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Can rapeseed oil replace olive oil as part of a Mediterranean-style diet?

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Running title

Rapeseed versus olive oil

Keywords

Rapeseed oil; Canola oil; Olive oil; Mediterranean diet

Abstract

This narrative review compares evidence from experimental, epidemiological and clinical studies of the health benefits of rapeseed (Canola) oil and olive oil in order to assess if rapeseed oil is suitable as a sustainable alternative to olive oil as part of a Mediterranean-style diet in countries where olive trees do not grow. From epidemiological studies, the evidence for cardiovascular protection by extra virgin olive oil is "convincing", and for cancers "limited-suggestive", especially oestrogen receptor negative breast cancer, but more studies are required in relation to cognitive impairment. Evidence for rapeseed oil is limited to short term studies on biomarker risk factors for cardiovascular disease. Any benefits of rapeseed oil are likely to be due to α-linolenic acid, but this is prone to oxidation during frying. We conclude that due to a lack of evidence from observational or intervention studies indicating that rapeseed oil has comparable health benefits to extra virgin olive oil, rapeseed oil cannot currently be recommended as a suitable substitute for extra virgin olive oil as part of a Mediterranean-style diet.

Abbreviations

MD	Mediterranean diet
EVOO	extra virgin olive oil
OO	either virgin or non-virgin olive oil (not specified)
RO	rapeseed (Canola) oil
ALA	α-linolenic acid
TFA	*trans* fatty acid
UFA	unsaturated fatty acid

Introduction

The traditional Mediterranean diet (MD) is widely recognised as one of the healthiest in the world, and it is likely that more widespread adoption of this diet in non-Mediterranean countries would lead to a significant reduction in the incidence of many chronic diseases[1]. Some health organisations in non-Mediterranean countries now recommend a MD. For example, in the UK a MD is recommended by NICE (National

Institute for Health and Care Excellence) for secondary prevention following a myocardial infarction[2]. However, despite this type of targeted advice, there is only limited promotion of a MD to the general population in non-Mediterranean countries[3], and campaigns for healthy eating tend to focus on promoting diets that are compatible with the cultural heritage of a people. For example, Public Health England promotes the Eatwell Plate - a dietary pattern modelled on a healthy UK-based diet[4], and in Norway the traditional Norwegian diet has been promoted as being more appropriate for this country than adopting a MD[5].

Nevertheless, it can be argued that the well-proven health benefits of the MD justify it being more widely promoted in non-Mediterranean countries. Promoting a MD in non-Mediterranean countries is a viable public health approach since there is usually good compliance to this diet by individuals in non-Mediterranean countries who adopt it, and, in general, eating habits in many countries are becoming more flexible[6, 7]. In addition, local produce can be used, rather than foods that only grow in Mediterranean countries, since food choices for a MD are mostly based on food groups, such as "fruits" or "vegetables", rather than on specific foods[8]. Indeed, it has been argued that many features of recommended dietary patterns in Northern Europe, such as high consumption of fruit and vegetables and low consumption of meat, are quite similar to the MD[9].

One exception to the generalised recommendation of food groups, rather than specific foods, is to consume olive oil (OO) as the main source of added fat. Indeed, it is the consumption of OO - more than any other single factor - that distinguishes the traditional MD from other dietary patterns[10]. However, adopting OO as the main dietary fat as part of a MD in non-Mediterranean populations may present an obstacle since it is relatively costly compared with other cooking oils, and consumption of OO in non-Mediterranean populations is low[11]. Consuming large quantities of OO in non-Mediterranean countries also raises issues of food security. The food security agenda aims to increase production of foods within national borders in order to guarantee food production independent of international influences. Since olive trees only grow in Mediterranean type climates this may not be compatible with food security issues, although this is less of an issue between EU countries which share interdependent policies.

The health benefits of OO are attributed both to its high content of the MUFA oleic acid[12] and to various minor components[13]. Rapeseed oil (RO) (known as Canola oil in the US, Canada and some other countries) is a potential substitute for OO since it has a similar MUFA content to OO and its overall fatty acid profile is favourable due to a low content of SFA and high content of PUFA, including α-linolenic acid (ALA). Consumption of RO is now high in many non-Mediterranean countries, partly due to low cost, and also because it is perceived as being a healthy oil. There is increasing substitution of RO for OO, such as in recipes for the home cook, and in the UK NICE do not specify OO in their description of a MD but instead refer to "vegetable oil" - which in the UK generally refers to RO[2]. Hence, perhaps not surprisingly, consumption of RO in the UK may now be starting to displace that of OO since OO sales have seen their first fall in over 20 years[14].

Rapeseeds are widely grown - both for biofuel and for human consumption - in many EU countries, Canada, China, Australia and India[15]. In the UK, rapeseeds are the only oilseeds harvested in significant quantities. In view of the relatively low cost and the ready availability of RO, we examine if the health benefits of RO justify it replacing OO as part of wider recommendations for consumption of a MD in non-Mediterranean countries, and so ask if RO can be regarded as an ersatz "Northern OO" for the domestic consumer.

Methods

We used a narrative review approach, and searched electronic databases PubMed and Scopus up until April 2014. Key words "olive oil", "virgin olive oil", "rapeseed oil" and "Canola" were used in combination with keywords "composition" (and related words such as "phenolics", "antioxidants"), "cardiovascular disease" (and related words such as "coronary heart disease" and "myocardial infarction"), "cancer" and "neurodegenerative disease" (and related words such as "Alzheimer's disease" and "dementia") and the study method (such as "cohort" and "meta analysis").

Composition

Fats

As well as a high MUFA content (mainly oleic acid), OO also contains a range of other FAs[16]. Levels of the various FAs in OO vary quite widely between oils depending on factors such as the type of olive tree cultivar used for oil production (see Table 1). RO also has a high MUFA content, as well as considerably higher levels of ALA than OO (see Table 1). Consumption of ALA is linked to cardioprotective benefits (see below). However, RO also contains approx. 1% *trans* isomers of ALA, which are produced during the deodorisation step of oil production[17, 18]. There is a well-established link between *trans* fatty acid (TFA) consumption and increased risk of CHD[19] and although the level in RO does not in itself constitute a health risk, it is desirable to keep levels of TFA to a minimum.

RO is very low in SFAs, comprising only approx. 6% of total FAs. This is about half the average content of SFA in OO, and it has been argued that this gives RO an advantage over OO[20]. However, the quite low proportion of SFA even in OO means that it would not normally be a significant daily source of SFA compared to other dietary sources such as meat or dairy produce. For example, 20 ml OO contains 128 mg SFA giving 9.62 kJ (2.3 kcal) as SFA. Current UK intake of SFA is 12.7 % of total energy intake[21]. Hence, consumption of 20 ml OO represents less than 1% of the average daily intake of energy in the UK from SFA (0.9% total calories in women based on an intake of 8368 kJ (2000 kcal) and 0.7% in men based on an intake of 10460 kJ (2500 kcal)).

Minor components

There are significant differences between the minor components in RO and extra virgin olive oil (EVOO), due not only to the source of the oil but also to production methods. EVOO is produced using mild conditions that include pressing olive fruits at low temperature, washing with water, filtration and centrifugation. These conditions retain many of the original components of the olives. The most abundant minor component is the hydrocarbon squalene, and there are smaller quantities of carotenoids, triterpenoids, phytosterols (eg β-sitosterol, Δ^5-avenasterol and campesterol) and tocopherols (approx.

95% α-tocopherol) (Table 1). EVOO also contains a wide variety of phenolic compounds including secoiridoids (eg oleuropein) and their phenolic derivatives (eg tyrosol, hydroxytyrosol), flavonoids (eg luteolin, apigenin), and lignans (pinoresinol and acetoxypinoresinol). EVOO is the best quality OO and must meet predefined criteria in terms of sensory qualities and limits of acidity. Other OOs have substantially lower levels of most of the minor components, and phenolic compounds in particular are reduced[16].

Many potentially beneficial biological actions have been described for the minor components in EVOO. EVOO phenolics reduce markers for inflammation and oxidative stress *in vitro* and *in vivo*[22, 23]. Squalene reduces oxidative stress in human mammary epithelial cells[24]. Lignans are phytoestrogens with possible anticancer activity[25], and it is noteworthy that OO (both EVOO and other OO) was found to be the major dietary source of lignans in participants in the PREDIMED study[26]. Secoiridoids such as oleuropein and its derivatives are of particular interest in relation to the health properties of EVOO since they are not found in other food plants.

Standard production of RO requires a far higher level of processing including solvent extraction of the oil from the pressed seeds, and refining by degumming, neutralization, bleaching and deodorization. As a consequence, most of the minor constituents that were originally present in the rapeseeds are significantly depleted in the oil. Some of the phytosterols (which include β-sitosterol, campesterol and brassicasterol) and tocopherols (mainly α- and γ-tocopherol, in a ratio of approx. 1:2) are lost, as are most or all of the phenolics originally present (which includes a high proportion of sinapic acid and its derivatives)[27]. Phytosterols are best know for their ability to reduce cholesterol uptake from the gut, although some, such as Δ^5-avenasterol, possess antioxidant activity.

Cooking

Consumption of raw EVOO is often quite high in Mediterranean cuisine, and this may be important since compositional changes can occur to oils during cooking (see below). Raw EVOO is used as a salad dressing or simply poured on bread, as a main ingredient in many dips and sauces and as an addition to stews at the end of cooking to

enhance flavour. Whereas some people prize EVOO for its flavour, it is unclear if the flavour of raw RO would be an acceptable substitute. OO is also consumed after frying and baking due to oil being absorbed into the cooked food. Large quantities of OO are consumed in the *lathera* dishes of some eastern Mediterranean countries since the cooking oil in which vegetables are cooked is consumed as an integral part of the dish. OO is more commonly used for shallow frying (which typically requires an oil temperature of 140-160°C) rather than deep-frying (180-190°C) due to its relatively low smoke point.

There can be significant thermal degradation of fatty acids and minor components in oils during cooking, and this may potentially have detrimental health effects. Undesirable changes include the hydrolysis and polymerisation of triglycerides, oxidation of fatty acids and sterols, and generation of TFAs. Lipid oxidation is influenced by various factors such as the type of food present, the proportion of oil exposed to the air, and the amount of unsaturated fats (UFA) in the oil. Oxidation increases with the degree of unsaturation: ALA (18 : 3*n*-3) is 2.4 times more reactive than linoleic acid (18 : 2*n*-6) which is 40 times more reactive than oleic acid (18 : 1*n*-9)[28]. This is of potential concern for RO due to its high ALA content. Prolonged and repeated deep frying with RO, as may occur in commercial establishments, can also lead to the generation of quite high levels of TFAs[29].

Loss of antioxidants

During frying, antioxidants in oils are lost due both to direct thermal degradation and by acting as antioxidants and so being consumed during the thermal oxidation of unsaturated fats[30]. EVOO contains a favourable ratio of antioxidants to PUFAs compared to other types of oils, and this reduces both the rate at which antioxidants are lost and the rate of lipid oxidation that occurs during frying[31, 32]. Antioxidants in EVOO deplete at different rates, as demonstrated in a study by Gomez-Alonso et al who found that hydroxytyrosol was depleted to a far greater extent than tyrosol when EVOO was used for frying potatoes at 180°C for 10 min[33]. Phenolics in EVOO help stabilise vitamin E during heating and vitamin E in turn helps protect PUFAs from oxidative degradation[31].

Despite losses of minor components due to frying, heated virgin OO (VOO) has been shown to retain beneficial effects on postprandial inflammation. VOO repeatedly heated to 180°C suppressed postprandial inflammation in obese subjects (determined as NFκB activation in peripheral blood monocytes) compared to a seed oil with similar fat content (a blend of high oleic acid sunflower oil and RO)[34]. Although the heating protocol completely depleted hydroxytyrosol in the VOO, other minor components, including some phenolics, were retained.

In summary, although antioxidants in EVOO are reduced during frying, using EVOO rather than other types of OO for frying may be justified as a means to minimise oxidation of the relatively low content of PUFAs and to reduce postprandial inflammation. Antioxidants in EVOO have also been to shown to migrate into the food during cooking and so may confer health benefits in the body[35, 36].

Antioxidants in RO include phytosterols, vitamin E and Coenzyme Q, although levels of phenolics are very low compared to EVOO (see Table 1). Vitamin E content was reduced by two-thirds when RO was heated at 150°C for 6 h[30], and vitamin E was also significantly depleted using conditions designed to replicate RO being used for deep frying[37]. The concentration of ALA in RO is a major determinant of the extent of fatty acid oxidation[38]. The relatively low ratio of antioxidants to PUFAs in RO may lead to significant losses of antioxidants and increase lipid peroxidation, although this will depend on the time period and temperature used for frying. The more favourable balance between antioxidants and PUFAs in EVOO may retain more antioxidants.

Generation of toxic compounds

Insufficient protection of PUFAs from oxidation leads to their conversion to hydroperoxides and these may break down to various volatile compounds[39]. Some, like acetaldehyde and acrolein (2-propenal), are toxic. Acetaldehyde is classified as a carcinogen by the EU, whereas the main health effect of exposure to acrolein is irritation of the eyes, the mucosae and the skin[40]. It is therefore desirable to minimise exposure of the cook to toxic volatile compounds produced during frying. Fullana et al reported that acetaldehyde production at 180°C was twice as high for RO compared

with either OO or VOO[41], although levels from all oils were low, and no acetaldehyde emissions were detected by Katragadda et al at 180°C[42]. Production of acrolein by RO at 180°C was found to be approximately five times higher than acrolein production by either EVOO or OO[41, 42]. This is probably due to the high ALA content of RO since recent studies indicate that thermal degradation of ALA is the main source of acrolein in RO[43, 44]. The presence of antioxidants in EVOO such as chlorophylls, pheophytins and carotenoids, may also reduce acrolein formation compared with RO[45]. Despite the generation of some toxic volatiles, especially by RO, there is no evidence that, under normal domestic conditions, using fresh RO for shallow frying is likely to pose a health risk through inhalation.

In summary, there exists a clear advantage for EVOO over RO in terms of the former's richer composition, limited processing without solvent extraction and deodorization, and safety of use in cooking.

Health

Various studies have assessed the health benefits of OO and RO. Several expert committees have described the basis for making a robust judgement of a causal relationship between a nutrient or food and disease risk[46, 47]. Consistency between several observational studies is necessary, with prospective studies favoured over case-control studies. When available, there should be randomized controlled trials (RCT) of sufficient size and duration, with more weight being given to disease incidence as an endpoint rather than to biological markers. Experimental studies, both *in vivo* and *in vitro,* can provide biological plausibility. We follow these guidelines for assessing the respective health benefits of OO and RO. Epidemiological studies are summarised in Tables 2 and 3.

OO and health

Cardiovascular diseases

Many epidemiological studies, including RCT, have shown that a Mediterranean dietary pattern that includes OO is convincingly associated with a reduced risk of CVD, and is probably associated with a reduced risk of certain cancers and

neurodegenerative diseases (reviewed in[48]). Only a few of these epidemiological studies have focused on the specific effect of OO. Ancel Keys, the pioneer advocate of the MD, first proposed that it was the ratio of MUFA:SFA that was the key component for the health benefits of the MD[49]. Although this suggested that the importance of OO was to provide MUFA, later on it was established that MUFA from sources other than OO (animal fat contains 40 to 45 % of MUFA) did not have the same beneficial effect[50].

Consequently, studies were undertaken to decipher the specific effect of OO. In the Three-City Study, those with intensive use of OO showed a lower risk of stroke compared to those who never used OO[51]. In the Italian-EPIC cohort, women with a high OO consumption had reduced incidence risk of non-fatal and fatal myocardial infarction[52], although it should be noted that this study has been criticised because it was not fully adjusted. In another analysis conducted on the EPIC population in Spain, a high intake of OO decreased the risk of overall mortality by 26% and of CVD deaths by 44%[53]. A recent meta analysis by Martinez-Gonzalez et al comparing high versus low intake of OO found a significant risk reduction for stroke, but the risk reduction for CHD was not significant (Table 2)[54].

In the studies included in the meta analysis by Martinez-Gonzalez et al, only that by Buckland et al distinguished between OO and EVOO. In this well-conducted study from Spain, there was a reduction of CVD incidence of 7% for each 10g increase of OO per 8.4 MJ ingested, and this effect was greater for EVOO (risk reduction 14%)[55]. The role of EVOO was examined in the PREDIMED randomised control trial. Participants at high vascular risk were randomly allocated to three groups. Two groups received a typical MD supplemented with either EVOO (1 litre/week) or mixed nuts (30 g/day). The third, control group was advised to follow a low-fat diet. In the two groups that received advice on the MD, the risk of CVD (myocardial infarction, stroke or death from cardiovascular disease) was reduced by approximately 30%[56]. Recent additional analysis of the PREDIMED study provides further evidence for a superior benefit for EVOO versus non-virgin OO in CVD risk. This observational prospective cohort analysis was based on baseline consumption of OO ie prior to randomisation into groups. In individuals at high cardiovascular risk, there was a statistically significant reduction in total cardiovascular risk and stroke (but not myocardial

infarction) for total OO consumption or for consumption of EVOO, but not for consumption of non-virgin OO[57] (see Table 2). These results remained even after adjusting for adherence to a MD. The results highlight the possible important contribution of minor components in EVOO for cardiovascular protection.

Short-term studies with cardiovascular risk factors as end-points also suggest that phenolics are important for the cardiovascular benefits of VOO. For example, the EUROLIVE study, comparing OO high and low in phenolics, found a linear increase in HDL cholesterol levels for low-, medium-, and high-polyphenol olive oils, and a linear decrease in oxidized LDL levels[58]. A reduction in LDL oxidation for EVOO with a minimum hydroxytyrosol content is the basis for a recent health claim issued by the European Food Safety Authority for the health benefits of OO[59]. VOO, as part of a Med diet, has also been shown to reduce levels of circulating inflammatory molecules associated with increased cardiovascular risk[60].

Experimental models *in vitro* and *in vivo* suggest that VOO can favourably alter many stages in atherosclerosis. VOO was shown to reduce atherosclerosis in apo-E deficient mice and hamsters[61]. Anti-inflammatory activities of minor components in VOO include reducing prostacyclin synthesis in human vascular smooth muscle cells, inhibiting cyclo-oxygenases[62], and inhibiting endothelial adhesion molecule expression[63]. Phenolics also have favourable effects on haemostasis[64]

Although many studies indicate that cardiovascular risk is reduced when MUFA replaces dietary SFA or carbohydrates[65], epidemiological evidence for a specific role for the oleic acid in OO for cardiovascular protection is limited. However, short term feeding studies in humans suggest that one benefit of diets rich in OO is that they do not have the adverse effects on post-prandial inflammation and haemostasis seen with diets rich in SFA[12]. OO also has beneficial hypotensive effects in short term feeding studies[12], and oleic acid is implicated in these effects since, in rat models, triolein (the main TAG in OO, consisting of 3 oleic acid moieties) reduced blood pressure as effectively as VOO[66].

Cancers

A beneficial effect of adherence to a MD (as assessed by a Mediterranean diet score) and reduced cancer risk is found to be greater in Mediterranean, rather than non-Mediterranean, populations[8]. The overall cancer mortality in the Spanish study quoted above showed a RR <1 but was non significant[53]. In the PREDIMED study, no statistically significant associations were found for consumption of any type of OO and mortality from all types of cancer[54]. However, different cancer sites are characterized by different risk factors and for some types of cancer there are indications of a specific effect of OO, and this is supported by several *in vitro* and *in vivo* experimental studies[67]. A meta-analysis of 25 studies reported risk reduction for upper digestive and respiratory tract cancers, breast and, possibly, colorectal and other cancer sites[68]. Similarly, *a posteriori* dietary pattern analysis has demonstrated a greater risk reduction in breast cancer when OO was present in the pattern[69-71]. A more recent study addressed the question of OO and breast cancer in the Mediterranean countries of the EPIC study and observed a non-significant risk reduction for oestrogen receptor negative (ER-) progesterone receptor negative (PR-) breast cancers with a high OO intake[72]. These cancers are independent from hormonal factors and differ from ER+ breast cancers in terms of risk factors. However, they represent only 25 to 30% of all breast cancers and the lack of statistical power might explain the large CI seen in this study (see Table 2). This epidemiological observation is supported by an experimental model showing that the OO phytochemical oleuropein is more cytotoxic for basal-like ER- MDA-MB-231 cells than for luminal ER+ MCF-7 cells[73].

Neuro-degenerative diseases

In the prospective Three City Study, OO was associated with a decrease in cognitive impairment[74]. In participants of the PREDIMED study, consumption of some foods was independently associated with better cognitive function. Among them, total OO positively correlated with immediate verbal memory and EVOO with delayed verbal memory[75]. More recently, in the PREDIMED-Navarra trial, 285 participants at high vascular risk were randomly allocated to three groups: a MD supplemented with EVOO, a MD supplemented with mixed nuts, a low-fat diet. Lower mild cognitive impairment was observed in the EVOO group compared to the control group[76]. Participants assigned to the MD + nuts group did not differ from controls. Various anti-oxidant and anti-inflammatory phenolics in EVOO may contribute to these beneficial effects since oxidative stress and inflammation are associated with neuro-

386 degeneration[77]. More specific effects have also been described for EVOO phenolics.
387 Tyrosol and hydroxytyrosol have been shown to decrease activation by β amyloid (Aβ)
388 of the pro-inflammatory transcription factor NFκB in cultured neuroblastoma cells[78].
389 In mouse models of Alzheimer's disease where there is increased Aβ, the EVOO
390 phenolics oleocanthal and oleuropein reduced Aβ levels and plaque deposits[79, 80] and
391 improved memory[81].
392
393 The severity of skin photo-aging was significantly attenuated by the consumption of
394 MUFA from OO in subjects of the SUVIMAX cohort[82]. Only MUFA from OO was
395 efficient, suggesting that phenolics or squalene in OO might be responsible for the
396 beneficial effect on skin photo-aging.
397
398 In summary, based on recognised criteria of evidence in human studies, the level of
399 evidence for the relationship of EVOO with CVD can be qualified as "convincing",
400 and for cancers as "limited-suggestive", especially ER- breast cancer. For aging and
401 cognitive impairment, fewer data exist in favour of a specific beneficial effect of OO,
402 and require confirmation. There is good evidence from both human and experimental
403 studies that phenolics present in EVOO are important for the cardiovascular benefits.
404 More limited experimental studies also suggest that phenolics are important for the
405 anti-cancer and neuro-protective effects of EVOO.
406

407 ***RO and health***

408 Whereas many studies have examined the relationship of OO with disease incidence or
409 mortality as well as biomarkers for disease, studies with RO are mainly limited to
410 outcomes based on biomarkers. Two recent reviews received funding from the food
411 industry and the RO industry[83, 84], hence leading to possible conflicts of interest[85, 86].
412 Most studies with RO have used raw RO. This limits the interpretation of these studies
413 since most RO is consumed after frying and this can cause significant changes in
414 composition, especially of ALA, as discussed above.
415

Cardiovascular disease

A number of reports comparing RO with a source of SFA on biomarkers of CVD risk (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, lipid peroxidation and inflammatory biomarkers) have found that RO is relatively beneficial, as it is an oil low in SFA and high in MUFA+PUFA[84]. As the U.S. Food and Drug Administration put it in the qualified health claim for canola (rapeseed) oil in 2006: "Limited and not conclusive scientific evidence suggests that eating about 1.5 tablespoons (19 grams) of canola oil daily may reduce the risk of coronary heart disease due to the unsaturated fat content in canola oil. To achieve this possible benefit, canola oil is to replace a similar amount of saturated fat and not increase the total number of calories you eat in a day."[87]

It is the generally accepted view that the benefits to heart health are greater when SFA is replaced with PUFA, rather than when SFA is substituted with MUFA[50]. Since there are no observational studies with RO, a review of epidemiological studies of the specific effect of ALA is relevant, albeit with the proviso of possible changes due to frying. These are summarised in Table 3. A review by the Afssa expert group in 2008 concluded that results on mortality were inconsistent[88]. Whereas Folsom et al 2004 observed a modest risk reduction of total mortality in the IOWA women study[89], two studies from the Nurse's Health Study cohort found an effect on mortality only from a sudden cardiac event[90, 91]. Similarly, two studies from the Health Professional Study showed a risk reduction of myocardial infarction[92, 93]. An interesting finding was the observation that there was a risk reduction by ALA when the EPA + DHA consumption was < 100 mg/day, and that this effect was lost when EPA + DHA consumption was ≥ 100 mg/day with a significant interaction ($p = 0.003$ for myocardial infarction and $p = 0.006$ for total CVD) between the two intakes. Similarly, the risk reduction observed for fatal IHD in a prospective study based on measurement of ALA in phospholipids was abolished after adjusting for EPA+DHA[94]. Two prospective studies based on ALA intake and conducted in Northern Europe, the ATBC study[95] and the Zutphen study[96] did not show any significant association.

More recently, another study based on circulating and dietary ALA found no effect of this fatty acid on congestive heart failure[97]. In a meta-analysis published in 2012,

449 there was a borderline significant risk reduction for CVD, and only fatal CHD was
450 significant [98]. A large unexplained heterogeneity was present in this meta-analysis,
451 casting doubts on the results. A more recent analysis using a pooled study design found
452 a non-significant inverse association between ALA intake and CHD risk in men, but no
453 consistent association in women[99]. There has also been a report of a moderate non-
454 linear association of ALA with heart failure[100], and one showing no association of
455 ALA with atrial fibrillation[101].
456
457 Several studies have compared RO with OO on risk factors for CVD. A hypoenergetic
458 RO-containing diet (supplied as oil and margarine) reduced systolic blood pressure,
459 and total and LDL cholesterol to a comparable extent as a refined OO diet, and also
460 resulted in a greater reduction in diastolic blood pressure, probably because of the
461 higher ALA content of the RO diet[102]. In another study, RO resulted in a reduction of
462 total cholesterol of 12% versus 5.4% for OO, but HDL was also significantly reduced
463 in the RO group, but not with OO[103]. In a further study, 18 subjects in 6 experimental
464 cross-over groups received 50g of oil / 10 MJ in a diet of 15 MJ. After three weeks,
465 there was a significant reduction of LDL cholesterol in the RO group which is
466 expected since RO contains 21% PUFAs[104]. All other biomarkers were not
467 significantly different. With the same study design, the same group later published
468 results on TAG. After three weeks, fasting TAG were significantly higher for the OO
469 regimen, with no difference on either post-prandial TAG nor on susceptibility to
470 lipoprotein oxidation[105].
471
472 In conclusion, despite limited evidence of benefits of RO in short term studies on
473 biomarker risk factors for CVD, there are currently no observational and intervention
474 studies to suggest that RO has the cardiovascular benefits of EVOO. Any benefits of
475 RO are likely to be due to ALA.
476
477 *Cancer*
478 ALA has been associated with an increased risk of prostate cancer, but results are
479 inconsistent. A meta-analysis did not find an association between dietary ALA intake
480 and prostate cancer risk[106], although a more recent study has found that ALA
481 increased the risk of advanced prostate cancer in elderly men[107] (Table 3). There are

indications of risk for gastric cancer[108]. Inhalation of the vapours from unrefined RO with a high content of ALA used for cooking was associated to cancers in China[109].

We did not conduct searches for the effects of RO on other diseases.

Recent developments

The increased susceptibility of ALA to oxidation has led to the commercial development of modified ROs with decreased ALA. These include a low linolenic acid canola oil (LLCO), which has an increased linoleic acid content, and a high oleic canola oil (HOCO)[15]. These modified oils have better heat stability[37], but they are more expensive than standard RO. There are currently no clinical studies on their effects on health. However, as noted above, reducing ALA and increasing MUFA may reduce possible cardioprotective benefits of RO.

A second approach has been to increase the level of antioxidant phytochemicals in RO. In 2006 the EU funded project "Optim'Oils" was initiated with the aim of improving production methods for RO. An oil with significantly lower 18:3 *trans* and improved phytochemical composition (minimised losses of phytosterols, tocopherols and phenolics) was successfully developed[17]. In a clinical study, total-/HDL-cholesterol and LDL-/HDL-cholesterol were increased by 4% ($p<0.05$) with consumption of raw standard RO and there were also non-significant increases in ox-LDL. These increases were not seen with the optimised oil[110], and hence there were modest benefits of the optimised RO compared to the standard RO.

Another interesting way forward is to incorporate olive phenolics into RO. The waste water from OO production (olive mill waste water, OMWW) contains high levels of some olive phenolics[111], and disposal of OMWW is of major environmental concern[112]. An OMWW extract has been used to improve the oxidative stabilities of lard[113], sunflower oil[114] and refined OO[115]. A seed oil comprising 30% high-oleic sunflower oil and 70% RO enriched with OMWW was found to reduce postprandial inflammation in obese subjects as effectively as VOO, even after 20 cycles of heating the oils at 180°C[34]. Incorporation of phenolics from OMWW also has the potential to

improve the cardiovascular health benefits of RO since OMWW, which has high levels of hydroxytyrosol, has been shown to reduce LDL oxidation[116].

Conclusions

The extensive evidence for health benefits of EVOO is not matched by similar data for RO, and based on current evidence, RO cannot be recommended as equivalent in terms of health benefits compared to EVOO. There are significant losses of minor constituents during the processing of standard RO and there may also be deleterious changes in FA composition when RO is used for cooking. New initiatives to alter the production methods and composition of RO are addressing some of these issues and could lead to a far healthier, albeit more expensive, product for the consumer in the future. Nevertheless, RO lacks many of the constituents in EVOO, such as secoiridoids and derivatives, which are thought to be important for its health benefits and desirable stability during cooking. The use of OMWW to stabilise RO and improve its health benefits may be of mutual benefit to both industries by using an environmentally polluting waste product from the OO industry to the benefit of producing a healthier product for the RO industry. However, the current high fungicide usage on the oilseed rape crop is also of concern[117].

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871

Table 1 Compositions of Rapeseed Oil and Olive Oils

	Rapeseed oil [15, 17]	**Olive oils** [16]
Main fatty acids (g/100g)		
Palmitic acid (16:0)	3.6	7.5 - 20.0
Oleic acid (18:1)	61.6	55 - 83
Linoleic acid (18:2)	21.7	3.5 - 21.0
α-Linolenic acid (18:3)	9.6	0.0 - 1.0
Minor components (g/kg)		
Squalene	0.28	0.7 - 12.0
Carotenoids	0.01	0.001- 0.01
Phytosterols	6.9	1.0 - 2.3
Tocopherols	0.43 - 2.68	0.036 - 0.37
Phenolics	0.05	0.05 - 0.8

Table 2. Recent epidemiological studies on the health effects of olive oil

Study	Disease outcome	Study design	Subjects/cases Age range	Olive oil type	Exposure measurement	Statistics adjustments	Intake categorisation	Relative Risk (95% CI)	Trend
Samieri et al, 2011[51] (Three-City study, France)	Stroke	Prospective Median follow-up 5.25 years	7 625/148 ≥ 65 years (37.7% males)	Total OO	Frequency of broad categories food and preferred added fat	Cox model 1-Age, sex, education, study centre 2-Foods of the Med diet; other oils; animal fat; smoking; alcohol; PA; other stroke risk factors; BMI, TG, Total cholesterol	Moderate (dressing or cooking), intensive users (dressing and cooking) versus no users	Intensive users: 0.59 (0.37, 0.94)	0.02
Bendinelli et al, 2011[52] (EPICOR study, Italy)	Myocardial infarction	Prospective Follow-up average 7.85 years	29 689/144 Women 35-74 years	Total OO	Validated EPIC FFQ	Cox model 1-Energy 2- education, fruit, vegetables, meat , smoking; alcohol body weight and waist circumference	≥ 31.2 g/d versus ≤ 15.9 g/d	0.56 (0.31, 0.99)	0.04
Buckland et al, 2012[53] (EPIC-Spain)	Overall and CVD mortality	Prospective Follow-up 8 to 12 years	40 622/1 915 deaths/ 416 CVD Women 29-69 years	Total OO	Validated dietary history questionnaire 600 items	Cox model 1-Age, sex, study centre 2-non-nutritional factors: BMI, waist circumference smoking; alcohol; PA 3- Foods of the Med diet score	29.4 g/d /8.4MJ versus < 14.9 g/d /8.4MJ	Overall mortality: 0.74 (0.64, 0.87); CVD mortality 0.56 (0.40, 0.79)	<0.001 <0.001

Buckland et al, 2012[55] (EPIC-Spain)	CHD incidence	Prospective Follow-up 8 to 12 years	40 142/587 29-69 years (38% males)	Total OO EVOO	Validated dietary history questionnaire 600 items	Cox model 1-Age, sex, study centre 2-nonnutritional factors: BMI, waist circumference smoking; alcohol; PA 3- Foods of the Med diet score, excluding olive oil and alcohol 4- Goldberg exclusions	≥28.9g versus <10g	0.78 (0.59, 1.03)	0.079
Guasch-Ferré et al, 2014[56] (PREDIMED Spain)	CVD events and mortality	Prospective Follow-up 4.8 years	7 216 subjects at risk for CVD/227 events/323 deaths; 67 ± 6 (42% males)	Total OO, non-virgin OO, EVOO	Validated dietary history questionnaire 137 items	Cox model 1-Age, sex, intervention group 2-non-nutritional factors: BMI, waist circumference smoking; alcohol; PA; markers of risk factors 3- Med diet score, excluding olive oil and alcohol	Total OO: 56.9 ± 10 versus 21.4 ± 8 g/d EVOO/ 34.6 ± 27.4 versus 9.1 ± 11 g/d Non virgin OO: 21.7 ± 25.1 versus 12.1 ± 11.7 g/d	*CV event total* OO; 0.65 (0.47, 0.91) EVOO 0.61 (0.44, 0.85) Non-virgin OO: NS *CV mortality* total OO 0.52 (0.73, 0.96) EVOO:NS OO: NS	0.01 <0.01 0.04
Buckland et al, 2012[71] Spain, Italy, Greece	Breast cancer	Prospective 9 year follow up	62 284/1 256 cases	Total OO	Validated FFQ	Cox model Age, education, reproductive factors fruit, vegetables, meat , smoking; alcohol body weight	30.1 g/d versus 11.1g/d	0.77 (0.48, 1.26)	
Berr et al, 2009[73]	Cognitive decline	Prospective Median	6 924 65 to ≥80	Total OO	Frequency of broad	Cox model 0-Age, sex, education,	No use versus intensive use	*Visual memory*: 0.83 (0.69,	0.01

(Three-City study, France)	follow-up 4 years	years (39.7% males)	categories food and preferred added fat	centre, baseline cognitive 1- health behaviours and health status; 2- smoking and dietary habits	0.99); *Verbal fluency* 0.85 (0.70, 1.03)

OO, olive oil; PA, physical activity; BMI, body mass index; TG, triglyceridaemia; Goldberg exclusion, exclusion of participants with poor concordance of energy intake to energy expenditure identified using Goldberg criteria

Table 3. Epidemiological studies on the health effects of dietary α-linolenic acid

Study	Disease outcome	Study design	Subjects/cases Age range	Exposure measurement	Statistics adjustments	Intake categorisation	Relative risk‡ (95% CI)	Trend
Folsom et al 2004[88] (Iowa women health study, USA)	Total mortality	Prospective Follow-up 14 years	41 836/4 653 55-69 years	FFQ 127 items	1) Age and energy and 2) covariates previously reported to be associated with total and CV mortality in this cohort	1.21 versus 0.96 g ALA/day (supplementary analysis)	0.85 (not given)	0.01
Albert et al, 2005[89] (NHS, USA)	SCD and other CHD	Prospective Follow-up 18 years	76 763 women/ 206 SCD, 641 other CHD deaths 30-55 years	Validated FFQ	Alcohol, menopausal status, HRT, PA, aspirin, vitamin supplements, hypertension, hypercholesterolemia, diabetes, family history of MI and history of prior CVD, *trans* FA, ratio of PUFA to SFA and *n*-3 fatty acids	0.74 versus 0.31% TEI as ALA	SCD 0.60 (0.37–0.96); Other outcomes NS	0.02
Hu et al, 1999[90] (NHS, USA)	Fatal and non fatal IHD	Prospective	76 283 /232 fatal /597 non fatal IHD 30-55 years	FFQ 116 items	Age, BMI, smoking, hypertension, diabetes, hypercholesterolaemia, menopausal status, HRT, parental history of MI, multiple vitamin use, alcohol , aspirin, PA, SFA, LA, vitamins C and E, total energy	1.36 versus 0.31 g ALA/d	Fatal IHD 0.55 (0.32, 0.94); Non fatal IHD NS	0.01
Lemaitre et al, 2012[96] (Cardiovascular health	Fatal and non-fatal IHD	Prospective Follow–up 10 years	Dietary analyses 4 432/1 072; Biomarkers	FFQ with pictures Plasma concentrat	Age, sex, race, education, smoking status, BMI, waist circumference, alcohol consumption	3.2 versus 1.4l ALA as % total fat intake; % total plasma	Dietary and biomarker NS	

study)			2 957/686	ion		FA concentration		
Vedtofte et al, 2014[98]	Incident CHD fatal and non-fatal	Pooled analysis of 11 prospective cohorts (criteria: ≥150 outcomes and validated FFQ or diet record) Follow-up 4–10 years	229 043 /4 493 CHD events and 1 751 CHD deaths	FFQ or diet record	BMI, education, smoking, PA, alcohol, total energy intake, SFA, *trans* FA, MUFA, LA, *n*-3 LC PUFA, dietary fibre, hypertension	women 1.64 versus 0.58 g ALA/d; men 1.62 versus 1.17 g ALA/d	Men: CHD event 0.85 (0.72, 1.01); CHD death 0.77 (0.58, 1.01). Women: CHD NS; CHD death NS	0.07§
Ascherio et al, 1996[91], (HPFUS)	Incidence of acute MI or coronary death	Prospective Follow-up 6 years	3 757/ 734 MI /229 deaths 40-75 years	Validated FFQ 131 items	Age, BMI, smoking, PA, alcohol, hypertension, cholesterol, family history of MI, fibre intake, energy	1.5 versus 0.8 g ALA/d; 1% energy increase/d	MI 0.80 (0.63 to 1.03) Death NS; MI 0.41(0.21-0.80) Death NS	0.07
Mozaffarian et al, 2005[92]	CHD	Prospective HPFUS Follow-up 14 years	45 722/ 2 306 total CHD/ 218 sudden deaths/ 1521 nonfatal MI 40-75 years	Validated FFQ 131 items	Age, BMI, smoking, PA, alcohol, hypertension, cholesterol, family history of MI, diabetes, aspirin use, protein, SFA, fibre, MUFA, *trans* FA, energy, *n*-6 fatty acids, EPA+DHA,	1g ALA/ d + <100mg EPA+DHA	Non fatal MI 0.42 (0.23-0.75) Total CHD 0.53 (0.34-	

						1g ALA/d + ≥100mg EPA+DHA	0.83) Death NS
Lemaitre et al, 2003[93]	Fatal and non fatal IHD	Case-control nested in Prospective Cardiovascular Health Study, Follow-up 3 years	179 controls/ 54 fatal (male 58%)/125 non fatal (male 64%) ≥65 years	Plasma measurements	Age, study centre, sex, smoking, alcohol, TAG, HDL-cholesterol, hypertension, diabetes, congestive heart failure, claudication, heart rate, family history of MI, fibrinogen, PA. Analyse on combined PUFAs	1 SD increase in plasma concentration of ALA	NS NS for fatal and non fatal
Pietinen et al, 1997[94] (ATBC cohort, Finland)	CHD	Prospective Follow-up 6 years	21 930/1 399 events/633 deaths	Validated FFQ 276 items	Age, supplement, group several coronary risk factors, total energy and fibre intake	2.5 versus 0.9 g ALA/d	NS
Oomen et al, 2001[95] (Zutphen elderly cohort)	Coronary artery disease	Prospective	667/98	Cross-check, dietary history method	Age, standard coronary risk factors, and intake of trans fatty acids and other nutrients,	≥ 0.58 versus <0.45 % energy intake as ALA	NS
Wilk et al, 2012[99] (Physician's Health study)	Heart failure	Prospective , nested case-control.	19 097/1 572	Plasma measurements and validated FFQ	Age at time of blood sampling, atrial fibrillation, hypertension, BMI, alcohol, smoking,	Plasma ALA concentration 0.306 versus 0.097 total % FA. Dietary ALA versus 0.576 g/d	Plasma Q4 0.66 (0.47, 0.94); Q5 NS; Dietary NS

Fretts et al, 2013[100] (Cardiovascular Health Study, USA)	Incident atrial fibrillation	Prospective	4 337 ≥ 65 years	Plasma measurements and validated FFQ, 131 items	Age, sex (and total calorie intake for dietary analyses), race, education, smoking, history of heart failure, history of stroke, BMI, waist circumference, PA, hypertension, LA (for plasma measurements)	0.21 versus 0.10 % total FA,	Plasma NS Dietary NS	NS NS
Pelser et al, 2013[106] (NIH-AARP, USA)	Prostate cancer	Prospective Follow-up 9 years	288 268/23 281 (18 934 non-advanced/ 2 930 advanced/ 725 fatal) 50-71 years	Validated FFQ, 124 items	Age, race, family history, marital status, education, diabetes, PSA screening, total energy, alcohol, tomatoes, BMI in 3 levels (<25, 25 to <30, and 30 kg/m^2 and above), PA, smoking	% energy 0.41 versus 0.88	Non advanced NS Advanced 1.17 (1.04, 1.3)	0.01
Chajes et al, 2011[107] (EPIC)	Gastric adeno-carcinoma	Prospective Nested in the cohort	626/238 43 to 72 years	Plasma concentration	*H. pylori* infection, BMI, smoking, PA, education, socioeconomic status, energy intake	ALA ≥0.24 versus <0.13 as % of total fatty acids	3.20 (1.70, 6.06)	0.001

‡ when nested case-control study; § p for sex interaction

ALA, α-linolenic acid; HPFUS, Health Professional Follow-up study; HRT, hormone replacement therapy; IHD, ischaemic heart disease; LA, linoleic acid; LC, long chain; MI, myocardial infarction; NHS, Nurse's Health Study; NIH-AARP National Institute of Health Aged American Retired Persons; PA, physical activity; PSA, prostate specific antigen; Q, quintile; SD, standard deviation; SCD, sudden cardiac death; SFA, saturated fatty acids; TEI, total energy intake