERARBEIT

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„Effects of olive oil on inflammation markers and markers of endothelial function – a meta-analysis“

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List of abbreviations

ADMA=asymmetric dimethylarginine
ALA=α-linoleic acid
ARIC= the Atherosclerosis Risk In Communities study
ASA=acetylsalicylic acid
BP=blood pressure
CAA=carotid artery atherosclerosis
CAM=cell adhesion molecules
CARE=secondary prevention Cholesterol and Recurrent Events
CHD=coronary heart disease
CHF=chronic heart failure
CHO=diet high in carbohydrates
CLA=conjugated linoleic acid
CRF=chronic renal failure
CRP=C-reactive protein
CV=cardiovascular
CVD=cardiovascular disease
DHA=docosahexaenoic acid
EGCG=epigallocatechin 3-gallate
EPA=eicosapentaenoic acid
EVOO=extra virgin olive oil
FFA=free fatty acids
FO=flaxseed oil
HRT=hormone replacement therapy
ICAM-1=intercellular adhesion molecule-1
IL=interleukin
LVEF=left ventricular ejection fraction
MD=Mediterranean Diet
MI=myocardial infarction
MUFAs=monounsaturated fatty acids
NCI=National Cancer Institute diet

NO=nitric oxide

OA=oleic acid

OGLAs=oral glucose-lowering agents

OO=olive oil

Ox-LDL=oxidized-low-density lipoprotein

PBMCs=peripheral blood mononuclear cells

PBOO=plant based olive oil diet

PC=phenolic content [mg/kg]

PHS=Physicians' Health Study

PP=polyphenols [mg/100 g]

PUFA=polyunsaturated fatty acids

ROO=refined olive oil

ROS=reactive oxygen species

SFA=saturated fatty acids

SO=sunflower oil

T2DM=type 2 diabetes mellitus

TLCD=low-fat therapeutic lifestyle changes diet

TNF-α=tumor necrosis factor- alpha

VCAM-1=vascular adhesion molecule-1

VOO=virgin olive oil

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Zusammenfassung

Die Entstehung von kardiovaskulären Erkrankungen, Arteriosklerose (und deren Vorläufer, der endothelialen Dysfunktion) und Entzündungsprozessen im menschlichen Körper im Zusammenhang mit der Aufnahme von Speiseölen und -fetten wird kontrovers diskutiert. Zum Verzehr von Olivenöl gibt es hierzulande keine Empfehlungen. Das Ziel der vorliegenden Masterarbeit war es, randomisiert kontrollierte Langzeit-Diätinterventionen zu analysieren und die Auswirkungen der Olivenölinterventionen auf Inflammationsmarker und Marker der Endothelfunktion zu untersuchen. Olivenölinterventionen wurden in Form von Supplementen als Olivenöl-Kapseln oder durch Darreichung von Olivenöl in bestimmten Dosen (zum Teil im Rahmen einer Mediterranen Diät) durchgeführt und mit entsprechend gleichen Dosen einer Kontrolle verglichen. Folgende Biomarker wurden in die Meta-Analyse inkludiert: C-reaktives Protein, Interleukin-6, Tumornekrosefaktor α, Adiponektin, Intercellular Adhesion Molecule 1, Vascular Cell Adhesion Molecule 1, Flow-Mediated Dilatation, E-Selektin und P-Selektin. Insgesamt erfüllten 28 Studien alle Einschlusskriterien. Die Datenanalyse wurde mit Hilfe des Programms Cochrane Collaboration Review Manager 5.3. durchgeführt. Die Diäten mit der Olivenölintervention zeigten, im Vergleich zu den Kontrollen, eine signifikante Verbesserung des C-reaktiven Proteins [-0.56 mg/L (Konfidenzintervall -0.91, -0.21), p=0.002], des Interleukin-6 [-0.29 pg/mL (Konfidenzintervall -0.57, -0.02), p=0.04], des Intercellular Adhesion Molecule 1 [-0.02 ng/L (Konfidenzintervall -0.04, -0.00), p=0.02], der Flow Mediated Dilatation [0.66% (Konfidenzintervall 0.27, 1.05), p=0.0009] und des E-Selektin [-3.16 ng/mL (Konfidenzintervall -4.07,-2.25), p<0.00001]. Die Ergebnisse dieser Meta-Analyse zeigen, dass Olivenöl, insbesondere im Rahmen einer Mediterranen Diät, einen positiven Einfluss auf die Herz- und Gefäßgesundheit haben kann, deswegen sollte eine Empfehlung zum gesteigerten Verzehr von Olivenöl in Betracht gezogen werden.

Keywords: Entzündung, Endothelfunktion, Arteriosklerose, CVD

Summary

The development of cardiovascular diseases, arteriosclerosis (and their predictor, endothelial dysfunction) as well as inflammatory processes in human body in relation with the intake of dietary oils and fats is controversially discussed. For the consumption of olive oil, no dietary recommendation exists round here. The aim of the present Master's thesis was to analyze long-term, randomized controlled dietary intervention trials and to investigate the effects of olive oil interventions on inflammation markers and markers of endothelial function. Olive oil interventions were conducted in form of supplemental olive oil capsules or olive oil administered in defined amounts (partly in the frame of Mediterranean Diet) and compared to similar doses of controls. The biomarkers taken into account were C-reactive protein, interleukin-6, tumor necrosis factor α, adiponectin, Intercellular Adhesion Molecule 1, Vascular Cell Adhesion Molecule 1, Flow-Mediated Dilatation, E-selectin und P-selectin. A total of 28 studies met the inclusion criteria. Data analysis was performed using the Review Manager 5.3. software. Significant improvements in the olive oil intervention groups could be observed with respect to C-reactive protein [-0.56 mg/L (confidence interval -0.91, -0.21), p=0.002], interleukin-6 [-0.29 pg/mL (confidence interval -0.57, -0.02), p=0.04], Intercellular Adhesion Molecule 1 [-0.02 ng/L (confidence interval -0.04, -0.00), p=0.02], Flow Mediated Dilatation [0.66% (confidence interval 0.27, 1.05), p=0.0009] and E-selectin [-3.16 (confidence interval -4,07, -2.25), p<0.00001]. The results of this meta-analysis show that olive oil, especially in the frame of a Mediterranean Diet, can have a positive effect on heart and vascular health, therefore a recommendation for increased olive oil intake should be taken into consideration.

Keywords: Inflammation, endothelial function, arteriosclerosis, CVD

1. Introduction

1.1 Olive oil

Through pressing the ripe olive fruit of the olive tree, Olea europaea, olive oil is received, which is a tasty, flavoursome and nutritious edible fat. The quality of the olive oil is, amongst others, depending on the degree of maturity of the used olives, on the process conditions and on the duration of stocking. The quality classes of olive oil (table 1) are regulated by EU-law by means of manufacturing, sensory characteristics and content of free fatty acids (Ricci et al. 2004).

Table 1: Quality classes of olive oil (modified after: Rimbach et al. 2010)

Cate-gorie	**Appellation**	**Process of manufacture**	**Content of FFA per 100 g**	**Further properties**
1	Native olive oils	Only mechanical and physical methods		
1a	Native olive oil extra	Cold-pressed (1. pressing); gentle production	≤0.8 g	Excellent suitable for consumption; excellent taste
1b	Native olive oil	Cold-pressed; gentle production	≤2 g	Slight blemish; suitable for consumption
1c	Lampante oil		≥2 g	Very blemish; unfit for consumption
2	Refined olive oil	Refining of native olive oils	≤0.3 g	Suitable for consumption; characteristic smell and taste of olive oil lacking
3	Olive oil	Mix of native and refined olive oils	≤1 g	Suitable for consumption; taste dependent on mix ratio
4	Raw olive pomace oil	Extraction from olive pomace by solvent or physical method		Unfit for consumption
5	Refined olive pomace oil	Refining of raw olive pomace oils	≤0.3 g	Suitable for consumption; tasteless
6	Olive pomace oil	Mix of native olive oils and refined olive pomace oils	≤1 g	Suitable for consumption

Mechanical and physical methods=washing, decantation, centrifugation, filtration; solvent=hexan.

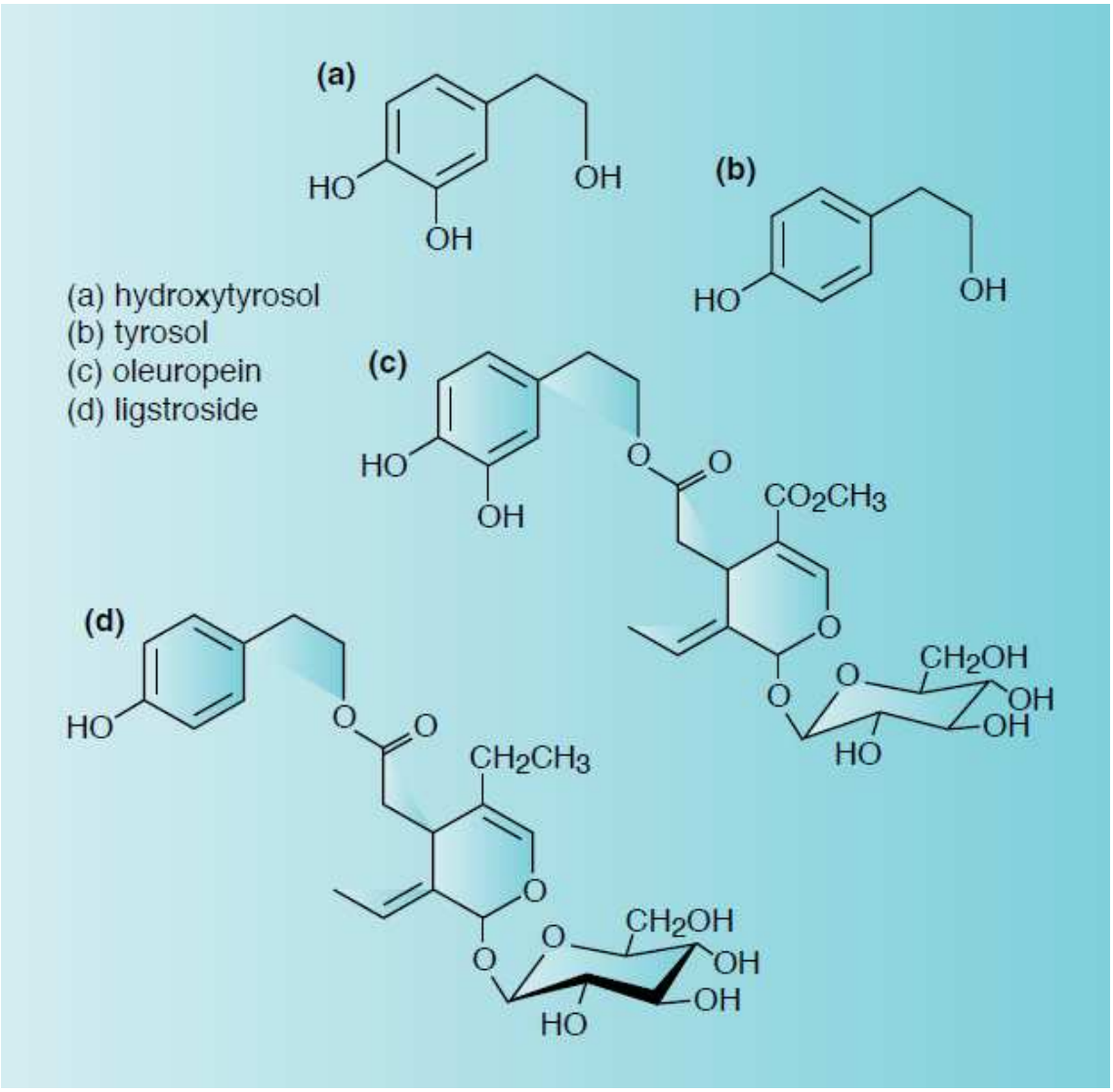
The fatty acid composition of olive oil (table 2) varies by region, cultivar, time of harvest, altitude and extraction process.

Table 2: Fatty acid composition of olive oil (modified after: Tous and Fergusen, 1996)

Fatty acid	**Chemical formula**	**Percentage**
Oleic acid	C18:1	55-83 %
Linoleic acid	C18:2	3.5-21 %
Palmitic acid	C16:0	7.5-20 %
Stearic acid	C18:0	0.5-5 %
α-Linolenic acid	C18.3	0-1.5 %

The minor constituents are consisting of lipid molecules one the one hand, like squalene, fatty alcohols, tocopherols, 4-methylsterols, triterpenic alcohols, polar pigments and plant sterols and on the other hand hydrophilic compounds, mostly polyphenols, of which at least 30 phenolic compounds can be differentiated (Tuck and Hayball 2002). The total phenolic content of an olive oil can vary between 196 and 500 mg/kg (Owen et al. 2000). The phenols in olive oil are divided into three classes: simple phenols, secoiridoids and lignans. Figure 1 shows some of the major olive oil phenols, whereupon hydroxytyrosol and tyrosol are simple phenols, oleuropein and ligstroside are secoiridoids (Owen et al. 2000; Perona et al. 2006).

Figure 1: Olive oil phenols (Waterman and Lockwood 2007)



This composition of potentially beneficial compounds is only present in virgin olive oils, while in ordinary or refined olive oils these minor components are lost through the refining process. Regardless of which sort of olive oil is used, it shows a high resistance to elevated temperatures because of its high monoun-saturated fatty acid (MUFA) content, and that is why it can be used more often for frying than polyunsaturated-rich oils (Esposito et al. 2009).

1.2 Markers of inflammation and endothelial function

To detect also minor changes in risk profiles for diverse diseases, in this master's thesis different biomarkers were analyzed. The importance of these biomarkers is not always clear, because the underlying mechanisms in human body are very complex and not fully understood. Of the markers of endothelial function, the E- and P-selectins are key primary adhesion molecules in the inflammatory process. They are expressed on the surfaces of activated endothelial cells, platelets and leukocytes and are mediating leukocyte trafficking and hemostasis, which are implicated in many human diseases (Ley 2003; Witz 2008; Laubli and Borsig 2010). The adhesion molecules are released as an answer to the formation of (interleukin) IL-1ß, IL-6, IL-8 and tumor necrosis factor-alpha (TNF-α), thus as a result of severe injury or subsequent onset of systematic inflammation (Siemiatkowski et al. 2001). Intercellular adhesion molecule-1 (ICAM-1) interacts with endothelium in the way that neutrophils are binding to ICAM-1 during the initiation of inflammation. ICAM-1, which is expressed on endothelial cells, is highly inducible upon stimulation (Kayal et al. 1998). Vascular adhesion molecule-1 (VCAM-1), as well as the selectins, acts in the adhesion of leukocytes to the endothelium, but also has a mechanical function. It therefore plays a role in the intercellular signal transduction. The upregulation of VCAM-1 is mainly activated by the cytokines TNF-α and IL-1 (Rao et al. 2007; Cook-Mills et al. 2011). To assess endothelial function, the standard non-invasive tool is the flow-mediated dilatation (FMD). If FMD is reduced, this is an early marker of atherosclerosis (Celermajer et al. 1992) and it can predict future cardiovascular disease events (Schroeder et al. 1999; Suessenbacher et al. 2005; Inaba et al. 2010). The principle of FMD is a nitric oxide (NO) assay (Koller et al. 1993; Green et al. 2011), but also other dilatory molecules, released from endothelium, may contribute to FMD, mostly prostacyclin (Koller et al. 1993) and endothelial-derived hyperpolarizing factor (Taylor et al. 1988; Bryan et al. 2005). In the literature, FMD is widely used, which represents its establishment in science. Of the inflammation markers, C-reactive protein (CRP) is the best studied (Martin-Moreno et al. 1994). It is produced by hepatocytes and regulated by upstream pro-inflammatory cytokines, for example inter-

leukin-6 (IL-6), circulating CRP is therefore massively elevated in response to inflammatory stimuli. In the past, assays were only able to detect the acute phase response of CRP, whereas nowadays “high sensitivity” immunoassays can also measure the circulating “baseline” levels and chronic low-grade inflammation (Casas et al. 2008). Serum CRP levels can predict long-term risk of incidence of myocardial infarction, ischemic stroke, peripheral vascular disease and all-cause mortality (Morrow 2007). In response to inflammatory stimuli, also IL-6 is formed by T cells, macrophages and endothelial cells, which propagates inflammatory cascades (Yudkin et al. 2000; Abeywardena et al. 2009). In several prospective studies, an association between circulating IL-6 levels and CHD risk was observed (Danesh et al. 2008). Although TNF-α is a relevant triggering factor during the inflammatory response, it has been rarely assessed in epidemiological studies (Kritchevsky et al. 2005). TNF-α is a cytokine which is mostly produced by monocytes and macrophages, but also lymphocytes, mast cells, keratinocytes, neutrophils, smooth muscle cells and some other cell types (Matthews 1981; Vassalli 1992). The formation of TNF-α is induced by many stimuli, such as cytokines including IL-1 and TNF-α itself or lipopolysaccharids (Tracey and Cerami 1994). Adiponectin is a major adipocyte-secreted adipokine, which has insulin-sensitizing and anti-inflammatory properties. In obesity and its related diseases, including type 2 diabetes and CVD, adiponectin is down-regulated, in contrast to most other adipokines (Zhu et al. 2008). In diabetic patients, an independent association of hypoadiponectinaemia with endothelial dysfunction, which was measured by FMD, was observed (Tan et al. 2004). In case of cardiovascular protection, it has been extensively studied.

In the following, the theoretical background and the state of the art referring to CVD and arteriosclerosis, endothelial function and inflammation are depicted. Derived from the hypothesis, the methodical approach and the results of the meta-analysis are presented. In the discussion, the results are highlighted and it is especially gone into the relevance of the used biomarkers.

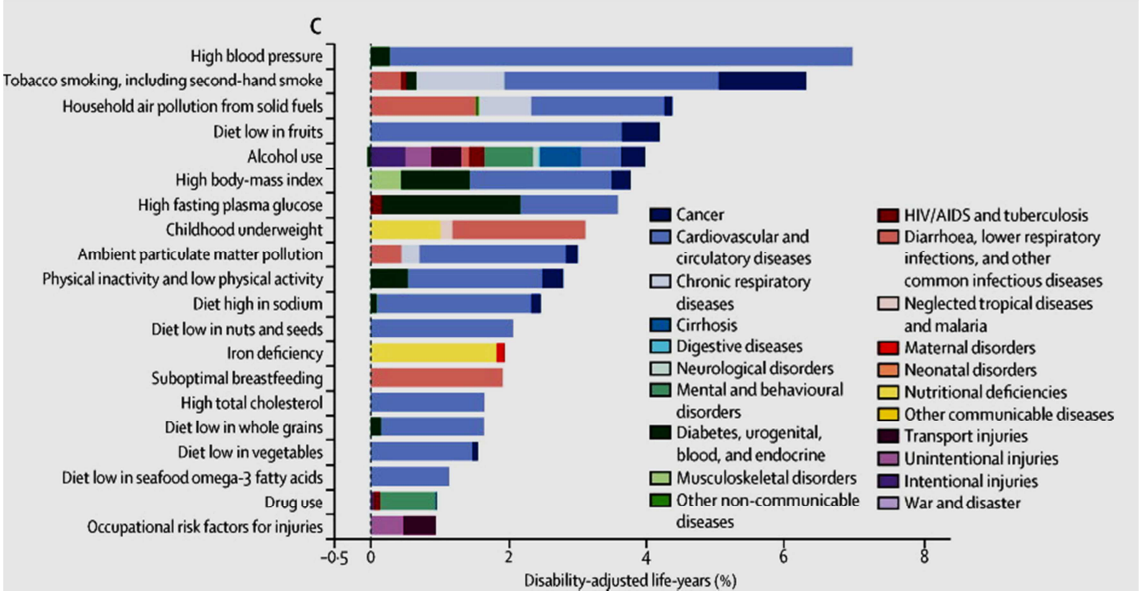
2. State of the art

2.1 CVD and arteriosclerosis

In industrialized countries, cardiovascular disease is the main cause of disability and death, whereas in other areas of the world, such as Japan and the Mediterranean countries, incidence rates are much lower than in Eastern and northern Europe and the USA (Plotkin et al. 2005). To explain this health advantage in Southern Europe, one prevalent mentioned factor is the traditional adherence to the Mediterranean diet, which is “rich in virgin olive oil as a major fat source, fruits, vegetables, legumes and other plant foods and low in saturated and trans fatty acids and cholesterol” (Perez-Martinez et al. 2007).

Risk factors for the development of CVD are high blood pressure, tobacco smoking (including second-hand smoke), diets low in fruits, household air pollution from solid fuels, high body-mass index, ambient particulate matter pollution, diets high in sodium, physical inactivity or low physical activity, diets low in nuts and seeds, high total cholesterol, high pasting plasma glucose, diets low in vegetables, diets low in whole grains, diets low in seafood omega-3 fatty acids, alcohol use, diets high in sugar-sweetened beverages and lead exposure (figure 2) (Lim et al. 2012).

Figure 2: Burden of disease attributable to 20 leading risk factors in 2010, expressed as a percentage of global disability-adjusted life-years (modified after: Lim et al. 2012).



Lipid accumulation in the artery wall has long been considered the primary cause of atherosclerosis. But now there is compelling evidence that inflammatory processes play an important role in the development of atherogenesis and also in the vulnerability of atherosclerotic lesions to rupture. They therefore are involved in all phases of atherogenesis. Critical early events in the pathogenesis of atherosclerosis are affected by “the recruitment of inflammatory cells from the circulation, their adhesion to the endothelial surface, and their final migration to the subendothelial space—a complex process mediated by inflammatory stimuli that involves cytokine production and up-regulation of adhesion molecules on endothelial cells and circulating peripheral blood mononuclear cells (PBMCs)” (Mena et al. 2009). Critical events in advanced stages of the disease are the development of instability and rupture of atheromatous plaques and also the appearance of ischemic events, such as myocardial infarction, stroke and sudden cardiac death (Bartelt et al. 2008; Lauritzen et al. 2008). Because inflammation plays such an important role in the pathogenesis of atherosclerosis, it was believed that dietary interventions would modify related inflammatory pathways. In fact, cross-sectional studies (Damsgaard et al. 2008; Damsgaard et al.

2009), feeding trials in Mediterranean populations (Eschen et al. 2004; Eschen et al. 2005) and the Nurses' Health Study (Gardella et al. 2001) ascertain that the Mediterranean diet has anti-inflammatory effects.

2.2 Endothelial function

Endothelial dysfunction, a predictor of atherosclerosis and CVD in patients with hypertension (Roos et al. 1997), is particularly characterized by a decrease in bioavailability of nitric oxide (NO) (Eschen et al. 2010) and an increase in levels of oxidized-low-density lipoprotein (ox-LDL) (Esposito et al. 2010). NO inactivation is dominated by perturbation of the L-arginine-NO pathway by oxidative stress, which leads to elevations of plasma asymmetric dimethylarginine (ADMA) (Genovese et al. 2009). Reactive oxygen species (ROS) are able to promote intracellular ADMA accumulation and are playing a role in ADMA export (Mazzon et al. 2009). A pro-oxidant status as well as an increase in ADMA are usual features of disease states associated with hypertension (Eschen et al. 2005) and atherosclerosis (Esposito et al. 2009; Genovese et al. 2009).

Vascular reactivity is strongly affected by food intake. A potential to improve endothelial function was shown for certain foods by short-term feeding trials, better than isolated nutrients or a healthy food pattern do (West 2001). Atherogenetic development may be slowed by some antioxidant compounds in food through limiting oxidative damage and restoring endothelial function (Karatzi et al. 2005). For example, polyphenol intake has been associated with low mortality rates caused by CHD (Hertog et al. 1995). Other studies indicate that endothelial function and lipid profile were improved by antioxidant and anti-inflammatory polyphenols (Zern et al. 2005). Therefore the minor components in virgin olive oil, especially the phenolic compounds may administer to health benefits.

2.3 Inflammation

On the one hand, to provide a full and effective immune response, complex and complementary mechanisms of inflammation as well as cell activation, antibody

synthesis and effector reactions are necessary. Therefore innate immune components such as granulocytes, natural killer cells, macrophages and belonging soluble mediators accompanied by more specialized adaptive lymphocytes are needed. Some evidence suggest that unsaturated fatty acids are able to influence plenty of immune system components, for example antigen presentation, cytokine production, lymphocyte proliferation, granulocytes and natural killer cell activity (de Pablo and Alvarez de Cienfuegos 2000; Calder 2003).

On the other hand, the baseline low-grade inflammation state, the postprandial state, in which humans reside most of the day, represents a stressful situation of homeostasis. This state is characterized by increased lipid pro-inflammatory particles released by human leucocytes and endothelial cells and increased oxidative stress (1997; 1997; Parks 2001). Vascular endothelium expresses vascular cell adhesion molecule-1 , ICAM-1, E- and P-selectins, whose levels are elevated over atherosclerotic plaques (Mead and Stenning 1997) and so appear to contribute to the development of atherosclerotic disease, as well as other increased inflammatory markers such as the number of white blood cells, serum amyloid A, nitric oxide (Ruano et al. 2005) and inflammatory cytokines (interleukin (IL)-1ß, IL-6, IL-8, and TNF- α) (Su et al. 1998).

3. Hypothesis

HO: Elevated intakes of olive oil, either in pure form or as supplemental capsules, have no impact on inflammation markers (CRP, IL-6, TNF-α, adiponectin) as well as on markers of endothelial function (ICAM-1, VCAM-1, FMD, E-selectin, P-selectin).

H1: Elevated intakes of olive oil, either in pure form or as supplemental capsules, have a positive impact on inflammation markers (CRP, IL-6, TNF-α, adiponectin) as well as on markers of endothelial function (ICAM-1, VCAM-1, FMD, E-selectin, P-selectin).

The aim of this master's thesis was to emphasize the effects of olive oil on inflammation markers and markers of endothelial function. Therefore studies providing olive oil, either in form of supplemental capsules or in the frame of dietary use of olive oil, with other supplements or other diets, were used to conduct a meta-analysis.

4. Methods

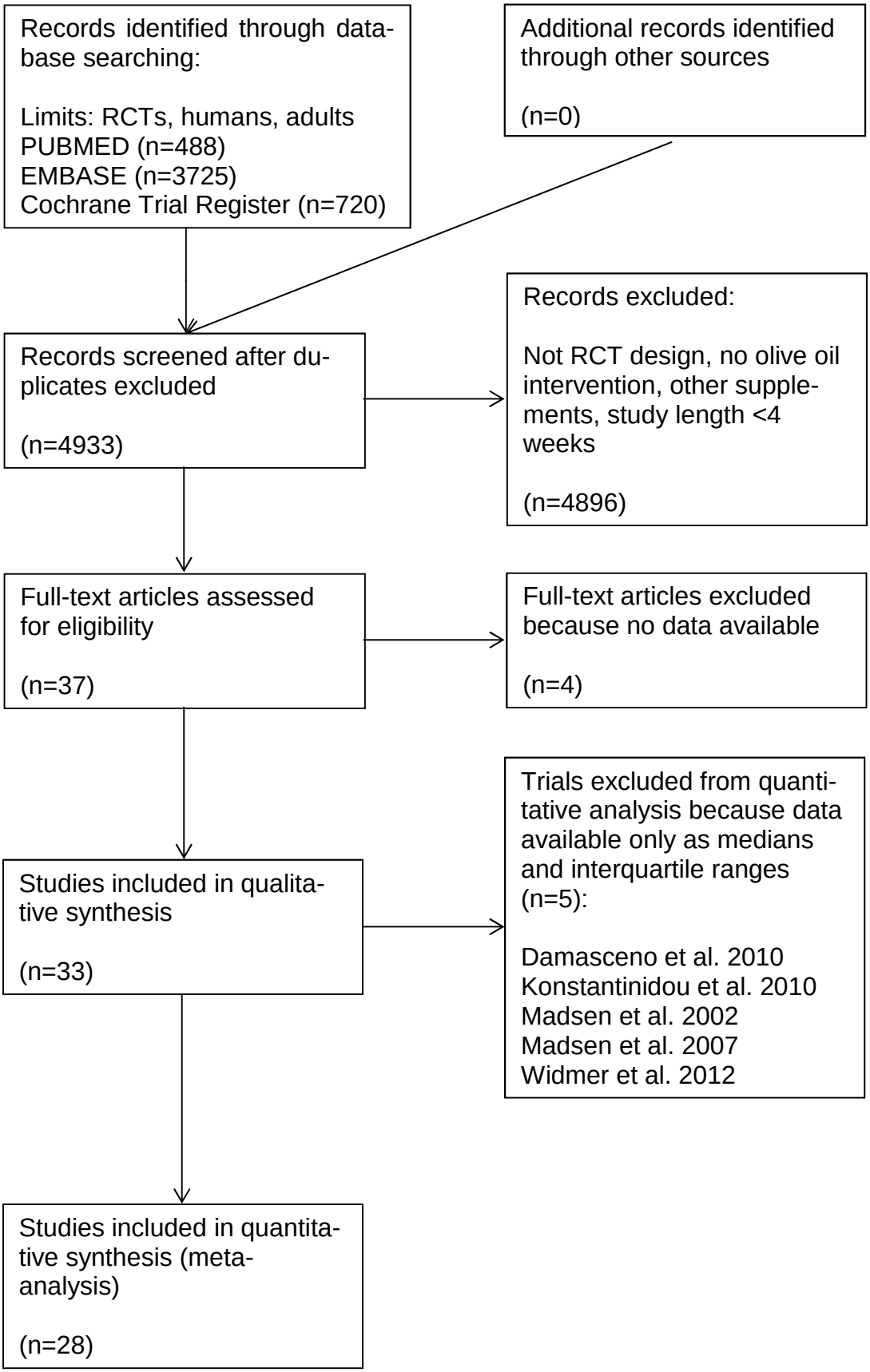
4.1 Search strategy and selection criteria

For the selection process of the studies, the recommended methods of the Cochrane Collaboration were used (Avenell et al. 2004). Systematic refurbishment was conducted using the electronic databases MEDLINE (1966-2014), EMBASE (1980-2014) and the Cochrane Trial Register (until 2014) until July 2014. Systematic refurbishment of the literature in the databases (MEDLINE, EMBASE and the Cochrane Trial Register) was performed using the following search terms: (“olive oil”) AND (“endothelial” OR “inflammation” OR “CRP” OR “FMD”) AND (“randomized controlled trial” OR “randomized” OR “clinical trials as topic” OR “placebo” OR “randomly” OR “trial”) NOT (“animals” NOT “humans”).

Clearly defined inclusion criteria were: (I) intervention with OO in pure form or as supplement (capsules); (II) randomized controlled trials or crossover design; (III) participants ≥19 years; (IV) minimum intervention period of 4 weeks; (V) no other supplementation; (VI) sample size: no exclusion criteria; (VII) assessment of the “outcome of interest” markers descriptive of inflammation (CRP, IL-6, TNF-α, adiponectin) and endothelial function (ICAM-1, VCAM-1, FMD, E-selectin, P-selectin); (VIII) report of post-intervention mean values (or if not available, change from baseline values were used instead) with standard deviation (or basic data which allow to calculate these parameters: standard errors, 95 % confidence interval, p-values).

The flow diagram, shown in figure 3, illustrates the process of searching literature.

Figure 3: Flow diagram



In the following, the different study types and their characteristics as well as the procedural method are described. Also the measuring methods, study quality, statistical analysis and the handling of missing data are specified.

4.2 Study types

The aim of this systematic review was to determine if olive oil, either in frame of the Mediterranean Diet or as supplement, has an influence on inflammation markers or markers of endothelial function. The following dietary interventions were evaluated. Mediterranean Diets with an intended amount of olive oil (partly extra virgin/virgin OO, partly not specified) compared to other diet forms and studies comparing capsules of OO (range from 1 g/d to 10g/d) to other specific oil types. Belonging to the different forms of intervention, the studies were classified in subgroups according to OO intervention and control as follows:

MD+OO vs.

(1) low-fat diet (LFD);
(2) healthy diet;
(3) Mediterranean Diet and nuts (MD+nuts);
(4) western diet/diet high in carbohydrates (western/CHO diet);

OO vs.

(1) flaxseed oil;
(2) coconut oil/palm olein (CO/PO);
(3) OO with n-3 fatty acids (OO with n-3);

OO capsules vs.

(1) conjugated linoleic acid mix capsules (CLA mix capsules);
(2) n-3 fatty acid capsules (n-3);

and also

(1) plant based olive oil diet (PBOO) vs. National Cancer Institute diet (NCI);
(2) monounsaturated fatty acid diet (MUFA) vs. saturated fatty acid diet (SFA) and low-fat diet (LFA).

General characteristics of the used studies are shown in table 3.

Table 3: General study characteristics

Reference	Sample size, mean baseline BMI (kg/m²)	Mean age (yrs), Female (%)	Duration (weeks)	Diseases/ Health status/ Medication/	Study design	Olive oil intervention	Comparison group	Outcome parameters
Bellido et al. 2006	20 21,6	23 0	4 run-in, 2x4 intervention	healthy, no medication, no intensive sports	RCT	MD + VOO	CHO diet	no data
Camargo et al. 2012	20 31,9	67,1 50	3x4 intervention	healthy or high BP/hyperlipidaemia/T2DM	RCT	MD + VOO	SFA diet, CHO-PUFA diet	no data
Casas et al. 2014	164 28,1	67,7 53,9	52 intervention	high risk for CVD (T2DM or 3 or more major cardiovascular risk factors)	RCT	MD + EVOO (50 ml/d)	low-fat diet	CRP, sE-selectin, sP-selectin, sVCAM-1
Damasceno et al. 2011	18 25,7	56 50	4 run-in, 4x4 intervention	moderate hypercholesterolemia, no medication, no HRT	RCT	MD + 30-50 g/d VOO (PP 34,3)	MD + walnuts (PP 1,3); MD + almonds (PP 1,1)	CRP, sICAM-1, sVCAM-1
Damsgaard et al. 2008	64 22,8	25,4 0	8 intervention	healthy, no medication	RCT	5 ml/d unrefined EVOO capsules	5 ml/d fish oil capsules	adiponectin, CRP, IL-6, VCAM-1

Damsgaard et al. 2009	63 22,8	25 0	2 run-in, 8 intervention	healthy, no intensive sports	RCT	5 ml/d unrefined EVOO capsules	5 ml/d fish oil capsules	
Eschen et al. 2004	60 24,6	38 41,7	12 interven-tion	healthy, no medication	RCT	10 g/d OO cap-sules	6,6 g/d n-3 PUFA capsules; 2,0 g/d n-3 PUFA + 7 g/d OO capsules	ICAM-1, VCAM-1, P-selectin
Eschen et al. 2010	138 27,1	59,5 14,5	24 interven-tion	CHF and LVEF<40 or stable oral medication	RCT	1 g/d OO cap-sules	0,9 g/d n-3 PUFA capsules	SICAM-1, sVCAM-1, sP-selectin
Esposito et al. 2004	180 28,0	43,9 45	104 interven-tion	≥3 criteria of metabolic syn-drome, no medication, no intensive sports	RCT	MD + OO	generally healthy diet	hsCRP, IL-6
Esposito et al. 2009	195 29,6	52,15 47	208 interven-tion	overweight, new diagnosed T2DM, no medication	RCT	MD + 30-50 g OO/d	low-fat diet	adiponectin
Flynn et al. 2010	28 27,9	59,2 100	8 weight loss, 24 follow-up	overweight women with invasive breast cancer, stable medication	RCT	PBOO diet with at least 3 table-spoons EVOO/d	NCI diet with canola oil	CRP
Fuentes et al. 2008	20 24,65	23,3 0	3x4 interven-tion	healthy, no medication, no intensive	RCT	MUFA diet based on EVOO (38 % fat)	SFA diet; low-fat n-3 enriched diet based on	sVCAM-1, sICAM-1

				sports			ALA	
Gammelmark et al. 2012	50 30,15	56,7 52	6 intervention	abdominally obese, women postmenopausal, no medication except ASA	RCT	2 g/d OO capsules	2 g/d fish oil capsules	Adiponectin, hsCRP, IL-6
Kelley et al. 2009	34 29,2	54,05 0	1 baseline, 12 intervention	moderately hyperlipidemic	RCT	7,5 g/d OO capsules	7,5 g/d DHA oil capsules	no data
Konstantinidou et al. 2010	90 25	44 70,25	12 intervention	healthy	RCT	MD + VOO (PC 328)	MD + washed VOO (PC 55); habitual diet	sP-selectin
Kontogianni et al. 2013	37 21,9	25,6 78,4	2x6 intervention, 6 washout	healthy, no medication, no intensive sports	RCT	15 ml/d EVOO	15 ml/d FO	Adiponectin, hsCRP, TNF-α
Madsen et al. 2003	60 24,6	38 41,7	12 intervention	healthy, no medication	RCT	7 g/d OO capsules	6,6 g/d n-3 PUFA capsules; 2 g/d n-3 PUFA + 4,9 g/d OO capsules	no data
Madsen et al. 2007	46 28	59 34,78	8 intervention	CRF but no dialysis, CVD, cerebrovascular diesease, intermittent claudication, atherosclerosis	RCT	2,4 g/d OO capsules	2,4 g/d n-3 PUFA capsules	no data

Madsen et al. 2007	41 24,6	63 17,1	12 intervention	stable, previous MI	RCT	5,2 g/d OO capsules	5,2 g/d n-3 PUFA capsules	no data
Maki et al. 2009	76 32,7	48,8 82,9	4 intervention	healthy, abdominally obese	RCT	2 g/d OO capsules	2 g/d krill oil capsules; 2 g/d menhaden oil capsules	CRP
Mena et al. 2009	106 28,1	68 43	12 intervention	T2DM or ≥3 CVD risk factors, ACE inhibitors, diuretics, antihypertensive agents, statins, lipid-lowering agents, insulin, OLAGs, aspirin or antiplatelet drugs	RCT	MD + VOO (1 l/week)	MD + nuts (30 g/d); low-fat diet	sE-selectin, sP-selectin, sVCAM-1, sICAM-1, IL-6, CRP
Mori et al. 2003	51 29,5	61,2 23,5	3 baseline, 6 intervention	hypertension, T2DM, antihypertensive therapy, OGLAs but no insulin	RCT	4 g/d OO capsules	4 g/d EPA capsules; 4 g/d DHA capsules	CRP, IL-6, TNF-α
Perez-Martinez et al. 2007	16 n.d.	n.d. 0	3x4 intervention	healthy, no medication, no intensive sports	RCT	MD + VOO	SFA diet; high-CHO diet	VCAM-1
Pfeuffer et	85	n.d.	4 intervention	overweight or	RCT	4,5 g/d OO cap-	4,5 g/d CLA	hsCRP,

al. 2011	28,3	0		obese, metabolic syndrome, CHD		sules	mixture capsules; 4,5 g/d safflower oil capsules; 4,5 g/d heated safflower oil capsules	sICAM, sVCAM, sE-selectin,
Sanders et al. 2011	367 26	55 56,25	4 run-in, 52 intervention	no CVD, medication: statins, antihypertensive med., HRT, thyroxine	RCT	3 g/d ROO capsules	0,45/0,9/1,8 g/d EPA + DHA capsules	CRP, FMD
Singhal et al. 2013	324 23,6	27,6 63	16 intervention	healthy, no medication	RCT	4 g/d OO capsules	1,6 g/d DHA + 2,4 g/d carrier oil capsules	CRP, FMD
Sofi et al. 2010	11 29,3	54,5 16,65	52 intervention	non-alcoholic fatty liver disease	RCT	6,5 ml/d OO	6,5 ml/d OO enriched with n-3 PUFA	adiponectin
Stirban et al. 2010	34 31,2	56,8 n.d.	2x6 intervention	T2DM, aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, ß-blockers, diuretics, statins	RCT	2 g/d OO capsules	2 g/d n-3 PUFA capsules	FMD
Taylor et al.	40	46	12 interven-	overweight,	RCT	4,5 g/d OO cap-	4,5 g/d CLA	adiponectin,

2005	33	0	tion	healthy		sules	mixture capsules	CRP, FMD, TNF-α
Theobald et al. 2007	39 24,0	48,65	2x12 intervention, 16 washout	healthy, no medication	RCT	1,5 g/d ROO capsules	0,7 g/d DHA capsules	IL-6, CRP, sE-Selectin
Tholstrup et al. 2008	69 25,4	60,2 100	16 intervention	healthy, postmenopausal women, no medication	RCT	5,5 g/d OO capsules	5,5 g/d CLA mixture capsules; 5,5 g/d CLA milk capsules	IL-6, ICAM-1, VCAM-1
Thomazella et al. 2011	40 26,4	54,8 0	12 intervention	≥1 coronary event, clinical stablility, aspirin, antiplatelet drugs, statins (+ezetimibe), nitrates, ACE inhibitors, ß blockers	RCT	MD + EVOO (30 ml/d)	TLCD	hsCRP, sICAM-1, sVCAM-1, FMD
Urpi-Sarda et al. 2012	516 29,4	67 50,8	52 intervention	T2DM or ≥3 CVD risk factors	RCT	MD + VOO (1 l/week)	MD + nuts; low-fat diet	ICAM-1, IL-6
Voon et al. 2011	45 23,1	30 80	3 baseline 3x5 intervention	healthy	RCT	OO (2/3 of total fat)	coconut oil (2/3 of total fat); palm olein (2/3 of total fat)	hsCRP, IL-6, TNF-α
Widmer et al. 2013	52 27,65	41,55 56	16 intervention	early atherosclerosis	RCT	30 ml/d OO	30 ml/d OO with EGCG	no data
Wong et al. 2010	97 25,8	60,1 55,7	12 intervention	T2DM, no CV events,	RCT	4 g/d OO capsules	4 g/d fish oil capsules	hsCRP, FMD

				OGLAs/insulin				
Woodman et al. 2003	59 29,47	61,2 30,8	3 baseline 6 intervention	obese, T2DM and hypertension, OGLAs and treatment for hypertension	RCT	4 g/d OO capsules	4 g/d EPA capsules; 4 g/d DHA capsules	FMD, P-selectin

OO = olive oil, EVOO = extra virgin olive oil, SO = sunflower oil, FO = flaxseed oil , PC = phenolic content (mg/kg), PP = polyphenols (mg/100g), MD = Mediterranean diet, CHO = diet high in carbohydrates, ALA = α-linoleic acid, PUFA = polyunsaturated fatty acids, CLA = conjugated linoleic acid, EGCG = epigallocatechin 3-gallate, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, T2DM = type 2 diabetes mellitus, CV = cardiovascular, OGLAs = oral glucose-lowering agents, CHF = chronic heart failure, HRT = hormone replacement therapy, CVD = cardiovascular disease, BP = blood pressure, MI = myocardial infarction, CRF = chronic renal failure, CHD = coronary heart disease, TLCD = low-fat therapeutic lifestyle changes diet, PBOO = plant based olive oil diet, NCI = National Cancer Institute diet

4.3 Biomarkers

The following biomarkers were analysed:

Markers of endothelial function: Intracellular adhesion molecule-1, vascular adhesion molecule-1, flow-mediated dilatation, E-selectin, P-selectin.

Inflammation markers: C-reactive protein, interleukin-6, tumor necrosis factor-alpha, adiponectin.

ICAM-1, VCAM-1, E-selectin and P-selectin

Serum was stored at -80°C until analysis was performed using commercially available test-kits applying ELISA assays.

Flow-mediated dilatation (FMD)

Endothelium-dependent vascular reactivity was assessed by FMD of the brachial artery with a high-resolution ultrasound system (ultrasonographer) with a 7-10-MHz/12-15-MHz linear-array transducer.

C-reactive protein (CRP)

Serum was used freshly or stored at -80°C and then analysed using sensitive double antibody sandwich ELISA, with rabbit anti-human CRP and peroxidase conjugated rabbit anti-human CRP, a high-sensitivity monoclonal antibody assay or a turbidometric immunoassay on a chemistry analyzer.

Interleukin-6 (IL-6)

IL-6 was measured with an ultrasensitive assay using LIminex 100 xMAP-TM equipment on multiplex antibody beads, a high-sensitivity quantitative sandwich enzyme immunoassay or with commercially available ELISA test-kits.

Tumor necrosis factor-alpha (TNF-α)

TNF-α was measured using an ELISA test-kit, a paired antibody enzyme-linked immunosorbent assay or a solid phase, two-site chemiluninescent immunometric assay.

Adiponectin

Adiponectin levels were assessed using commercially available ELISA test-kits, enzyme immuno-linked assays or by radioimmunoassay.

4.4 Statistical analysis

All data were analyzed using the software REVIEW MANAGER 5.3. as provided by the Cochrane Collaboration (http://ims.chochrane.org/revman). In a random-effect-model, the post-mean values or the changes from baseline values and belonging standard deviations of intervention and control groups were compared. The outcomes were illustrated in form of forest plots. Pooled effects of the different interventions were investigated as mean difference. Heterogeneity was tested with a chi-square-test. $x^2=X^2$, $I^2 = [(Q-d.f]/Q \times 100$ %, here Q is the x^2 statistic and d.f. are the degrees of freedom. An I^2-value of greater than 50 % was considered to represent considerable heterogeneity. To identify a possible publication bias, funnel plots were used. Publication bias is the statistically biased depiction of dates in scientific journals as a result of favoured publication of studies with “positive” or significant outcomes. Within the scope of a meta-analysis, a funnel plot is a graph that facilitates to monitor a suspicion of publication bias. The diagram is a scatterplot in a Cartesian coordinate system, in which the therapy effect on the x-axis is plotted against the standard deviation on the y-axis. Simple looking at the plot leads to an intuitive evaluation: a symmetric form arises from a balanced study publication, which maps the results in the frame of a natural statistical variance. Because of this, greater studies should reach more precise outcomes, being closer connected to the mean values of all study results.

4.5 Risk of bias

The Cochrane Collaboration’s tool for assessing risk of bias was used to elucidate the risk of bias of the included studies. This tool is attaching a low, unclear or high risk of bias to the seven domains “(namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome

assessment, incomplete outcome data, selective outcome reporting and ‘other issues’)” to each study (Higgins et al. 2011). The following figures show the distribution of the risk of bias for all domains and all studies (figure 4 and 5).

Figure 4: Risk of bias graph (reviews authors' judgements about each risk of bias item presented as percentages across all included studies)

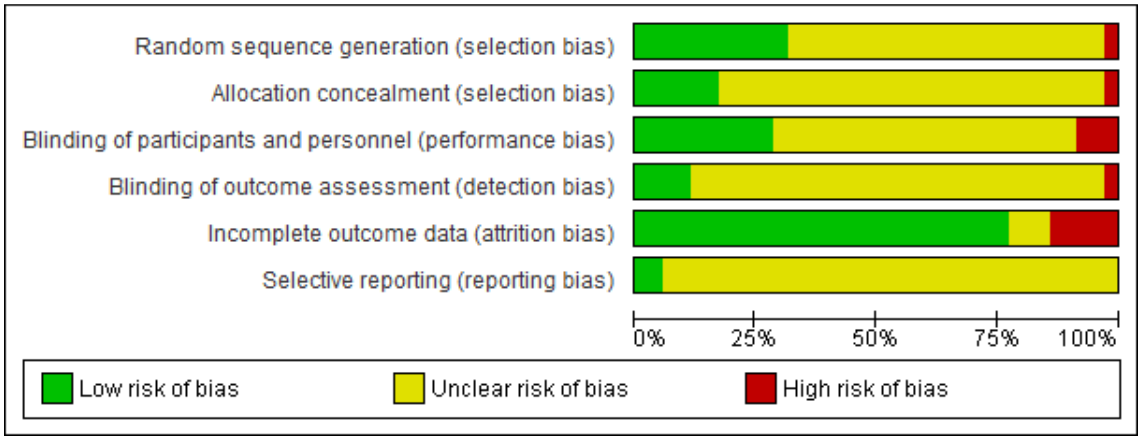
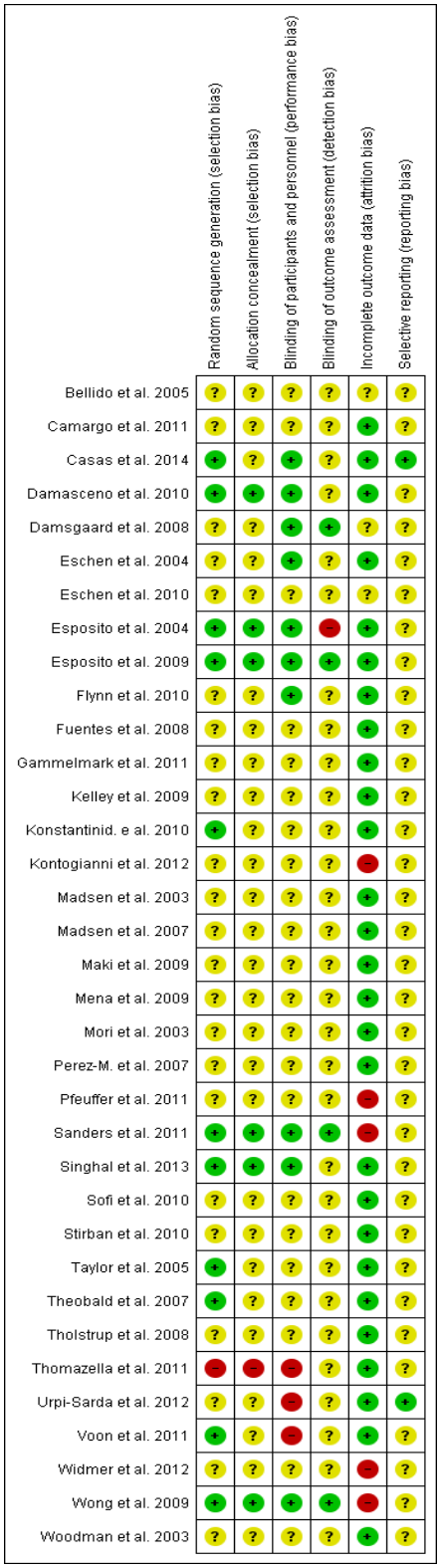


Figure 5: Risk of bias summary (reviews authors' judgements about each risk of bias item for each included study)



+: low risk of bias, ?: unclear risk of bias, −: high risk of bias

4.6 Handling of missing data

Of altogether 12 studies, either the post mean values or the standard deviations were missing. Thereupon, the corresponding authors were contacted, but only the lacking data of one additional study (Damasceno et al. 2011) and the CRP data of one study (Sanders et al. 2011) could be added to the meta-analysis. All the other authors did either not answer or the data were not normally distributed so that it would not have made sense to depict them as means and standard deviations.

4.7 Publication bias

To assess for potential publication bias (e.g. it is harder for studies without significant results to be published), the symmetry of the funnel plots in which mean MDs were plotted against their corresponding SEs were assessed.

5. Results

5.1 Study participants

The predetermined selection criteria were fulfilled by 37 studies with altogether 3379 participants (Bellido et al. 2006; Camargo et al. 2012; Casas et al. 2014; Damasceno et al. 2011; Damsgaard et al. 2008; Damsgaard et al. 2009; Eschen et al. 2004; Eschen et al. 2010; Esposito et al. 2004; Esposito et al. 2009; Flynn et al. 2010; Fuentes et al. 2008; Gammelmark et al. 2012; Kelley et al. 2009; Konstantinidou et al. 2010; Kontogianni et al. 2013; Madsen et al. 2003; Madsen et al. 2007; Madsen et al. 2007; Maki et al. 2009; Mena et al. 2009; Mori et al. 2003; Perez-Martinez et al. 2007; Pfeuffer et al. 2011; Sanders et al. 2011; Singhal et al. 2013; Sofi et al. 2010; Stirban et al. 2010; Taylor et al. 2006; Theobald et al. 2007; Tholstrup et al. 2008; Thomazella et al. 2011; Urpi-Sarda et al. 2012; Voon et al. 2011; Widmer et al. 2013; Wong et al. 2010; Woodman et al. 2003) (Table 3).

5.2 Study characteristics

The study duration was varying between 4 and 208 weeks. One part of the RCTs was comparing Mediterranean diets supplemented with (virgin/extra virgin) olive oil and a control diet. These control diets were a diet high in carbohydrates (Bellido et al, 2006), a diet rich in saturated fatty acids and a diet rich in carbohydrates and PUFAs (Camargo et al. 2012), a low-fat diet (Casas et al. 2014; Esposito et al. 2009), a Mediterranean diet supplemented with walnuts and a Mediterranean diet supplemented with almonds (Damasceno et al. 2011), a generally healthy diet (Esposito et al. 2004), a National Cancer Institute diet with canola oil (Flynn et al. 2010), a Mediterranean diet supplemented with washed olive oil and a habitual diet (Konstantinidou et al. 2010), a low-fat therapeutic lifestyle changes diet (Thomazella et al. 2011), a Mediterranean diet supplemented with mixed nuts and a diet rich in saturated fatty acids (Mena et al. 2009), a diet rich in saturated fatty acids and a diet rich in carbohydrates (Perez-Martinez et al. 2007) or a Mediterranean diet supplemented with nuts

and a low-fat diet (Urpi-Sarda et al. 2012). Fuentes et al. tested a MUFA diet based on EVOO against a low-fat n-3 enriched diet based on ALA (Fuentes et al. 2008), whereas Kontogianni et al. tested a diet providing 15 ml EVOO per day against 15 ml flaxseed oil per day (Kontogianni et al. 2013). Sofi et al. provided 6.5 ml OO per day and checked it against 6,5 ml OO enriched with n-3 PUFAs (Sofi et al. 2010). Voon et al. substituted 2/3 of total fat intake for OO, coconut oil and palm olein were used as control (Voon et al. 2011). Another study supplemented diet with 30 ml/d OO or OO enriched with EGCG (Widmer et al. 2013). The other part of the RCTs was checking olive oil capsules against capsules containing other fats. These fats were fish oil (Damsgaard et al. 2008; Damsgaard et al. 2009; Gammelmark et al. 2012; Wong et al. 2010), (n-3) PUFAs (Eschen et al. 2004; Eschen et al. 2010; Madsen et al. 2003; Madsen et al. 2007; Stirban et al. 2010), DHA oils (Kelley et al. 2009; Singhal et al. 2013; Theobald et al. 2007; Woodman et al. 2003), EPA and DHA oils (Mori et al. 2003; Sanders et al. 2011), krill oil and menhaden oil (Maki et al. 2009), CLA mixture (Taylor et al. 2005); CLA mixture and milk (Tholstrup et al. 2008) or CLA mixture and (heated) safflower oil (Pfeuffer at al. 2011). Suitable data were available from 28 of the above mentioned studies.

5.3 Inflammation markers

5.3.1 CRP

Decrease in CRP was significantly more pronounced following OO dietary protocols as compared to their respective control groups [MD -0.56 mg/L (95 % CI -0.91, -0.21), P=0.002)] (figure 6).

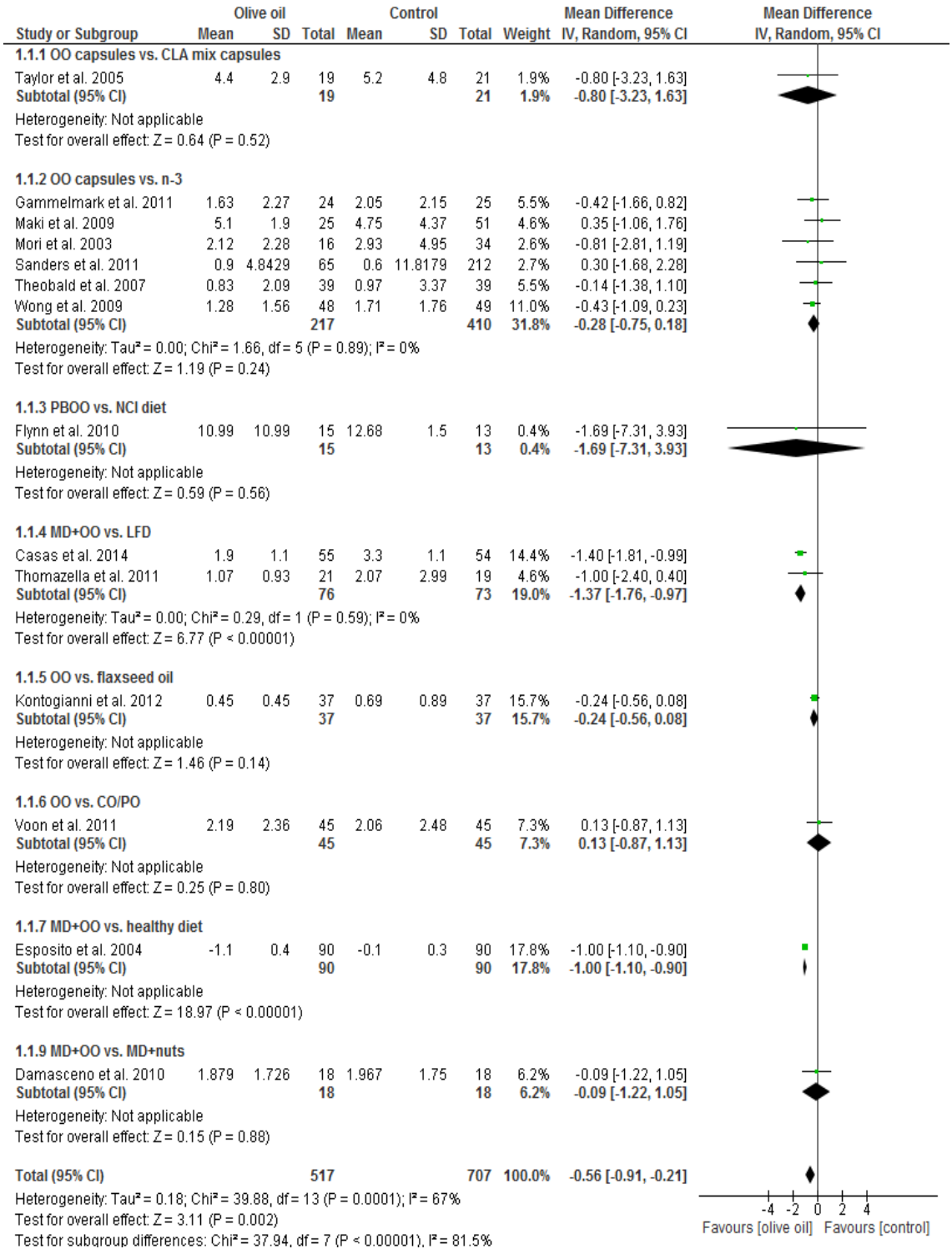


Figure 6: Forest plot summarizing aggregated weighted mean differences including 95 % CI for CRP following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize

the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. OO=olive oil, CLA=conjugated linoleic acid, n-3=n-3 fatty acids, PBOO=plant based olive oil diet, NCI=National Cancer Institute diet, LFD=low-fat diet, CO=coconut oil, PO=palm olein, MD=Mediterranean diet, CI=confidence interval, I^2=heterogeneity.

5.3.2 IL-6

Changes in serum levels of IL-6 were significantly stronger in the intervention groups treated with OO as compared to dietary controls [MD -0.29 pg/mL (95 % CI -0.57, -0.02), P=0.04] (figure 7).

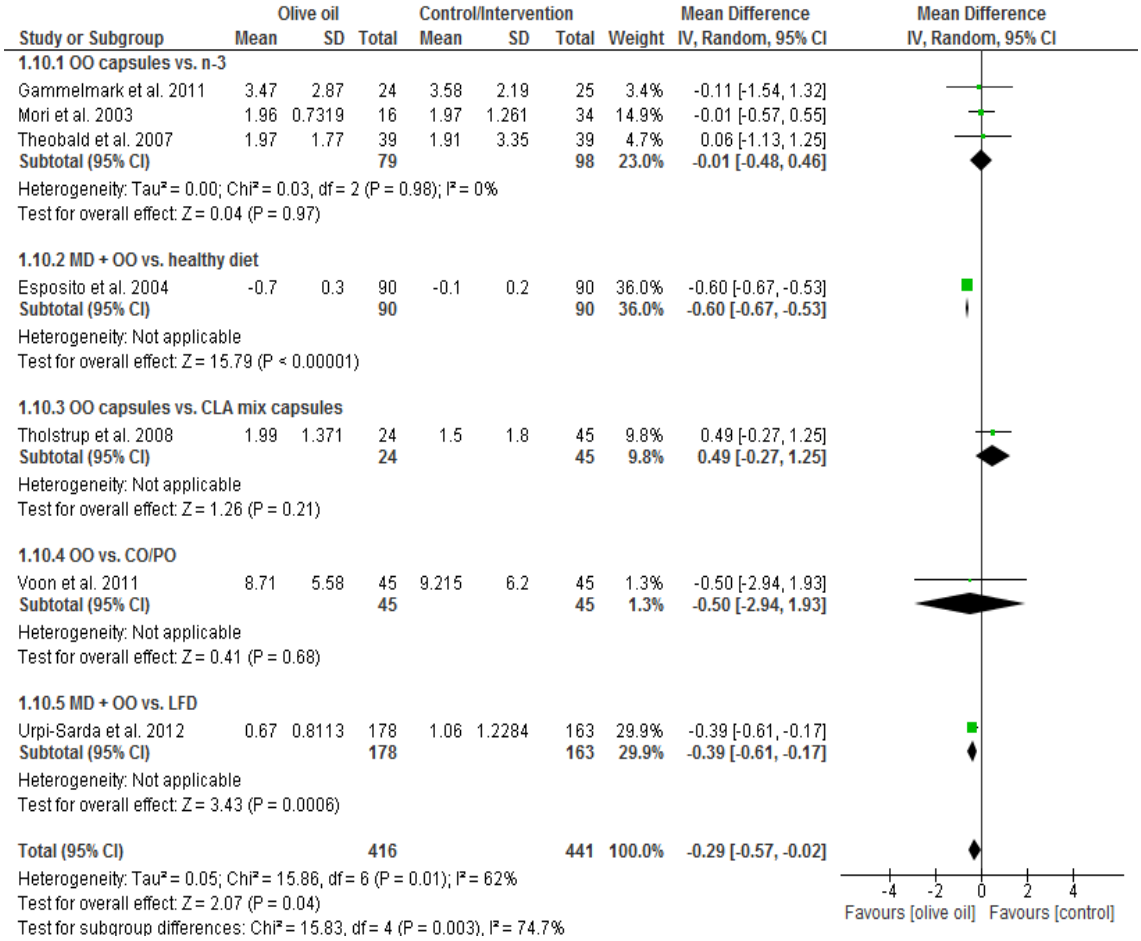


Figure 7: Forest plot summarizing aggregated weighted mean differences including 95 % CI for IL-6 following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize

the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. OO=olive oil, MD=Mediterranean diet, CLA=conjugated linoleic acid, CO=coconut oil, PO=palm olein, n-3=n-3 fatty acids, LFD=low-fat diet, CI=confidence interval, I²=heterogeneity.

5.3.3 TNF-α

For TNF-α serum levels, a not significant lowering in mean differences [MD 0.02 µg/L (95 % CI -0.02, 0.07), P=0.36] could be observed for control dietary protocols compared to intervention groups treated with OO (figure 8).

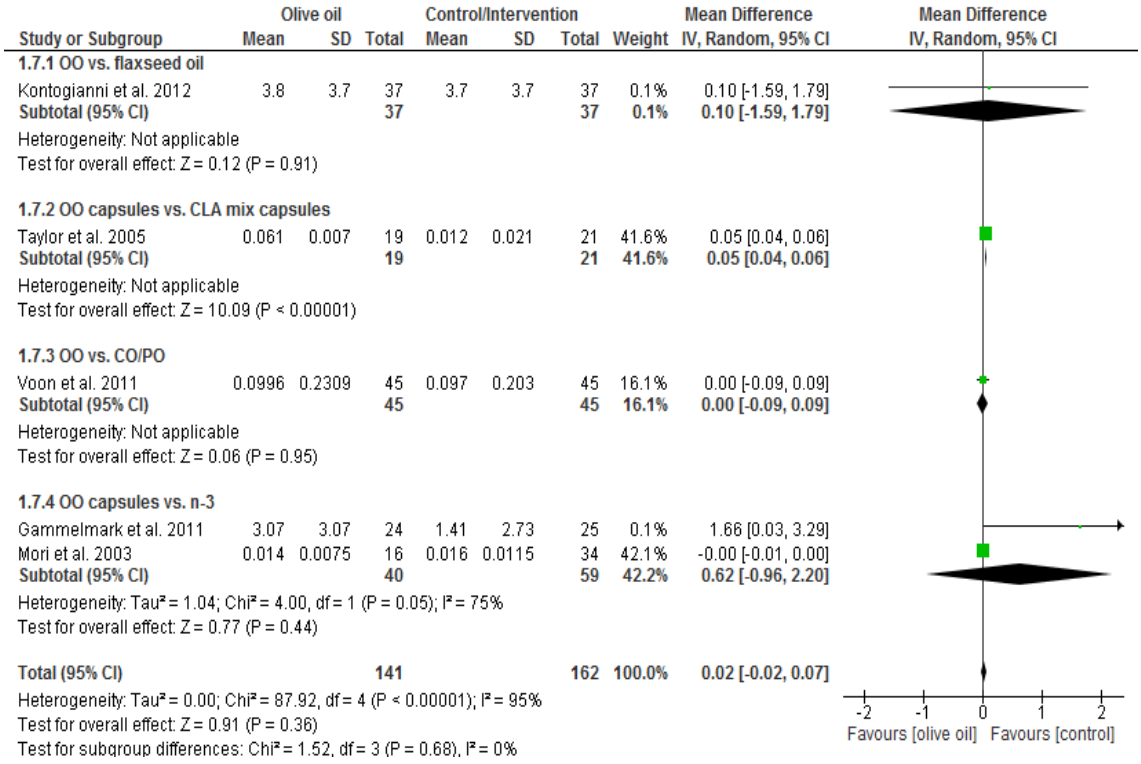


Figure 8: Forest plot summarizing aggregated weighted mean differences including 95 % CI for TNF-α following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. TNF-α=tumor nekrosis factor α, OO=olive oil, CLA=conjugated linoleic acid, CO=coconut oil, PO=palm olein, n-3=n-3 fatty acids, CI=confidence interval, I²=heterogeneity.

5.3.4 Adiponectin

When comparing OO and control regimen, no significant differences could be found with respect to MD in change of adiponectin [MD 0.44 mg/L (95 % CI -0.20, 1.09), P=0.18] (figure 9).

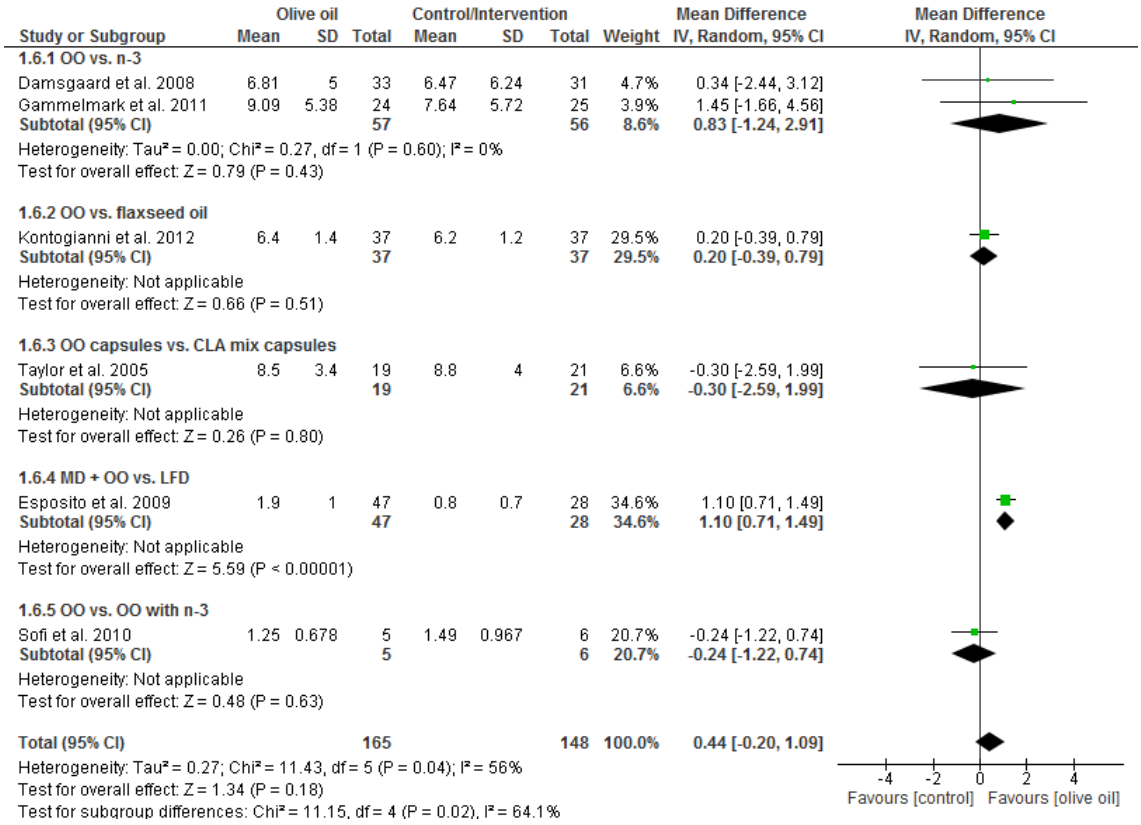


Figure 9: Forest plot summarizing aggregated weighted mean differences including 95 % CI for adiponectin following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. OO=olive oil, n-3=n-3 fatty acids, CLA=conjugated linoleic acid, LFD=low-fat diet, CI=confidence interval, I^2=heterogeneity.

5.4 Markers of endothelial function

5.4.1 ICAM-1

Changes in serum levels of ICAM-1 were significantly more prominent in the intervention groups treated with OO as compared to dietary controls [MD -0.02 ng/L (95 % CI -0.04, -0.00), P=0.02] (figure 10).

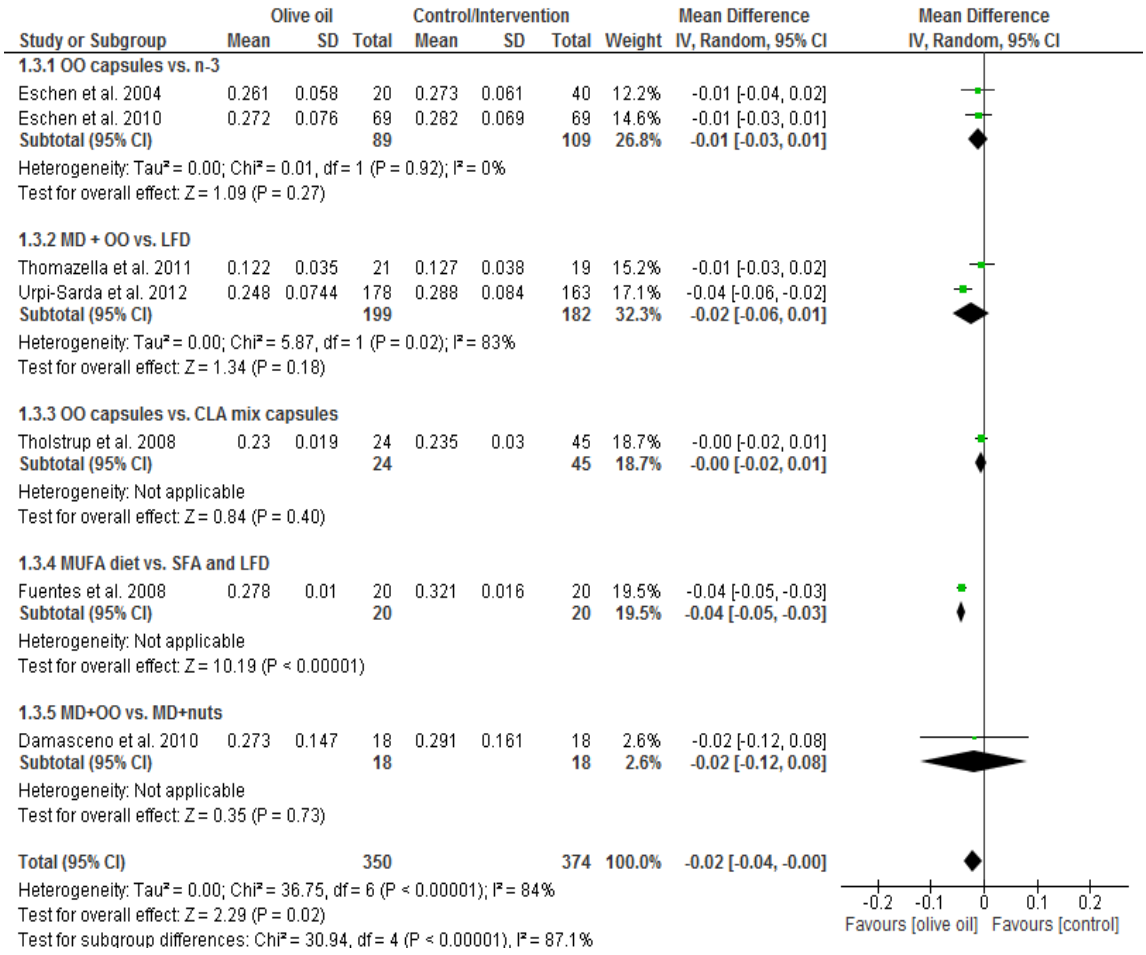


Figure 10: Forest plot summarizing aggregated weighted mean differences including 95 % CI for ICAM-1 following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. ICAM-1=intercellular cell adhesion molecule-1, OO=olive oil, n-3=n-3 fatty acids, LFD=low-fat diet, CLA=conjugated linoleic acid, MUFA=monounsaturated fatty acids, SFA=saturated fatty acids, LF=low-fat, CI=confidence interval, I^2=heterogeneity.

5.4.2 VCAM-1

Mean differences in change of VCAM-1 levels [MD -0.02 ng/L (95 %CI -0.05, 0.01), P=0.14] were not statistically significant when comparing OO vs. control dietary protocols (figure 11).

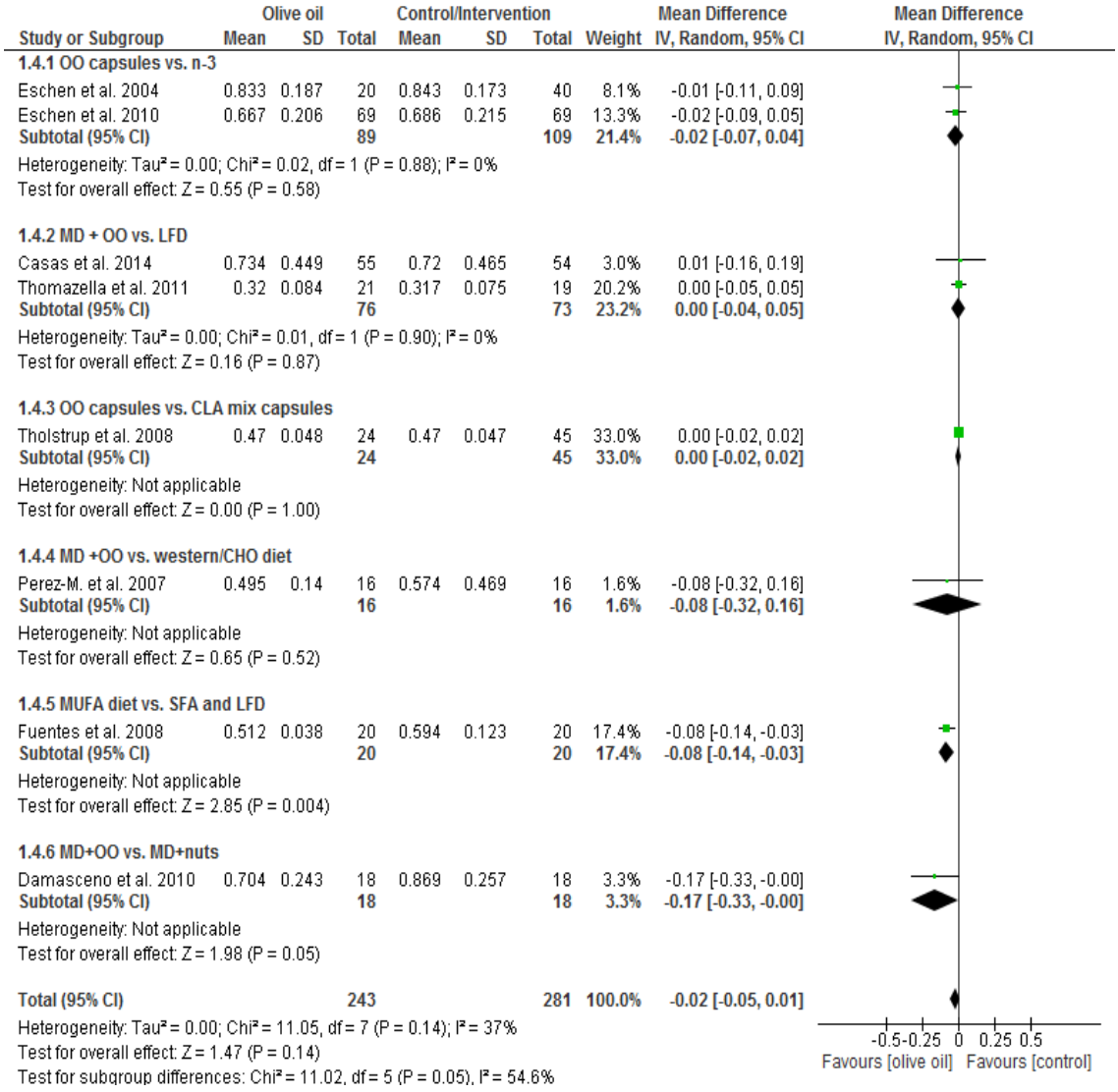


Figure 11: Forest plot summarizing aggregated weighted mean differences including 95 % CI for VCAM-1 following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. VCAM-1=vascular cell

adhesion molecule-1, OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet, CLA=conjugated linoleic acid, CHO=diet high in carbohydrates, MUFA=monounsaturated fatty acids, SFA=saturated fatty acids, CI=confidence interval, I^2=heterogeneity.

5.4.3 FMD

Increase in FMD was significantly more pronounced following OO dietary protocols as compared to their respective control groups [MD 0.66 % (95 % CI 0.27, 1.05), P=0.0009] (figure 12).

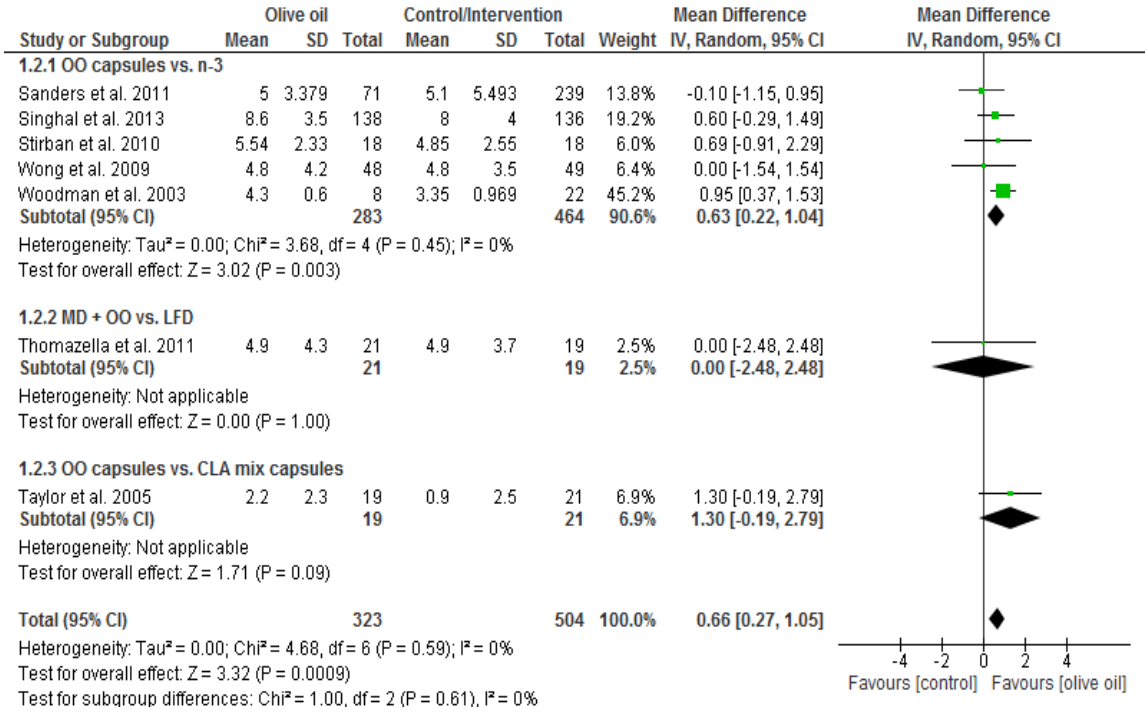


Figure 12: Forest plot summarizing aggregated weighted mean differences including 95 % CI for FMD following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. FMD=flow-mediated dilatation, OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet, CLA=conjugated linoleic acid, CI=confidence interval, I^2=heterogeneity.

5.4.4 E-selectin

Compared to their respective control groups, decrease in serum E-selectin levels was significantly more distinct following OO dietary [MD -3.16 ng/mL (95 %CI -4.07, -2.25), P<0.00001] (figure 13).

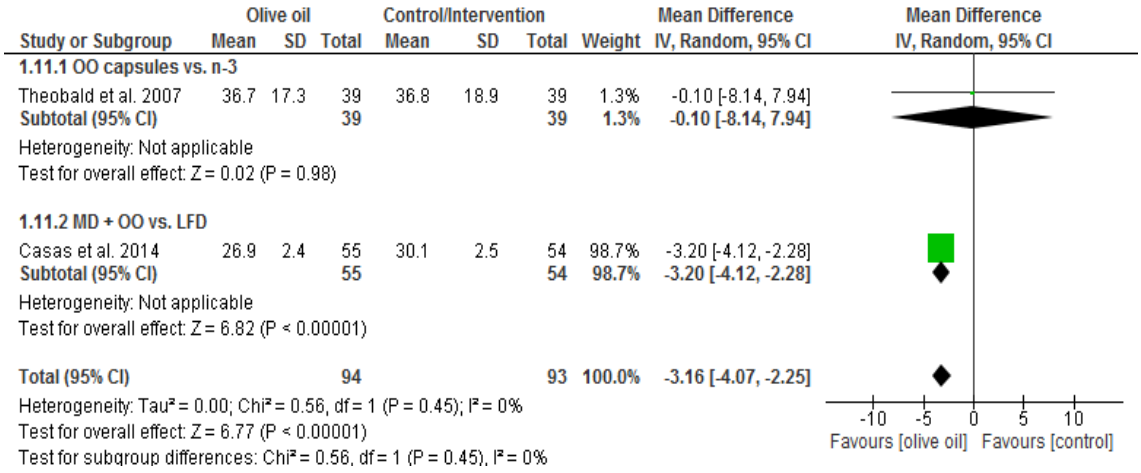


Figure 13: Forest plot summarizing aggregated weighted mean differences including 95 % CI for E-selectin following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials. OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet, CI=confidence interval, I^2=heterogeneity.

5.4.5 P-selectin

In case of P-selectin, decrease in serum levels was significantly more explicit in dietary controls than in the intervention groups treated with OO [MD 10.78 ng/mL (95 % CI 4.01, 17.54), P=0.002] (figure 14).

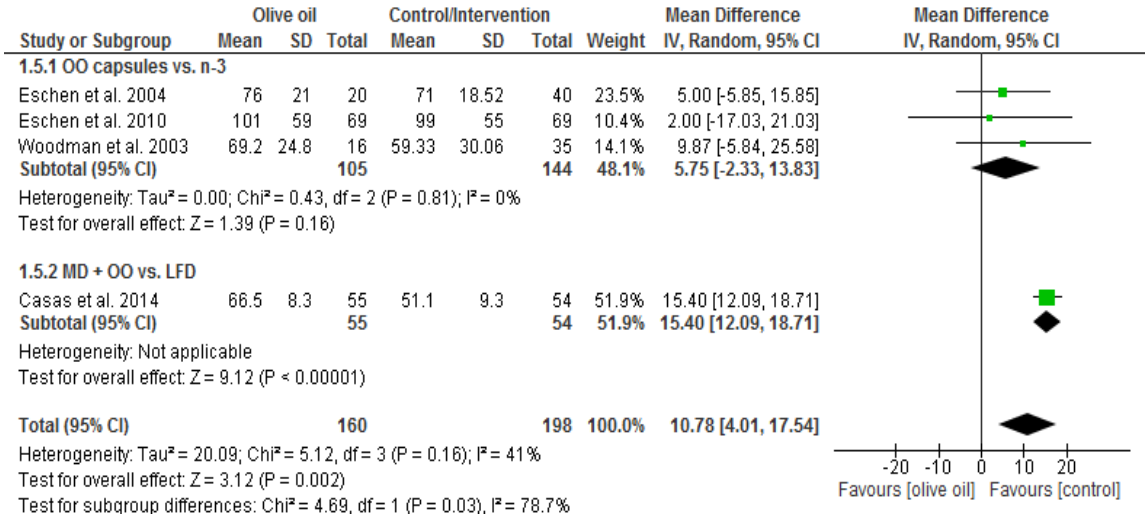


Figure 14: Forest plot summarizing aggregated weighted mean differences including 95 % CI for P-selectin following olive oil vs. corresponding controls (as indicated by subgroups). Green squares represent the point estimates of olive oil interventions, horizontal lines represent 95 % CI. Dimension of green squares indicate the weight of each trial within the meta-analysis. Diamonds summarize the effect estimates of each subgroup, the diamond at the bottom of the plot represents the synthesized effect for all trials.OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet, CI=confidence interval, I^2=heterogeneity.

5.5 Funnel plots

For CRP (figure 15), ICAM-1 (figure 18) and FMD (figure 19) only low to middle asymmetry can be seen, this indicates low to moderate probability for publication bias. For IL-6 (figure 16), TNF-α (figure 17), E-selectin (figure 20) and P-selectin (figure 21), high asymmetry occurs, leading to the assumption that there is probability for publication bias.

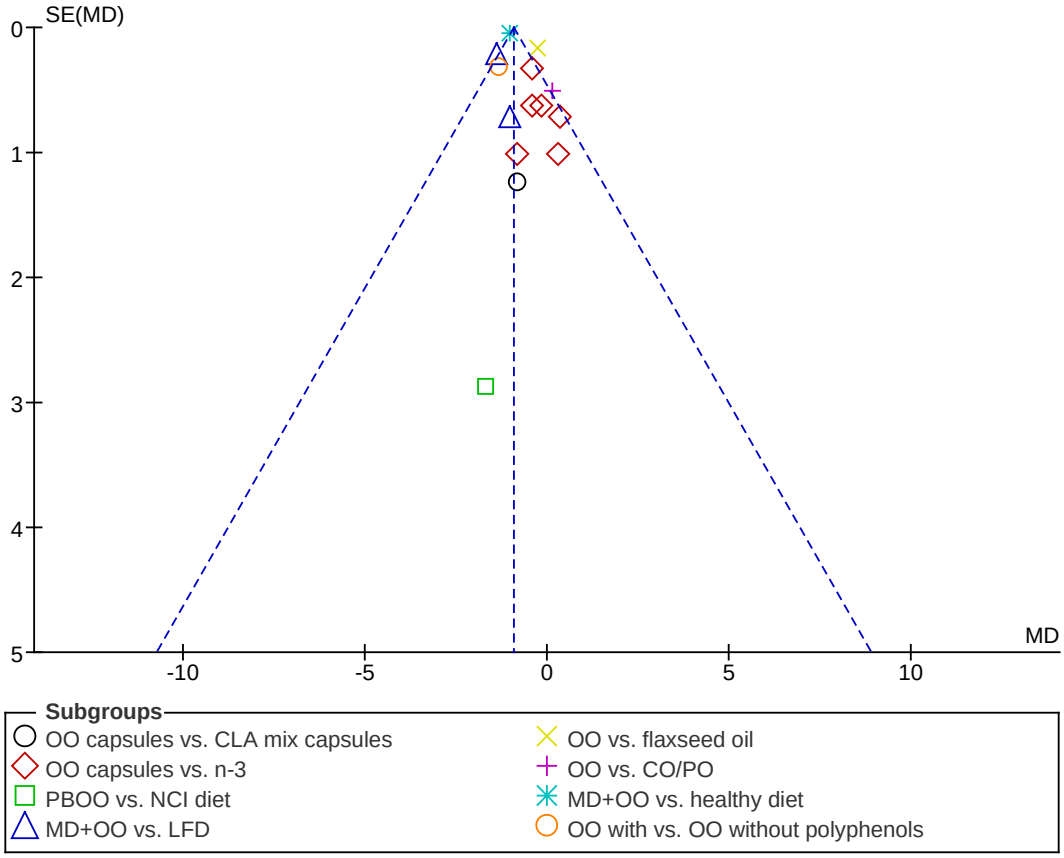


Figure 15: Funnel plot showing the study precision against the MD effect estimated with 95 % CIs for CRP (mg/L). OO=olive oil, CLA=conjugated linoleic acid, n-3=n-3 fatty acids, PBOO= plant based olive oil diet, NCI=National Cancer Institute diet, MD=Mediterranean diet, LFD=low-fat diet, CO=coconut oil, PO=palm olein; MD=mean difference, SE=standard error.

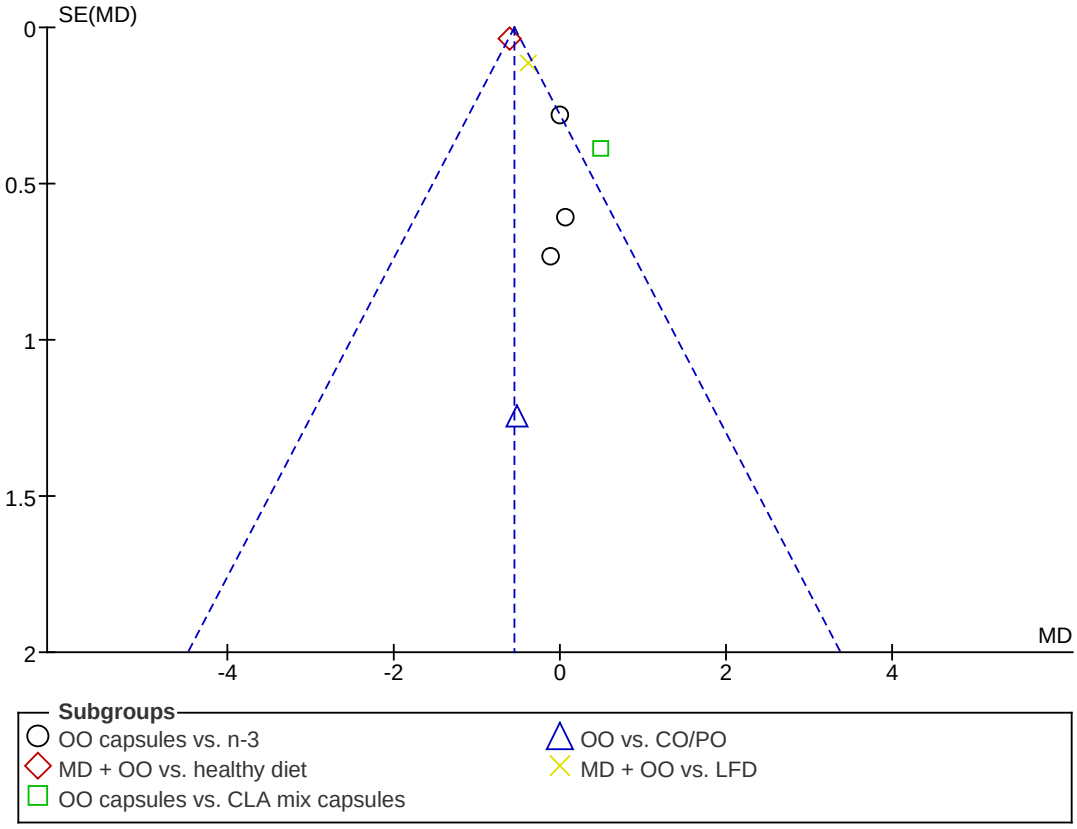


Figure 16: Funnel plot showing the study precision against the MD effect estimated with 95 % CIs for IL-6 (pg/mL). OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, CLA=conjugated linoleic acid, CO=coconut oil, PO=palm olein, LFD=low-fat diet; MD=mean difference, SE=standard error.

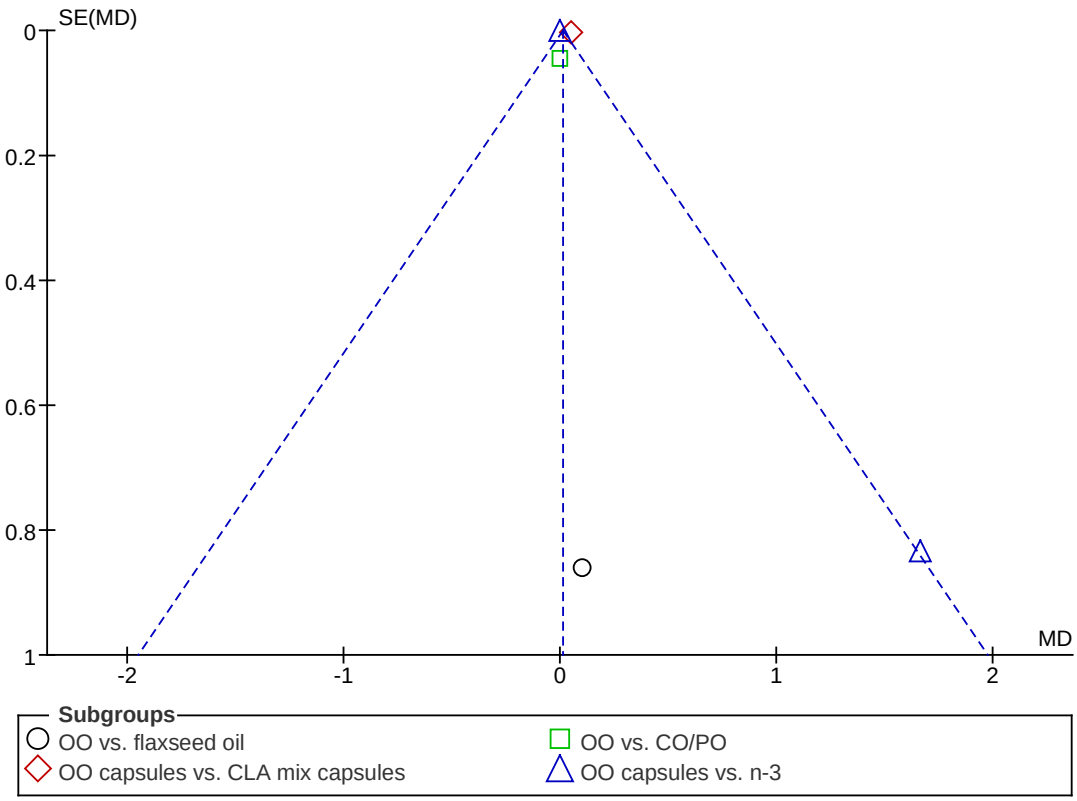


Figure 17: Funnel plot showing the study precision against the MD effect estimated with 95 % CIs for TNF-α (µg/L). OO=olive oil, CLA=conjugated linoleic acid, CO=coconut oil, PO=palm olein, n-3=n-3 fatty acids; MD=mean difference, SE=standard error.

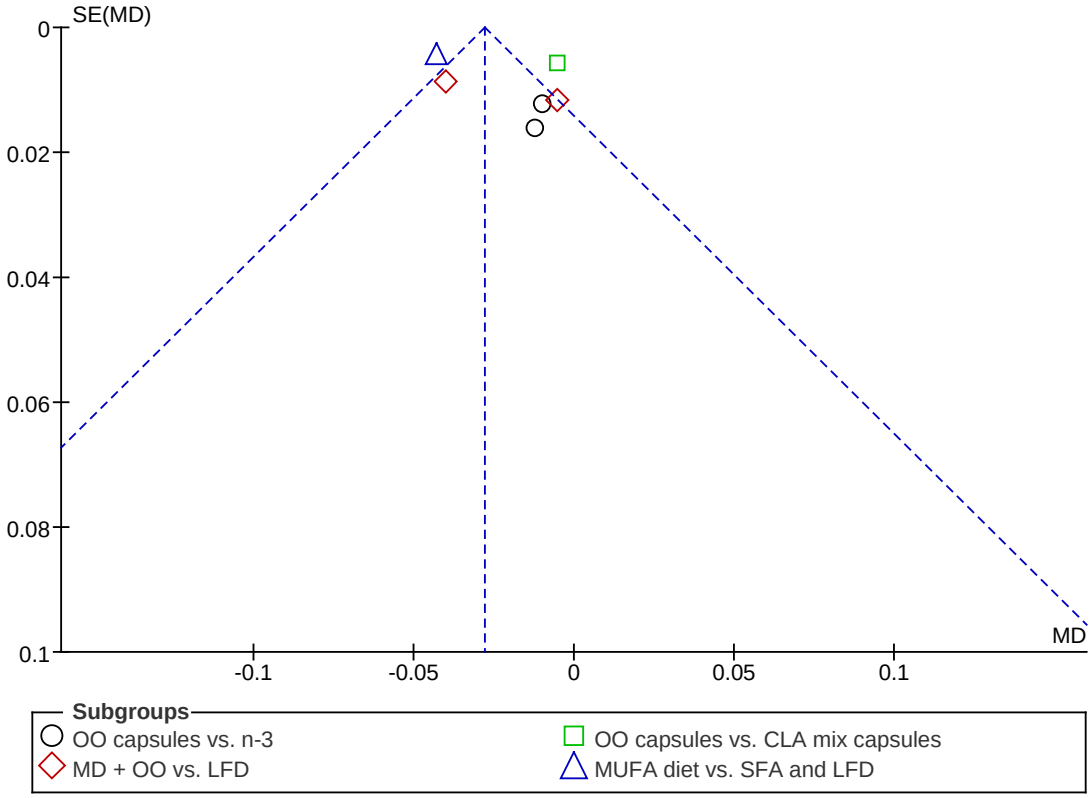


Figure 18: Funnel plot showing the study precision against the MD effect estimated with 95 % CIs for ICAM-1 (ng/L). OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet, CLA=conjugated linoleic acid, MUFA=monounsaturated fatty acids, SFA=saturated fatty acids; MD=mean difference, SE=standard error.

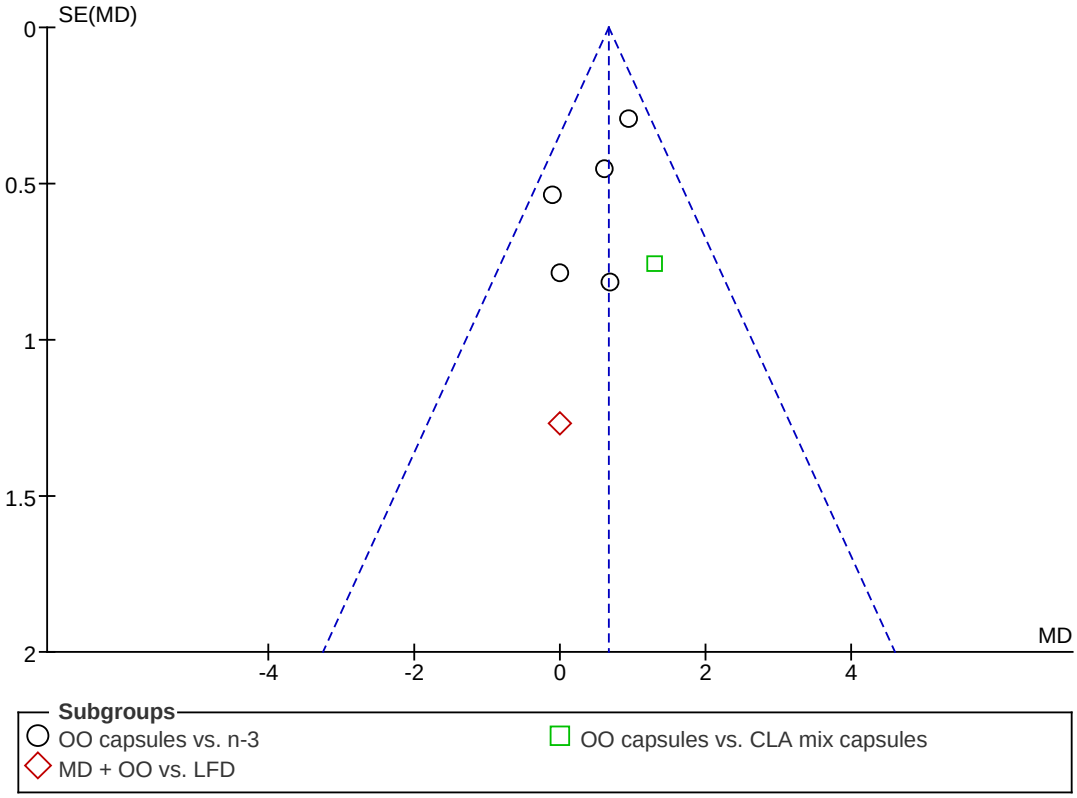


Figure 19: Funnel plot showing the study precision against the MD effect estimated with 95 % CIs for FMD (%). OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet, CLA=conjugated linoleic acid; MD=mean difference, SE=standard error.

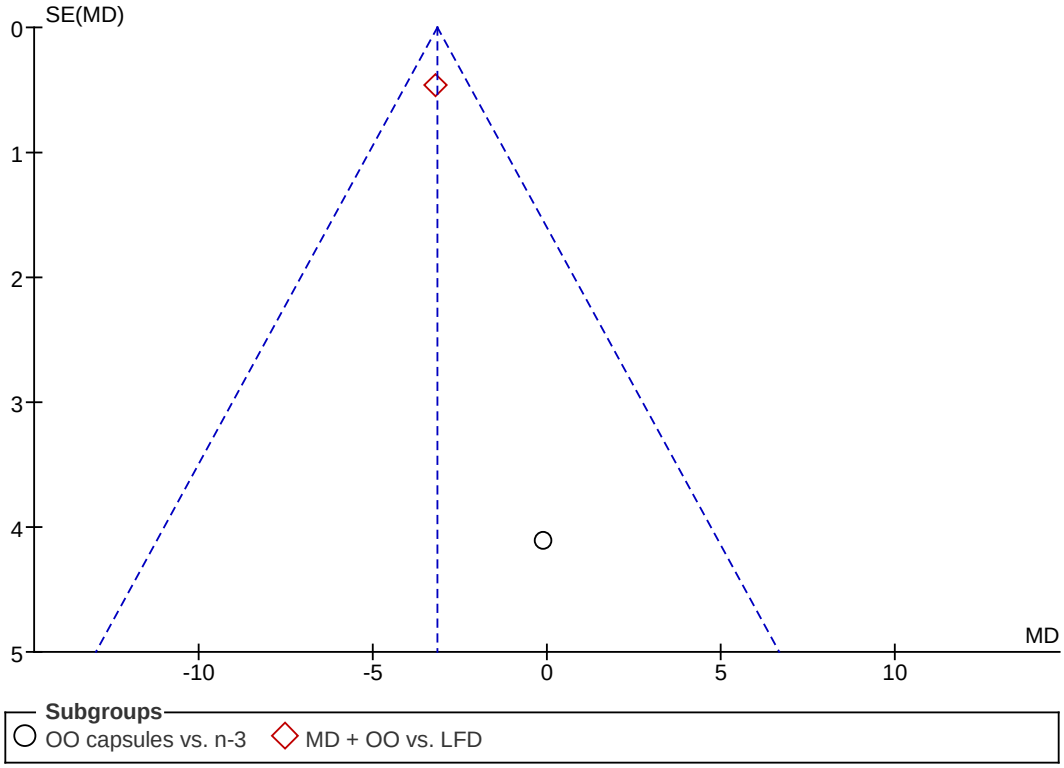


Figure 20: Funnel plot showing the study precision against the MD effect estimated with 95 % CIs for E-selectin (ng/mL). OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet; MD=mean difference, SE=standard error.

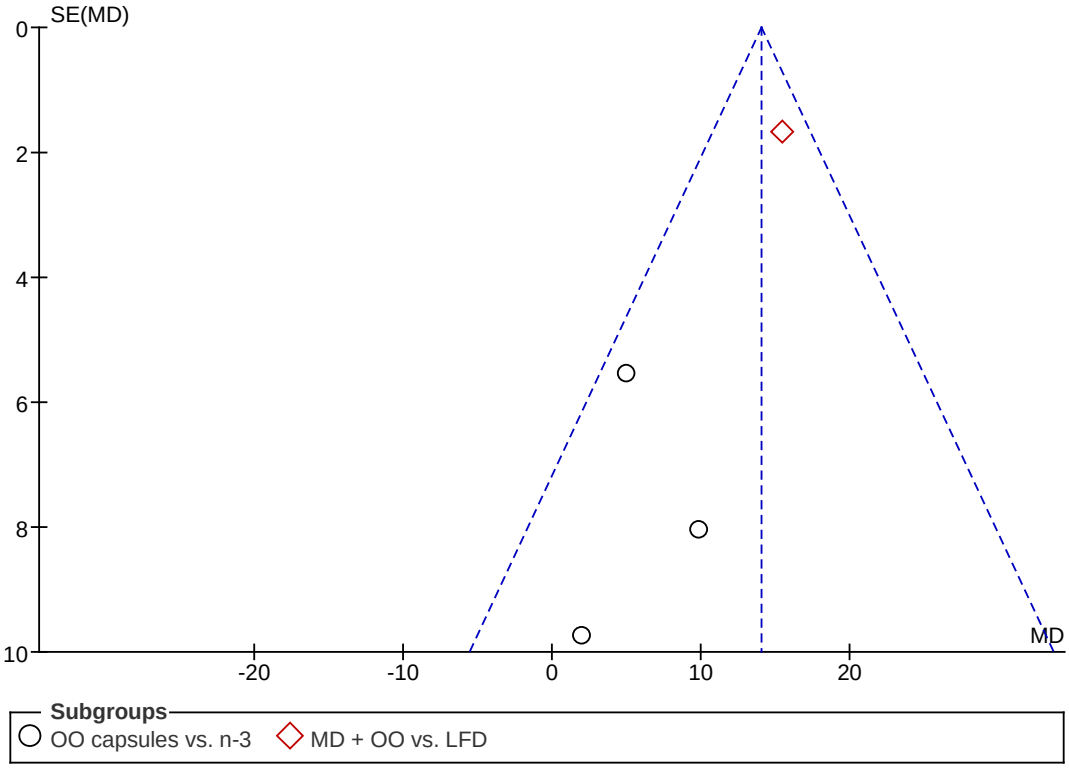


Figure 21: Funnel plot showing the study precision against the MD effect estimated with 95 % CIs for P-selectin (ng/mL). OO=olive oil, n-3=n-3 fatty acids, MD=Mediterranean diet, LFD=low-fat diet; MD=mean difference, SE=standard error.

5.6 Heterogeneity

As described in the “Cochrane Handbook for Systematic Reviews of Interventions”, a heterogeneity value of 0 % to 40 % might not be important, a value of 30 % to 60 % may represent moderate heterogeneity, a value of 50 % to 90 % may represent a substantial heterogeneity and a value of 75 % to 100 % may represent considerable heterogeneity.

Unimportant heterogeneity in the statistically significant results was observed for FMD (I^2=0 %) and E-selectin (I^2=0 %). Moderate heterogeneity was seen for P-selectin (I^2=41 %). A substantial heterogeneity was monitored for CRP (I^2=67 %) and IL-6 (I^2=62 %). TNF-α (I^2=95 %) and ICAM-1 (I^2=86 %) represent a considerable heterogeneity. This is pointing to the fact, that the data are relatively heterogenous.

6. Discussion

Olive oil is the major source of fat in the Mediterranean diet, which is one of the "healthiest" diets known, but less common in Western nutrition patterns. Inflammation and endothelial function are directly linked to cardiovascular and general health. In the current review and meta-analysis, the impact of olive oil in matters of this topic has been investigated. For most analysed biomarkers, an improvement in the olive oil groups could be observed. More precisely, in the group of inflammation markers, a significant lowering of the serum levels of CRP and IL-6 was monitored, which favours olive oil groups. In contrast, TNF-α levels were significantly higher in olive oil groups, so control groups are favoured. For adiponectin, no benefit could be observed for one of the groups. In the group of markers of endothelial function, ICAM-1, FMD and E-selectin values were significantly positive influenced by olive oil interventions. P-selectin levels were significantly lowered in the control groups, so favours control. VCAM-1 levels were reduced by olive oil interventions, but not significantly, so showed an indifferent effect.

The analysed biomarkers can be consulted in risk prediction of several diseases, especially for cardiovascular disease. They are used in addition to the traditional risk factors, such as diabetes mellitus, hypertension, hyperlipidemia and smoking. To detect people at risk, biomarkers are of important meaning, because half of the patients have only one or none of the traditional risk factors (Khot et al. 2003). Relating to the validity of the used biomarkers it is to say that the largest body of evidence exists for CRP.

An association between CRP concentrations and future cardiovascular risk has been generally supported by multiple epidemiological reports (Danesh et al. 2004). The US Preventive Services Task Force recently performed a meta-analysis of 22 studies, which showed that CRP concentrations greater than 3.0 mg/dL were associated with approximately 60 % excess risk of incident coronary heart disease (Buckley et al. 2009).

The pro-inflammatory cytokine IL-6 is the main hepatic stimulus for CRP (Heinrich et al. 1990). Increased baseline levels of IL-6 can also predict future cardio-

vascular events. It was found out that patients “with IL-6 levels in the highest quartile were at a 2.3-fold elevated risk of future cardiovascular events compared with those in the lowest quartile” (Blake and Ridker 2002). Elevated IL-6 levels were also a strong predictor for increased mortality amongst patients with acute coronary syndromes (Lindmark et al. 2001). Related to the short half-life and high within-individual turnover in circulating IL-6 concentrations, the magnitude of any association of IL-6 levels with CHD risk may be underestimated (Danesh et al. 2008).

TNF-α is another cytokine mediating the amplification of pro-inflammatory signals within atherosclerotic plaque. A study from the secondary prevention Cholesterol and Recurrent Events (CARE) showed that patients in the stable phase after a MI with increased TNF- α levels were at higher risk of recurrent coronary events. Especially those with baseline levels higher than the 95th percentile had a 2.7-fold elevated risk of recurrent events (Ridker et al. 2000).

The majority of adipokines, which are produced by adipocytes and other cells present in the adipose tissue, is pro-inflammatory and contributes to atherogenesis (Lau et al. 2005). One exception to that is adiponectin with its insulin-sensitising and anti-inflammatory properties. Other differences to adipokines are that it is solely secreted by adipose tissue, is plentiful in the circulation and is found in reduced levels in obese individuals (Arita et al. 1999). Epidemiological studies initially showed positive findings on the association between adiponectin and cardiovascular risk, but these studies are recently questioned by current studies. The US Health Professionals Follow-up Study associated high adiponectin levels with a significantly lower risk of myocardial infarction over a 6-year follow-up, independently of diabetes, body mass index, hypertension, physical activity, family history of myocardial infarction and alcohol consumption (Pischon et al. 2004). A study carried out on a German population, followed-up for 17 years, reported similar findings (Koenig et al. 2006), but both these studies only recruited male subjects. For patients, who are considered to be at high risk of cardiovascular complications, like such with T2DM or chronic renal failure on haemodialysis, adiponectin was also found to have protective effects (Schulze et al. 2005; Zoccali et al. 2002). Other studies, which were adequately pow-

ered, could not identify adiponectin as an independent cardiovascular risk factor (Lawlor et al. 2005; Lindsay et al. 2005). In contrast, high adiponectin levels among elderly people were actually associated with increased risk for coronary events (Kanaya et al. 2006; Kizer et al. 2008).

Flow-mediated dilatation, assessed with the use of ultrasound of the brachial artery, is another potential biomarker. It provides an index of endothelial function, because after shear stress, vasodilatation is a nitric oxide-dependant process. In individuals with cardiovascular risk factors like hypertension or hyperlipidemia, reduced FMD is often present. The association between reduced FMD and cardiovascular risk in individuals with varying baseline risk was shown by several studies (Chan et al. 2003; Gokce et al. 2003; Yeboah et al. 2009). A current meta-analysis with other 5500 participants from observational studies showed, that a reduction of FMD of 1 % causes a 13 % decreased risk for future cardiovascular events (Inaba et al. 2010).

Selectins and adhesion molecules as markers may be useful in the detection of general endothelial activation. Studies investigating their use as biomarkers exhibit that they can be utilized to observe for example specific organ's endothelium damage. They also seem to be good markers for the prognosis of the 1-year survival and the progression of disease provided that general endothelial damage has yet not occurred. However, the exact mechanisms of action of soluble adhesion factors are unclear and some factors that have influence on their plasma levels are yet not detected. In tests, the soluble adhesion molecules are often not detectable because they are binding to the activated endothelium (Paulus et al. 2011).

"In light of their central role in the recruitment of inflammatory cells to site of atheroma development, the CAM are promising candidates to reflect underlying vascular inflammation". In the Physicians' Health Study (PHS), amongst the males who seemed to be healthy, only these individuals with raised baseline levels of ICAM-1 turned out to get a MI. The "relative risk of future MI for those in the highest quartile of ICAM compared with those in the lowest quartile was 1.8 ($P = 0.03$). In this study, the risk of MI associated with elevated levels of sICAM-1 appeared to increase over time, a finding consistent with the early role

for ICAM-1 in atherosclerosis" (Blake and Ridker 2002). The Atherosclerosis Risk In Communities (ARIC) study, conducted on healthy subjects, demonstrated that levels of circulating ICAM-1 can forecast carotid artery atherosclerosis (CAA) and future CHD "and that this relationship cannot be accounted for by the confounding effects of other CHD risk factors" (Hwang et al. 1997). Additionally, the secondary prevention Bezafibrate Infarction Prevention study showed "that elevated plasma levels of ICAM-1 were associated with an increased risk of future coronary events independent of other traditional risk factors amongst individuals with documented coronary artery disease" (Blake and Ridker 2002).

In contrast, plasma levels of VCAM-1 were not predictive of future cardiovascular risk in apparently healthy individuals in both PHS and ARIC. Within a population with previously documented coronary artery disease, those subjects who subsequently died because of cardiovascular causes had increased baseline plasma levels of ICAM-1 as well as VCAM-1 (Blankenberg et al. 2001). Adjusted analysis of this study found out that VCAM-1 was the stronger predictor of risk with the risk of death being over two times higher in the highest quartile compared to the lowest quartile. ICAM-1 "may be a less specific marker than VCAM-1, which is mainly expressed on atherosclerotic plaques by activated endothelial cells and smooth muscle cells. Thus the predictive value of VCAM-1 may be limited to those with more advanced atherosclerosis at the time of measurement" (Blake and Ridker 2002).

Elevated concentrations of E-selectin, a biomarker of endothelial activation which is expressed by endothelial cells in an early step of atherogenesis, were found to be associated with ischemic stroke independently of traditional risk markers by the PRIME study (Prugger et al. 2013). This finding was affirmed by a case-control study with 200 stroke patients, which showed a 3.4-fold and 7.9-fold increased likelihood of ischemic stroke among individuals with E-selectin levels in the third and fourth quartile (Cherian et al. 2003). Another study observed that levels of E-selectin were significantly higher in CHF patients who did not survive than in survivors, therefore E-selectin was defined a predictor for short-term mortality in CHF patients (Czúcz et al. 2011).

P-selectin, an adhesion molecule produced by activated endothelial cells, which mediates initiate leukocyte “rolling”, plays a role in early inflammatory steps leading to atherogenesis (Frenette et al. 1995). In a cohort of apparently healthy women, baseline levels of P-selectin were also shown to be a predictive biomarker for future cardiovascular risk. In the highest quartile of P-selectin levels, the risk of future cardiovascular events was 2.2 times higher than in the lowest quartile, this effect was independent of traditional risk factors (Ridker et al. 2001).
In addition, biomarkers are influenced by a large and not completely known number of factors, for example a “high self-reported degree of physical activity is associated with attenuated circulating levels of TNF-α, IL-6 and CRP compared with those devoted to a sedentary lifestyle” (Aron et al. 2012). In sum, because of the complexity of the inflammatory process, including interrelations with cytokines as well as the response of acute-phase proteins, it is probable that no single biomarker is able to contain all the important risk information (van Hylckama Vlieg and Rosendaal 2003).

Olive oil is the main source of fat in the Mediterranean diet, used as culinary fat and for dressing dishes, so that substantial quantities are ingested. It is proved by a large body of evidence to have beneficial effects on conventional risk factors for coronary heart disease (CHD) like adiposity, blood pressure, especially on lipid and DNA oxidation, serum lipid profile, insulin resistance, and inflammation (Bellido et al. 2005; Chamorro et al. 2005; Nolasco et al. 2005; Sanchez-Criado et al. 2005; Damasceno et al. 2011). The evidence that olive oil can influence stages of carcinogenesis, cell membrane composition, signal transduction pathways, tumor suppressor genes, as well as transcription factors was provided by experimental studies (Plotkin et al. 2005). It is yet not fully understood, by which mechanisms the Mediterranean diet and olive oil apply their health effects. Possible mechanisms in the development and/or protection of chronic degenerative diseases could be the gene-environment and/or gene-diet interaction. Another possibility may be that the phenolic compounds present in virgin OO contribute to the health benefits derived from the Mediterranean Diet.

These polyphenols showed strong antioxidant properties in experimental studies (Martín et al. 2010; Sánchez-Fidalgo et al. 2012). A “study in 24 young women with high-normal BP or stage 1 essential hypertension” found out, that a “diet containing polyphenol-rich OO can decrease BP and improve endothelial function” (Moreno-Luna et al. 2012).

Olive oil receives little attention in western countries and because of this, polyunsaturated fatty acids (PUFAs) and oils rich in PUFAs got more common over time. Substituting saturated and trans fats by unsaturated ones and keeping up a low ratio of n-6:n-3 fatty acid intake are aspired to lower the risk for CHD (Gomez et al. 2005), primary through suppression of chronic inflammation (Gaytan et al. 2005; Jimenez et al. 2005; Perez-Martinez et al. 2005).

Oleic acid (OA) was held to be responsible for the generally health promoting properties of olive oil in the last years. Especially, the high OA content of olive oil was demonstrated to result in a reduction in atherogenesis risk and cholesterol levels (Di Matteo et al. 2009; Esposito et al. 2009; Genovese et al. 2009; Paz-Filho et al. 2009; Esposito et al. 2011), host versus graft response (Moinpour et al. 2010), as well as blood pressure and anti-hypertensive drug consumption (Holmes et al. 2014). Additionally, OA was shown to have beneficial anti-inflammatory effects on autoimmune diseases (Kremer et al. 1990; Linos et al. 1991), can be protective in breast cancer development and can improve the function of the immune system (Martin-Moreno et al. 1994; Assmann et al. 1997; Lipworth et al. 1997; Simonsen et al. 1998; Solanas et al. 2002).

Besides its high amount of MUFAs, olive oil is also a functional food containing other minor biologically active compounds, such as polyphenols. In *in vivo* studies on healthy volunteers and patients with hypercholesterolemia or stable CHD, these have demonstrated abilities to reduce lipid oxidative damage (Plotkin et al. 2005), prothrombotic profile (Bellido et al. 2005) endothelial dysfunction (Ruano et al. 2005), and inflammatory status (Almeida et al. 2005; Ruano et al. 2005; Kundig et al. 2006).

6.1 Limitations

This systematic review and meta-analysis does not incorporate unpublished data and it cannot be expulsed that lacking data have a (possibly only insignificant) effect on the results of this meta-analysis.

Another problem is up to the diversity of the included studies. One point of heterogeneity of the studies is their length. The minimum length was defined at 4 weeks of intervention, but the longest included study lasted 4 years (208 weeks). Other points of heterogeneity are the quality and quantity of the used olive oils. In studies where olive oil was given for example in the frame of the Mediterranean diet, mostly extra virgin or virgin olive oil was chosen. In contrast, studies where olive oil was the placebo checked against other oils, such as n-3 oils, partial olive oils of lower quality or oils not described in detail were utilized. The amount of olive oil given daily varied between 1 g (as capsule) and more than 100 ml (1 l per week provided), which demonstrates a really great discrepancy.

If the duration of the study is longer and the quality and quantity of the used olive oils is higher, so the chance to sustain significant changes in the examined biomarkers will be elevated.

6.2 Conclusion

This systematic review and meta-analysis included RCTs with intervention periods lasting at least 4 weeks, which were comparing olive oil in form of supplemental capsules or in natural form in the frame of specific dietary modifications. Statistically significant advantages of the olive oil interventions in matters of meaningful inflammation markers, like CRP and IL-6, as well as markers of endothelial function, which are ICAM-1, FMD and E-selectin, could be observed.

To evaluate, which one of the olive oil components or which combination of ingredients is responsible for the positive effects of olive oil on human health, further studies are needed.

The results of this meta-analysis encourage reconsidering a recommendation for increased olive oil intake into the dietary guidelines.

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8. Curriculum vitae

Educational dates

09/96 – 07/00	Primary school Tiefenbach
09/00 – 06/09	Auersperg Gymnasium Passau-Freudenhain Graduation: Allgemeine Hochschulreife
10/09 – 08/12	Bachelors study “Nutritional Sciences”, University of Vienna, graduation: bachelor of science
10/12 – today	Masters study “Nutritional Sciences”, focus “Molecular Nutrition”, University of Vienna

Work-related experiences

11/06 – 06/14	Müller Großhandels Ltd. und Co KG, Minijob, branches: Passau – Wien – Passau
05/09/11 – 23/09/11	Internship: Goldsteig Käsereien Bayerwald GmbH
09/13	Internship: AOK Bayern – Die Gesundheitskasse
09/14 – 02/15	Internship: Volker Laves/Circle L Ranch

Languages	German (native language), English (fluent), French (basics)
EDV – skills	Review Manager, Word, Excel, Powerpoint

9. Statement given upon oath

With this I affirm that I autonomously wrote this Master's thesis and used no other than the declared resources.

Date: 27.04.2015 Signature: Marina Christoph