How should we judge edible oils and fats? An umbrella review of the health effects of nutrient and bioactive components found in edible oils and fats

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How should we judge edible oils and fats? An umbrella review of the health effects of nutrient and bioactive components found in edible oils and fats
Running title: Health effects of edible oils

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Abstract

Dietary guidelines for many Western countries base their edible oil and fat recommendations solely on saturated fatty acid content. This study aims to demonstrate which nutritional and bioactive components make up commonly consumed edible oils and fats; and explore the health effects and strength of evidence for key nutritional and bioactive components of edible oils. An umbrellareview was conducted in several stages. Australian and American food composition databases and studies were examined to profile nutrient and bioactive content of edible oils and fats. PUBMED and Cochrane databases were searched for umbrella reviews, systematic literature reviews of randomized controlled trials or cohort studies, individual randomized controlled trials, and individual cohort studies to examine the effect of the nutrient or bioactive on high-burden chronic diseases (cardiovascular disease, type 2 diabetes mellitus, obesity, cancer, mental health, cognitive). Substantial systematic literature review evidence was identified for fatty acid categories, tocopherols, biophenols, and phytosterols. Insufficient evidence was identified for squalene. The evidence supports high mono- and polyunsaturated fatty acid compositions, total biophenol content, phytosterols, and possibly high α-tocopherol content as having beneficial effects on high burden health comes. Future dietary guidelines should use a more sophisticated approach to judge edible oils beyond saturated fatty acids.

Keywords: Guideline; Nutrition Policy; Fatty Acids; Tocopherols, Polyphenols, Phytosterols, Squalene; Plant Oils; Fats.

Introduction

Although edible fats and oils have complex properties, dietary guidelines in Western countries such as the United States of America (US), United Kingdom (UK), and Australia recommend edible oil or fat to be consumed as part of a healthy diet based solely on its saturated fatty acid content (SFA) ((NHMRC), 2013; Agriculture., 2015; England, 2018). Those low in SFA (predominantly of plant origin) are recommended by dietary guidelines and those high in SFA (predominantly of animal origin with the addition of palm and coconut oil) are discouraged. The basis for this recommendation has been that SFA increases total and non-HDL cholesterol, a risk factor for cardiovascular disease (CVD); whereas replacing SFA with monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) is cardioprotective (Committee, 2020). Further, the recommendation for oil is described as an allowance rather than as part of the core food groups, suggesting that there are no health benefits associated with regular consumption of edible oils and fats as part of a healthy diet ((NHMRC), 2013; Agriculture., 2015; England, 2018).

The first print of the US Scientific Report of the 2020 Dietary Guidelines Advisory Committee was released in July 2020 (Committee, 2020). In line with current US dietary guidelines (Agriculture., 2015), the 2020 Dietary Guidelines Advisory Committee report recommends replacing fats which are solid at normal room temperature with liquid oils, citing the SFA–CVD relationship (Committee, 2020). More specifically, the 2020 Dietary Guidelines Advisory Committee report specifies that SFA should be replaced with PUFA (INRA, 2015). In July 2020, the Australian Government announced funding for the Australian National Health and Medical Research Council to review and update the Australian dietary guidelines (Government, 2020).

It is an opportune time for a more sophisticated approach to dietary recommendations for edible oils and fats as the importance of fatty acid intake extends past CVD to a number of

other high burden diseases and conditions including diabetes, cancer, dementia and mental health (Afshin et al., 2019; Kyu et al., 2018). Further, in recent decades, potential health implications of edible oils at a biochemical level have emerged with compounds such as tocopherols, biophenols, phytosterols, stigmastadienes, terpenes, and squalene (Kris-Etherton et al., 2002). To progress to a more sophisticated approach to judging edible oils and fats in national dietary guidelines, there is a need to compare the nutrient and bioactive content between edible oils and fats to determine which components have the strongest evidence-base for preventing and improving high-burden diseases.

This study aims to: i) demonstrate which nutritional and bioactive components make up commonly consumed edible oils and fats, and ii) explore the potential health effects and strength of evidence for key nutritional and bioactive components of edible oils.

Materials and Methods

An umbrella review was undertaken. An umbrella review allows the examination of a broad scope of issues related to a topic of interest, with the predominant included study type being existing systematic reviews (*JBI Manual for Evidence Synthesis.*, 2020).

This umbrella review drew upon food composition databases and studies, umbrella reviews, systematic literature reviews (SLRs), randomized controlled trials (RCTs), and cohort studies. This study was not prospectively registered; and was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (de Oliveira).

Characterization of common edible oils and fats

In order to select which edible oils and fats are included in this review, two rounds of stakeholder consultation with edible oils and fats experts were undertaken. Edible oils and fats which were considered for their importance for culinary use in Western society and were grouped as "high", "medium", and "low" priority. High priority edible oils and fats were olive oil (separated by grade where possible), canola oil, palm oil, soybean oil, sunflower oil, rice bran oil, peanut oil, coconut oil (separated by grade where possible), cottonseed oil and grapeseed oil. Medium priority was assigned to butter, avocado oil, corn oil and tallow/lard. Low priority was assigned to sesame oil, safflower oil, mustard seed oil, almond oil, walnut oil, flaxseed oil, macadamia nut oil, hempseed oil, pumpkin seed oil, and apricot seed oil.

Target nutrients and bioactive components included in the review were identified through a brief review of the literature as well as through stakeholder engagement. The chosen target nutrients and bioactives were: fatty acid categories (monounsaturated fatty acids [MUFA], PUFA, SFA, and trans-unsaturated fatty acids [TFA]) and the bioactives: tocopherols, biophenols (also commonly referred to as polyphenols), phytosterols, squalene, stigmastadienes, and terpenes. However, the review identified that data on stigmastadienes

and terpenes content in edible oils and fats were extremely limited and were subsequently removed from the review, leaving five target nutrients/bioactives.

Edible oil and fat nutrient and bioactive matrix

To demonstrate which nutritional and bioactive components make up commonly consumed edible oils and fats, food composition databases and studies were drawn upon using the following method, executed by a single reviewer (ST or KA):

1. Food Standards Australia and New Zealand (FSANZ) Food Composition Database ((FSANZ), 2019) and the U.S. Department of Agriculture FoodData Central ((USDA), 2019) for vitamin, mineral, fatty acid, tocopherol and phytosterol composition on the 6th May 2020.
2. Industry websites: Olive Wellness Institute (Glanz & Scharf, 1985) and Australian Oilseeds Industry (Bedell & Shackleton, 1989) were reviewed for reports or links to studies on 6th May 2020.
3. Phenol explorer (version 3.0) was searched for biophenol composition data for edible oils and fats on 6th May 2020 (INRA, 2015).
4. PUBMED and Google Scholar databases were searched on 7th-11th May 2020, using targeted and rapid searching techniques based on keywords.

The nutrient and bioactive composition of the high, medium, and low priority edible oils and fats were extracted by a single reviewer (ST, KA, or ED) and reported as mean (and range when available) in mg per 100g/100mL in a matrix. For the fatty acid composition, data were reported as a percentage of the oil, rather than in mg. Where a study reported multiple analyses of the same edible oil or fat, the mean of these analyses was included in the report.

Eligibility criteria

The eligibility criteria according to the PICO(S) (Participant, Intervention, Comparator, Outcome, Source) format is described in Table 1. Edible oils which were considered high

priority were included for their association with the health outcomes. Health outcomes selected for inclusion were those relevant to population health and currently used as evidence in dietary guidelines (*Australian Dietary Guidelines*, 2013): CVD, type 2 diabetes mellitus (T2DM), obesity, cancer, mental health disorders, cognitive impairment, and inflammation and immune function.

Insert Table 1 about here

To fully understand the impact of the nutrient or bioactive components on health; studies were included when the nutrient or bioactive was consumed from any source rather than only edible oils and fats. Fatty acids which were marine derived (i.e. EPA/DHA) were excluded due to the minimal content in the majority of edible oils and fats used for culinary purposes, and the saturation of marine derived omega-3 in the peer-reviewed published literature. As it was anticipated that the systematic review evidence on fatty acids relation to the health outcomes would be exhaustive; search results were sorted by relevance to the search strategy and a maximum of 50 of the most relevant SLRs were included. Studies were included which reported on major classes and categories of fatty acids and major classes, categories and individual bioactives.

Search strategy

PUBMED and Cochrane Database of Systematic Reviews were searched on 3rd June 2020 to identify umbrella reviews, SLRs, RCTs, and cohort studies that investigated the effect of the five nutritional and bioactive components present in edible oils and fats on the health outcomes. The literature search was completed in two steps. In step 1, umbrella reviews, SLRs of RCTs, and SLRs of cohort studies for each nutritional component on the health outcomes. If no umbrella review or SLR evidence was found, we progressed to step 2. In step

2, RCTs and cohort studies for each nutritional and bioactive component on the health outcomes. The full search strategy is listed in Table S1. Reference lists of relevant narrative reviews were searched for additional eligible studies.

Data extraction

One reviewer (ST or KA) screened titles and abstracts for relevant studies against the inclusion/exclusion criteria. The full texts of potentially eligible studies were then screened to confirm eligibility by one reviewer (ST or KA). If insufficient umbrella or SLRs were included after full text screening, full text screening of RCTs and cohort studies followed. Data were extracted into summary tables according to study design. Data extracted were:

1. SLR**:** author, publication year, design, date of search, number of studies included, study sample, details of the intervention/cohort studies, control condition, health outcomes and their measurements, top line results, strengths/limitations.
2. RCTs and cohort**:** author, publication year, country, design, sample size, subject characteristics, bioactive details, control condition, health outcomes and measurements, top line results, strengths/limitations.

Studies that investigated health outcomes not eligible in this review were noted. One reviewer (ST) identified the key strengths and limitations for each included study, presented these in tables, and they were discussed.

Results

Edible oils and fats matrix

A summary of the nutrient and bioactive content of edible oils and fats are demonstrated as a summary in Table 2 (raw data are presented in the Supplementary Tables S2 to S10). Data on pumpkin seed oil and virgin avocado oil were not identified in the literature, and hence not included in the matrix. Data on different qualities of coconut oil were limited and included when available.

Insert Table 2 about here.

Health effects of nutrients and bioactives found in edible oils and fats

The number of studies identified according to the components are summarized in Table 3. Sufficient SLR literature was identified for fatty acids, tocopherols, biophenols, and phytosterols in step 1. The most frequent outcomes explored in fatty acid reviews was cardiovascular outcomes; however, research is building for other high-burden diseases and illnesses including mortality, cancer, and diabetes. Tocopherol outcomes were most frequently all-cause mortality, cardiovascular, and cancer. The phytosterol literature most frequently explored cardiovascular and cancer outcomes. Biophenol outcomes were broad and included all-cause mortality, cardiovascular, diabetes, cancer, neurodegenerative, and body composition outcomes. The squalene literature was limited to blood lipid outcomes.

Insert Table 3 about here

Health effects of fatty acids

The SLR and meta-analysis (MA) evidence for fatty acid categories and health outcomes was exhaustive and as such the first 50 relevant umbrella reviews and SLRs were included.

Snowball searching found three additional SLRs of high interest, leading to a total of 53 studies (Table S11). Twenty-four were SLRs and MA of RCTs, 13 SLRs and MA of cohort studies, 4 SLRs and MA of cohort studies and case-control studies, 4 SLRs of RCTs, 3 SLRs and MA of RCTs and cohort studies, 2 umbrella reviews of SLRs with MA, 2 SLRs of RCTs and cohort studies and 1 SLRs of RCTs, cohort studies and case-control studies.

All-cause mortality

SLRs of cohort studies and RCTs provided unclear consensus on fatty acid categories and all-cause mortality; with study duration ranging from 12 months to 8 years. In one review of cohort studies, TFAs were positively associated and SFAs had no association (De Souza et al., 2015); whereas in a second review, SFAs were positively associated (Brennan, Woodside, Lunny, Cardwell, & Cantwell, 2017). A third review of cohort studies found linolenic acid and gamma linolenic acid (GLA) had no association with all-cause mortality (Farvid et al., 2014). A review of RCTs found replacing SFA with MUFA and/or PUFA did not reduce total mortality (Hooper et al., 2012), nor did the substitution of SFAs and TFAs with omega-6 PUFA (Ramsden, Hibbeln, Majchrzak, & Davis, 2010).

Cardiovascular outcomes

There is a substantial amount of SLR research on fatty acid categories and cardiovascular outcomes. The most researched is the effect of SFAs via cohort studies and its manipulation with unsaturated fatty acids in RCTs. Cohort studies provided conflicting evidence, more frequently finding no association with cardiovascular outcomes (Chowdhury et al., 2014; Harcombe, Baker, & Davies, 2017; Siri-Tarino, Sun, Hu, & Krauss, 2010; Te Morenga & Montez, 2017; Zhu, Bo, & Liu, 2019). SLRs of RCTs that manipulated the ratio of fatty acid categories show strong evidence for the replacement of SFAs with PUFA, and potentially MUFA. These findings have been synthesized in two recent umbrella reviews and are in line

with current dietary recommendations (Clifton & Keogh, 2017; Foster & Wilson, 2013). Relevant to edible oils was a SLR and MA of RCTs that found no effect of replacing SFA with omega-6 PUFA on coronary heart disease outcomes, with the length of the RCTs ranging 1-8 years (Hamley, 2017).

The SLR evidence is progressing to an individual fatty acid level, demonstrating effects of individual fatty acids which differ to that portrayed in the corresponding fatty acid category. For example, one SLR found medium-chain SFAs improved HDL-C without affecting other lipids (Panth, Abbott, Dias, Wynne, & Garg, 2018). Another SLR found stearic acid improved the lipid profile more than TFAs but less than PUFA or MUFA (Hunter, Zhang, & Kris-Etherton, 2010).

The evidence for TFA being detrimental to cardiovascular health is consistent in both SLRs of cohort studies and SLRs of RCTs (Aronis, Khan, & Mantzoros, 2012; Chowdhury et al., 2014; De Souza et al., 2015; Hunter et al., 2010; Mensink, Zock, Kester, & Katan, 2003; Zhu et al., 2019). In contrast, a review of RCTs on ruminant TFAs found no effect on cardiovascular risk factors (Gayet-Boyer et al., 2014).

The health benefits of non-marine PUFA compared to omega-3, or combined omega-3 and omega-6 PUFA, were less clear as the majority of studies reported PUFA as a total, and limited studies explored the health benefits of non-marine PUFA individually, which did not suggest a clear health benefit or detriment (Chowdhury et al., 2014; Farvid et al., 2014; Haghighatdoost & Gh, 2018; Hooper et al., 2018), critical to the interpretation for edible oils and fats.

Diabetes and glycaemia

An SLR of cohort studies suggested SFAs and TFAs were not linked to T2DM incidence (De Souza et al., 2015), but alpha-linolenic acid (ALA) and fatty fish were associated with lower T2DM incidence (Muley, Muley, & Shah, 2014). In SLRs of RCTs, higher MUFA intake was found to improve glucose outcomes in two SLRs (Qian, Korat, Malik, & Hu, 2016; L. Schwingshackl, Strasser, & Hoffmann, 2011), one showing greater effect than PUFA (Qian et al., 2016). Replacing SFA or carbohydrate with plant-derived PUFA had a favorable albeit weak effect on glucose and insulin in predominantly healthy cohorts in a third review (Wanders et al., 2019); a fourth showed no effect of PUFA on glucose or insulin for people with T2DM (Telle-Hansen, Gaundal, & Myhrstad, 2019); and a fifth found replacement of liquids oils with palm oil did not affect glucose or insulin levels (Zulkiply, Balasubramaniam, Bakar, Rashed, & Ismail, 2019). TFAs did not affect glucose or insulin (Aronis et al., 2012).

Cancer

The evidence for fatty acid categories and cancer was predominantly reliant on reviews of cohort studies. In one review, positive associations were found for total fatty acids, SFAs, and TFAs on ovarian cancer, whereas PUFA and MUFA had no association (Qiu, Lu, Qi, & Wang, 2016). In a second SLR, MUFA was inversely associated with endometrial cancer incidence, whereas PUFA had no association (Zhao et al., 2016). No associations were found for PUFA with lung cancer in one review (Zhang, Lu, Yu, Gao, & Zhou, 2014); or fatty acid categories with breast, colorectal, or prostate cancer in other reviews (Cao, Hou, & Wang, 2016; M. Kim & Park, 2018; C. Xu et al., 2015). One SLR found SFA positively associated with breast cancer mortality (Xia, Ma, Wang, & Sun, 2015).

Inflammation

One SLR was identified for inflammation on RCTs, and found that conjugated linolenic acid increased inflammation (Haghighatdoost & Gh, 2018).

Health effects of tocopherols

Twenty-one SLRs were identified that examined the health effects of tocopherols including SLRs and MAs of cohort studies (N=8), SLRs and MAs of both RCTs and cohort studies (N=3), and SLRs and MAs of RCTs (N=10) (Table S12**)**. Tocopherol studies focused on α-tocopherol and γ-tocopherol. Cohort studies measured tocopherols through dietary intake and/or blood levels. Intervention studies generally used vitamin E (α-tocopherol) as a supplement and the dose ranged from 30mg/day to 5,500IU/day, while the intervention duration ranged from 1 month to 10 years.

The evidence demonstrates an inverse relationship between blood α-tocopherol and all-cause mortality (Aune et al., 2018; Jayedi, Rashidy-Pour, Parohan, Zargar, & Shab-Bidar, 2018), CVD mortality (Jayedi, Rashidy-Pour, Parohan, Zargar, & Shab-Bidar, 2019), and risk of stroke (Aune et al., 2018). The results for the association between blood α-tocopherol and cancer were conflicting across different types, but tended to have relevant associations: inverse relationship for total cancer, bladder, and colorectal cancer (marginal significance), and no association with gastric cancer in the single cohort study (Nurses Health Study) (Aune et al., 2018; Li et al., 2014; Longnecker et al., 1992; Miura & Green, 2015). Blood γ-tocopherol was positively associated with coronary heart disease (Irawati et al., 2019) and bladder cancer (Chen et al., 2015) in two separate studies, and had no association with all-cause or cardiovascular-specific mortality, or risk of coronary heart disease, stroke, or total cancer in a third study (Aune et al., 2018).

Dietary vitamin E intake was associated with all-cause mortality and CVD in one SLR in a non-linear analysis (Aune et al., 2018), but not associated with all-cause mortality (Jayedi et al., 2018) or CVD- mortality (Jayedi et al., 2019) in other reviews. Dietary vitamin E was inversely associated with coronary heart disease in one SLR (Ye & Song, 2008), but had no

association in a more recent SLR (Aune et al., 2018). Dietary intake of vitamin E was inversely associated with bladder cancer but there was no association when including both dietary and supplemental vitamin E intake (Chen et al., 2015), and was marginally significant for increased risk of gastric cancer (Li et al., 2014). A review of intervention and observational studies that included a single cohort study (the Nurses Health Study) did not find an association between dietary vitamin E intake and total cancer incidence (Miura & Green, 2015).

Health effects of biophenols

The search found 15 SLRs and MAs of RCTs, 6 SLRs of RCTs, 2 SLRs of RCTs and cohort studies, 12 SLRs and MAs of cohort studies, and 1 SLR of cohort studies that examined the health effects of biophenols (Table S13). Of the 36 included SLRs, 16 specifically examined the effect of flavonoids, two examined phenols; and one examined flavonoids and lignans. None examined secoiridoids nor single biophenol chemicals. Additional SLRs with and without MAs of either RCTs or cohort studies were identified for the following individual biophenols: curcumin (N=3); hesperidin (N=4); anthocyanin (N=3); flavan-3-ols (N=1); flavonoid subclasses (N=1); quercetin (N=2); resveratrol (N=3). Additional SLRs and MAs of RCTs or cohort studies were identified for one-specific food or beverage rich in biophenols: pomegranate juice (N=3), tea (N=1), green tea (N=1), green coffee bean (N=1), grapes (N=1), cocoa/chocolate (N=4).

Identified studies explored potential health benefits of biophenols through typical dietary intake, circulating blood levels, and supplementation in the form of capsules/tablets, fortified beverage, or high biophenol food or beverage in adults ≥20 years. Cohort studies generally included ≥100,000 people and >10,000 cases. Intervention reviews were mainly in healthy populations and less frequently in people with metabolic abnormalities such as

hypercholesterolemia. Intervention duration ranged from acute effects (testing within hours of intervention consumption) to 3 years. The range of dose was broad (1.55-1500mg/day), but most SLRs reported a minimum dose of ≥28mg/day. Findings are reported according to the health outcome below.

All-cause and cardiovascular-specific mortality

All-cause and CVD-mortality were assessed in SLRs and MAs of cohort studies focused on flavonoids (Grosso, Micek, et al., 2017; Y. Kim & Je, 2017; X. m. Liu et al., 2017; Wang, Ouyang, Liu, & Zhao, 2014). Flavonoid intake consistently had an inverse relationship with all-cause mortality across SLRs with MAs (Grosso, Micek, et al., 2017; Y. Kim & Je, 2017; X. m. Liu et al., 2017); however, an SLR without MA reported conflicting results (Del Bo et al., 2019). One SLR also assessed lignan intake and all-cause mortality for which there was no association found (Grosso, Micek, et al., 2017).

Effect on cardiovascular outcomes

There was a significant risk reduction for incidence of CVD, stroke, and hypertension when highest flavonoid intakes were compared to the lowest; and significant inverse relationships in some dose-response SLRs and MAs (Godos et al., 2019; Y. Kim & Je, 2017; X. m. Liu et al., 2017; Tang, Li, Zhang, & Hou, 2016; Wang et al., 2014). Contrary to the majority, one SLR only detected a significant relationship with CVD risk through sensitivity analysis (Grosso, Micek, et al., 2017) and an SLR without MA reported inconclusive results (Del Bo et al., 2019).

Evidence from SLRs of RCTs suggested olive oil specific biophenols improved cardiovascular risk factors, particularly oxidized-LDL and blood pressure, with mixed effects

on other outcomes (George et al., 2019; Hohmann et al., 2015; Sahebkar et al., 2017). Additional SLRs for RCTs of high-biophenol foods such as ginger, turmeric, green tea, and pomegranate skins suggest a beneficial effect of biophenols on blood pressure, triglycerides, and flow mediated dilation. However, evidence appeared conflicting and dependent, at least in part, on the food source of the biophenols (e.g. turmeric versus ginger versus pomegranate), and possibly the dose and concentration of active components, which is often not tested nor reported (Amiot, Riva, & Vinet, 2016; Ellwood, Torun, Bahar, & Fernandez, 2019; Hooper et al., 2008; Marx et al., 2017). SLRs using supplements found improved blood pressure and HDL cholesterol, flow mediated dilation, blood pressure, weight, and waist circumference; however, there was some inconsistency (i.e. some studies reported a significant effect; others reported no effect) for most of these outcomes, likely related to variations in sample and intervention characteristics (Akhlaghi, Ghobadi, Hosseini, Gholami, & Mohammadian, 2018; Amiot et al., 2016; Farhat, Drummond, & Al-Dujaili, 2017; Kay, Hooper, Kroon, Rimm, & Cassidy, 2012; Potì, Santi, Spaggiari, Zimetti, & Zanotti, 2019).

Effect on diabetes and glycaemia

Total biophenols and the flavonoid subclass had inverse relationships with T2DM risk across three SLRs (Y.-J. Liu et al., 2014; Rienks, Barbaresko, Oluwagbemigun, Schmid, & Nöthlings, 2018; H. Xu, Luo, Huang, & Wen, 2018). However, a fourth SLR found inconclusive results (Del Bo et al., 2019). There was no relationship overall in the one SLR which examined gestational diabetes; except for the drupes subgroup (nectarine, plum, cherry), which was associated with a higher risk of gestational diabetes (Pham, Van Do, & Lee, 2019).

For trials, one SLR found lower acute phase responses to glucose after consuming biophenol-containing foods or beverages with a source of carbohydrate, and the second, found

reductions in glycated haemoglobin (longer term response) through extracts, supplements, or foods (Coe & Ryan, 2016; Palma-Duran, Vlassopoulos, Lean, Govan, & Combet, 2017).

Effect on risk of cancer

There was preliminary evidence suggesting a relationship between total biophenol intake or biophenol subclasses, and risk of various cancers (Grosso, Godos, et al., 2017); however, no association was found between flavonoid intake and colorectal cancer in another SLR (He & Sun, 2016).

Effect on cognition and mental health

Supplementation of biophenols frequently resulted in improved cognitive performance and neuroprotective components, but effect sizes differed and may be related to variations in the age of participants and intervention dose regimens (Ammar, Trabelsi, Boukhris, et al., 2020; Ammar, Trabelsi, Müller, et al., 2020; Hein, Whyte, Wood, Rodriguez-Mateos, & Williams, 2019; Travica et al., 2019). The single SLR of RCTs and cohort studies on mental health explored the effect of supplements and specific biophenol-containing food categories within the Mediterranean diet, and found significant reductions in depressive symptoms (Bayes, Schloss, & Sibbritt, 2020). A single SLR of RCTs found curcumin reduced depressive symptoms (Ng, Koh, Chan, & Ho, 2017)

Effect on immune function and inflammation

The effect of supplementation with or without biophenol-rich foods on immune function and inflammation was predominantly based on flavonoid-specific interventions (Peluso, Raguzzini, & Serafini, 2013; Somerville, Braakhuis, & Hopkins, 2016; Speer et al., 2019; Suen, Thomas, Kranz, Vun, & Miller, 2016). The effects of flavonoids tended to favor reductions in at least one inflammatory and or oxidative stress markers analyzed (Peluso et

al., 2013; Speer et al., 2019; Suen et al., 2016); however, one meta-analysis found no difference between intervention and control for immune function (Somerville et al., 2016).

Individual biophenols

Briefly, regarding SLRs solely on individual biophenols: curcumin reduced depressive symptoms (Ng et al., 2017) and TNF-α concentration (Sahebkar, Cicero, Simental-Mendía, Aggarwal, & Gupta, 2016), but did not affect lipid levels (Sahebkar, 2014). Hesperidin improved vascular cell adhesion molecule 1 but no other inflammatory markers (Lorzadeh, Ramezani-Jolfaie, Mohammadi, Khoshbakht, & Salehi-Abargouei, 2019), improved endothelial function but no other biomarkers (Pla-Pagà et al., 2019), and had no effect on lipids, blood pressure (Mohammadi, Ramezani-Jolfaie, Lorzadeh, Khoshbakht, & Salehi-Abargouei, 2019), or blood glucose (Shams-Rad et al., 2020). Anthocyanin was inversely associated with both coronary heart disease and cardiovascular disease mortality but not myocardial infarction, stroke, or total cardiovascular disease in cohort studies (Kimble, Keane, Lodge, & Howatson, 2019), it improved markers of cardiovascular disease in RCTs (Wallace, Slavin, & Frankenfeld, 2016), and showed promising results on cognitive function (Kent, Charlton, Netzel, & Fanning, 2017). Flavan-3-ols improved cardiometabolic outcomes (Raman et al., 2019). Specifically, flavanols, flavanols, flavan-3-ols and isoflavones were inversely associated with T2DM risk (H. Xu et al., 2018); quercetin reduced blood pressure (Serban et al., 2016) but did not affect lipid levels (Sahebkar, 2017); resveratrol did not improve markers of oxidative stress apart from improving total antioxidant capacity (Koushki et al., 2020), but found improvements in cardiometabolic biomarkers as an adjunct to pharmacological management of T2DM (Hausenblas, Schoulda, & Smoliga, 2015), and did not reduce weight in overweight/obese people, but provided anti-inflammatory effects (Christenson et al., 2016).

Health effects of phytosterols

24 SLRs were identified and included: two SLRs of cohort and case/control studies, and 22 SLRs of RCTs (Table S14). Included studies ranged in duration from 3 weeks up to a year, and most studies included foods fortified with plant sterols, or a tablet or capsule based supplement of either plant sterols or plant stanols. Doses ranged from 0.1 to 9.0 g/day, with the majority using doses between 1.5 and 4.0 g/day. Findings are reported according to the health outcome below.

Effect on cardiovascular outcomes

Supplementation with phytosterols had a strong and consistent improvement on LDL cholesterol where most SLRs reported a decrease of LDL-cholesterol of 0.31-0.38 mmol/L. Effect sizes for LDL-cholesterol were comparable when phytosterols were delivered as fortified foods or as capsules consumed with food (AbuMweis, Barake, & Jones, 2008; Amir Shaghaghi, Abumweis, & Jones, 2013). The effect size in participants on statins was similar to those not on statins (Han et al., 2016; Scholle, Baker, Talati, & Coleman, 2009). There was a marginal decrease in triglycerides in one SLR (Wu, Fu, Yang, Zhang, & Han, 2009) but more frequently no effect was found (Baker, Baker, & Coleman, 2009; Chung et al., 2020; Del Bo et al., 2019; Han et al., 2016; Huang, Frohlich, & Ignaszewski, 2011; Moruisi, Oosthuizen, & Opperman, 2006; Scholle et al., 2009), and no effect on HDL was noted in any of the SLRs.

Two SLRs reported dose-response relationships between phytosterols and LDL-cholesterol (Demonty et al., 2009; Ras, Geleijnse, & Trautwein, 2014), and one SLR compared high (>2.5 g/day) vs low (<1.5 g/day) dose in a sub-group analysis (AbuMweis et al., 2008). There was evidence of a dose-response reduction in LDL cholesterol up to doses of 3 g/day, where

effects appeared to plateau, and no further reductions in LDL cholesterol were observed. A minimum effective dose could not be determined from the included SLRs.

There was some evidence that plant sterols delivered in solid foods or foods which are higher in fat (e.g. fat spreads, yoghurt, salad dressings) may be more efficacious than liquid mediums at lowering LDL cholesterol; however, this was inconsistent and subject to heterogeneity (AbuMweis et al., 2008; Ras et al., 2014). One SLR found that phytosterols fortified in a rapeseed (canola) oil medium lowered LDL cholesterol by an additional 0.1 mmol/L compared to a sunflower oil medium (Ferguson, Stojanovski, MacDonald-Wicks, & Garg, 2016).

One SLR directly compared the effect of plant sterols versus plant stanols on LDL cholesterol levels (Talati, Sobieraj, Makanji, Phung, & Coleman, 2010). At doses of up to 2.5g/day, there was no evidence of a statistical or clinical difference in their efficacy of lowering LDL cholesterol levels. There was also no evidence that plant sterol structure (e.g. ester, free sterols) influenced the effect size or function (AbuMweis et al., 2008; Amir Shaghaghi et al., 2013).

Only one SLR investigated the contribution of individual plant sterols in sub-group analysis, and compared high sitosterol/stanol (>80% sitosterol/sitostanol content) to low sitosterol/stanol phytosterols. Both formations lowered LDL cholesterol, with the high sitosterol/stanol group showing a significantly greater reduction.

Effect on body composition

One SLR investigated phytosterol effects on body composition and found there was no evidence of an effect of plant sterols on body weight, fat mass, or waist circumference (Ghaedi, Varkaneh, et al., 2019). There was a small decrease in BMI in the meta-analysis;

however, this was largely driven by only two studies, with the majority of studies showing no effect (Ghaedi, Varkaneh, et al., 2019).

Effect on blood pressure. One SLR investigated phytosterol effects on blood pressure (Ghaedi, Foshati, et al., 2019). There were small significant reductions in both systolic (-1.55mmHg, 95%CI: -2.67, -0.42) and diastolic (-0.84mmHg, 95%CI: -1.6, -0.08) blood pressure observed. However, the effects were largely driven by only a few included studies, and thus should be interpreted cautiously.

Effect on inflammation

C-reactive protein (CRP) was the only inflammatory marker reported but an effect was not seen in the healthy sample (Rocha et al., 2016).

Effect on cancer risk

There was a decreased incidence of cancer in adults with the highest dietary intake of phytosterols reported in a single SLR (Jiang et al., 2019).

Health effects of squalene

No SLRs and one 20-week double-blind placebo-controlled RCT was identified (Chan, Tomlinson, Lee, & Lee, 1996) (Table S15). The trial included four study arms: i) Squalene standalone (860mg/day), ii) Pravastatin standalone (10mg/day), iii) Combination of Squalene and Pravastatin, iv) placebo.

Squalene consumed in capsule form reduced total cholesterol (17% compared to baseline, $p < 0.05$) and LDL cholesterol (22% compared baseline, $p < 0.05$) significantly more than placebo but less than Pravastatin as standalone treatments (Chan et al., 1996). The combination of squalene and Pravastatin had greatest effect on total cholesterol, LDL cholesterol, and HDL cholesterol than standalone treatments or placebo.

Discussion

This critical review describes the key nutrients and bioactive components in edible oils and fats and their associations with high burden chronic diseases. The results show that edible oils and fats contain chemical properties which affect human health well beyond their SFA content; therefore, the findings demand dietary guidelines reconsider how edible oils and fats are judged. The total fatty acid composition, biophenols, and phytosterols all have well established favorable associations on chronic disease outcomes. There is further emerging evidence that dietary α-tocopherol, but not γ-tocopherol, and squalene may have beneficial effects on risk of chronic disease.

The greatest limitation within identified studies for fatty acids is conflicting results, particularly between SLRs of cohort studies and SLRs of RCTs. RCTs and SLRs are needed which compare MUFA (particularly oleic acid) against non-marine PUFA (particularly LA). In addition, a shift is required from viewing fatty acids, and their categories, as only influencing cardiovascular risk, and understanding their potential influence on other high-burden diseases such as diabetes, mental health, and dementia.

The literature around dietary intake and blood levels of tocopherols, particularly of α-tocopherol, is promising. For example, dose-response meta-analyses of dietary vitamin E cohort studies suggest that 30IU/day (20-27mg/day) incremental increases are associated with a 4% decreased risk of coronary heart disease (Ye & Song, 2008), and 10mg/day incremental increases are associated with a 17% reduced risk of bladder cancer (Chen et al., 2015). These values suggest edible oils could contribute to the health benefits of vitamin E/α-tocopherol as sunflower, rice bran, cottonseed, corn kernel, safflower, and extra virgin olive oil (EVOO) all have >20mg/100ml (range 22.4 to 51.5mg/100ml; Table S5) of α-tocopherol. Consideration is also needed for γ-tocopherol content, which is present in substantial

quantities in canola, soybean and corn oils, as this was linked to an increased risk of both coronary heart disease and bladder cancer (Chen et al., 2015; Irawati et al., 2019). However, further research is needed to examine the effect of increasing dietary a-tocopherol and decreasing γ-tocopherol on blood levels and subsequent disease risk.

Total biophenols and flavonoids were consistently linked with beneficial health outcomes in SLRs across a range of high-burden health diseases. Greater exploration into the dose requirements is needed given the large range of doses reported. The SLRs of RCTs which utilized supplements may not be directly applicable to the biophenol content in edible oils; however, are supported cohort study evidence. Despite potential accuracy limitations for biophenol intake assessment within cohort studies, strong favourable evidence was found for high biophenol olive oil compared to low biophenol olive oil across three SLRs (George et al., 2019; Hohmann et al., 2015; Lukas Schwingshackl et al., 2019). Directly applicable to judging edible oils, 25ml-70g per day of high biophenol olive oil or 3.4-31mg biophenols from extra virgin olive oil had clear health benefits to cardiovascular health compared to refined olive oil (George et al., 2019; Hohmann et al., 2015).

There was strong and consistent evidence of an LDL-lowering effect of phytosterols in a dose-dependent manner for up to 3g/day delivered in food or supplements. These findings were consistent in SLRs which included only high-quality studies. As some of the SLRs included people without hypercholesterolemia, the findings on LDL cholesterol are largely generalizable, but the doses identified (>1000mg/day) were generally well above that obtained from consuming edible oils (≤185mg/100g). However, it is possible that an effect is seen at lower doses, as an SLR of phytosterols in tree nuts, which used a dose range of 4.8-279mg/day, lowered LDL cholesterol, and phytosterol intake was inversely correlated with the change in LDL cholesterol (Del Gobbo, Falk, Feldman, Lewis, & Mozaffarian, 2015).

Further, edible oils and fats are a part of the whole diet, and should be considered together with other sources of phytosterols recommended in dietary guidelines, such as fruits and vegetables.

The literature on squalene was mostly limited to theoretical models, in-vitro studies, and animal studies (Ibrahim, Fairus, Zulfarina, & Naina Mohamed, 2020; Lou-Bonafonte et al., 2018). This pre-clinical evidence suggested a role for squalene in humans as an antioxidant, anticancer, anti-atherosclerotic, and anti-inflammatory age, but human data are lacking. While squalene may hold promise for human health, there is currently insufficient evidence to confirm health effects and dosage required; and if it has any effect when consumed as part of the diet as opposed to a pharmaceutical agent. The dosage used in the single identified RCT (Nergiz & Çelikkale, 2011) was substantially higher than that which would be typically obtained from edible oils: 175g of EVOO per day would be required. Further, outside edible oils, the only known dietary source is shark liver oil, and therefore intake from edible oils and fats would not be supported by intakes from other food groups in the dietary guidelines.

Although SLRs of RCTs which used fortification- or supplementation-based interventions frequently used doses which could not be achieved through usual dietary intake; though dietary guidelines typically do not only include foods which provide 100% of requirements. Demonstrating positive associations of edible oil components with health outcomes strengthens the argument that edible oils and fats form part of a healthy diet for populations and could be considered a core food rather than an allowance if judged on their full fatty acid profile, α-tocopherol, biophenol, and phytosterol content.

Limitations

This umbrella review was not able to draw upon all available literature, using a hierarchy of study designs, and a limited search strategy so as to focus the vast and exhaustive research

available. This umbrella review used transparent and comprehensive methodology; however, due to the broad searching and reviewing required to answer the research questions, did not use systematic review methodology such as searching four or more databases or duplicate screening. Methodology within studies and food composition databases appeared to differ for the different sources, and some may be outdated as highlighted summary tables.

Conclusion

A shift in how we judge edible oils and fats is required from judging based on their SFA content alone, to instead considering if they may be included as part of a healthy diet based on the full nutrient and bioactive component profile of each edible oil and fat; supported by potential health benefits beyond CVD including mortality, T2DM, cancer, inflammation, mental health, and cognition. This may also have flow on effects on how diet quality is judged in clinical practice, in research, and in epidemiology; and in how nutrient profiling and food rating systems are applied globally.

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Table 1. Inclusion criteria according to PICOS format

PICOS element	Inclusion Criteria
Participant	• Human • General population, 'high-risk' disease groups, and groups with a unifying health condition
Intervention	Edible oils and fats which were "high priority": • Fatty acids: MUFA, PUFA, SFA, TFA categories • Tocopherols: Total and individual tocopherols (focus on a-tocopherol) • Biophenols (a.k.a. polyphenols): total and subcategories (flavonoids, phenolic acids, lignans, secoiridoids (oleuropein and ligstrodise derivatives including oleocanthal) • Phytosterols: total level • Squalene
Comparator	• Placebo (for RCTs or SLR of RCTs) • Presence of the nutritional component versus no nutritional component • Varying levels of the nutritional component (high vs low)
Outcome	• Disease/disorder risk factors (all studies): Total cholesterol, low- and high-density lipoproteins, triglycerides, blood pressure, inflammatory (CRP, IL-6, IL-8, IL-10, TNF-α) and oxidative markers (8-iso PGF2a, ORAC, TBARS, FRAP, GSH-Px, SOD), blood glucose, insulin, glycated haemoglobin, body weight/composition change, mental health/wellbeing assessments, common mental illness symptomatology, measures of cognition. • Disease/disorder and event prevalence /incidence (cohort studies): Cardiovascular disease (CVD), CVD-event, CVD-death, T2DM, obesity, cancer, cancer-death, mental disorders, cognitive impairment/dementia.
Sources	• Umbrella reviews of SLRs of RCTs and/or cohort studies • SLRs of RCTs and/or cohort studies (with and without meta-analysis) • RCTs • Cohort studies

CRP: C-reactive protein, CVD: cardiovascular disease, FRAP: Ferric reducing antioxidant power assay, GSH: Glutathione, IL: Interleukin, MUFA: Monounsaturated fatty acids, ORAC: Oxygen radical absorbance capacity, PUFA: Polyunsaturated fatty acids, RCT: Randomized-controlled trial, SFA: Saturated fatty acids, SLR: Systematic literature review, SOD: Superoxide dismutase, T2DM: Type-II diabetes mellitus, TBARS: Thiobarbituric acid reactive substances, TFA: Trans-fatty acids, TNF: Tumor-necrosis factor

Table 2. Key summary of the differences in nutritional components across edible fats and oils

Fats & oils	Vitamins and minerals[a]	Fatty acids	Phytosterols	Biophenols	Squalene[b]
EVOO	Highest in Fe for all oils. Moderate in tocopherol.	High in MUFA, Low in PUFA, Low in SFA.	Moderate content.	High content.	High content.
Olive Oil (refined)	N/A	N/A	Moderate content.	Moderate content.	High content.
Canola oil	High in tocopherol. High in Al, Moderate in Cr, Cl, F & Ni.	High in MUFA, Moderate in PUFA, Low in SFA.	High content.	Moderate content.	Low content.
Palm oil	Low- Moderate in tocopherol. Minimal vit/min.	Moderate in MUFA, Low in PUFA, High in SFA.	N/A.	N/A	Low content.
Soybean oil	High in tocopherol. Presence of Cl.	Moderate in MUFA, High in PUFA, Low in SFA.	Moderate content.	Low content.	Low content.
Sunflower oil	High in tocopherol.	Moderate in MUFA, High in PUFA, Low in SFA.	Moderate content.	Low content.	Low content.
Rice bran oil	Moderate in tocopherol.	Moderate in MUFA, Moderate in PUFA, Moderate in SFA.	High content.	N/A	Low content.
Peanut oil	Moderate in tocopherol.	High in MUFA, Moderate in PUFA, Moderate in SFA.	Moderate content.	Not detectable.	Low content.
Coconut oil	Low in tocopherol.	Moderate in MUFA, Low in PUFA, High in SFA.	Low content.	HE- High content. CE- Moderate content	Low content.
Cottonseed oil	Moderate in tocopherol.	Moderate in MUFA, High in PUFA, Moderate in SFA.	N/A.	N/A.	Low content.
Grapeseed oil	Low in tocopherol.	Moderate in MUFA, High in PUFA, Low in SFA.	Moderate content.	Moderate content.	Low content.
Butter	Low in tocopherol.	Moderate in MUFA,	N/A..	N/A.	N/A.

Fats & oils	Vitamins and minerals[a]	Fatty acids	Phytosterols	Biophenols	Squalene[b]
		Low in PUFA, High in SFA.			
Avocado oil	Low- Moderate in tocopherol.	High in MUFA, Low in PUFA, Low in SFA.	Moderate content.	High content.	Low content.
Corn oil	Very high in kernel and wet milled germ High in bran Moderate in dry milled germ	Moderate in MUFA, High in PUFA, Low in SFA.	High content.	Total content NI	Low content.
Tallow/lard	Tocopherol NI	High in MUFA, Low in PUFA, High in SFA.	N/A.	N/A.	N/A.
Sesame oil	Tocopherol NI Low in Vitamin E	Moderate in MUFA Moderate in PUFA Low in SFA	High content	Low content.	N/A.
Safflower oil	Moderate in tocopherol	High in MUFA Low in PUFA Low in SFA	N/A.	Low content.	Low content.
Mustard seed oil	Low in tocopherol	High in MUFA Moderate in PUFA Low in SFA	N/A.	N/A.	N/A.
Almond oil	Moderate in tocopherol.	High in MUFA, Moderate in PUFA, Low in SFA.	Low-moderate content.	Not detectable.	Low content.
Walnut oil	Tocopherol NI	Moderate in MUFA, High in PUFA, Low in SFA.	Moderate content.	Not detectable.	Low content.
Flaxseed oil	Moderate in tocopherol.	Moderate in MUFA, High in PUFA, Low in SFA.	Moderate content.	N/A.	N/A.
Macadamia oil	Low- Moderate in tocopherol.	High in MUFA, Low in PUFA, Low in SFA.	Moderate content.	High content.	Low content.

Fats & oils	Vitamins and minerals[a]	Fatty acids	Phytosterols	Biophenols	Squalene[b]
Hemp seed oil	High in tocopherol.	Low in MUFA, High in PUFA, Low in SFA.	Moderate content.	High in total phenols and very high in total flavonoids.	Low content.
Apricot seed oil	Moderate -High in tocopherol.	High in MUFA, Moderate in PUFA, Low in SFA.	N/A	Low content.	N/A.

N/A- not applicable symbol is used when data were not obtained from the literature search.
Olive oil is reported as a combination of multiple grades in the Food Standards Australia and New Zealand database. Data on refined olive oil were identified for Phytosterols, Biophenols and Squalene.
Cr- Chromium; Cl- Chloride; F- Fluoride; Ni- Nickel; Al- Aluminium; Fe- iron; MUFA- monounsaturated fatty acids; PUFA- polyunsaturated fatty acids; SFA- saturated fatty acids.
a. Clinical relevance of most levels is questionable.
b. Note. Amaranth oil is reported to have significantly higher squalene that all other oils reviewed in this matrix.

Table 3: Number of studies included according to each component

Component	Umbrella reviews	Number of SLRs	Number of RCTs[a]	Number of cohort studies
Fatty acid categories				
Total	2	51	N/A	N/A
Multiple FA categories	1	19	N/A	N/A
MUFA	0	3	N/A	N/A
PUFA	0	8	N/A	N/A
SFA	1	10	N/A	N/A
SFA + TFA	0	2	N/A	N/A
TFA	0	2	N/A	N/A
Edible oils/fats[b]	0	9	N/A	N/A
Tocopherols	0	21	N/A	N/A
Biophenols[c]				
Total	0	36 *(+ 27 related[d])*	N/A	N/A
Flavonoids	0	16	N/A	N/A
Phenolic acids	0	2	N/A	N/A
Lignans	0	1	N/A	N/A
Secoiridoids	0	0	N/A	N/A
Phytosterols	0	32	N/A	N/A
Squalene	0	0	1	0

N/A: not applicable, PUFA: polyunsaturated fatty acids, RCT: randomized controlled trial, SFA: saturated fatty acids, TSFA: trans saturated fatty acid, SLR: systematic literature review

a. If sufficient SLRs were identified for a nutritional component, the number of RCTs and cohort studies were not quantified; as per the methodology on page 8.
b. Edible oil/fat studies identified in the FA search were noted and added to the end of the table. This is not a comprehensive list; however, may provide insight into the evidence base.
c. Some biophenol studies explored more than one subclass. These studies were tallied in each of the respective subclass categories.
d. Studies identified which were specific to one individual phenol-containing food such as cacao, or an individual biophenol were documented to further describe the breadth of the literature.