Original Article

The effects of palm oil on serum lipid profiles: A systematic review and meta-analysis

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Background and Objectives: Current guidelines recommend reducing intake of diets rich in saturated fats and replacing it with diets rich in unsaturated fats. Palm oil contains a high amount of saturated fatty acids, but its effect on serum lipid levels is unclear. The study aimed to compare the effects of palm oil consumption with other edible oils rich in monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) on serum lipid profiles. **Methods and Study Design:** We searched Medline, Embase, Cochrane Central Registry of Controlled Trials and CINAHL. Clinical trials were eligible if they compared palm oil-rich diets with diets rich in MUFAs or PUFAs. We pooled results of included studies using a random effects model and assessed the quality of the evidence and certainty of conclusions using the GRADE approach. **Results:** Intake of palm oil intake compared to oils rich in MUFA was associated with increased levels of total cholesterol (TC) [mean difference (MD)=0.27 mmol/L; 95% CI 0.08 to 0.45], LDL-C (MD=0.20 mmol/L; 95% CI 0.02 to 0.37) and HDL-C (MD=0.06 mmol/L; 95% CI 0.02 to 0.10). Similarly, for comparison with oils rich in PUFAs, palm oil showed increased in TC (MD=0.38 mmol/L; 95% CI 0.14 to 0.62), LDL-C (MD= 0.44 mmol/L; 95% CI 0.01 to 0.88) and HDL-C (MD=0.08 mmol/L; 95% CI 0.03 to 0.13). For both comparisons, there were no significant effects on triglycerides. **Conclusions:** Even though palm oil increases marginally the level of serum lipids, the evidence is mostly of low to moderate quality.

Key Words: palm oil, saturated fatty acid, unsaturated fatty acid, lipid levels, meta-analysis

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, including Malaysia, accounting for approximately 30% of all global deaths annually.[1] The strongest risk factor for CVD is hyperlipidaemia, a raised fasting total cholesterol (TC) levels, which may be associated with increased triglyceride (TG) levels.[2] The conventional plasma markers of CVD risk are TC, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and TG. Apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) have now emerged as more sensitive predictors of the occurrence of CVD events.[3,4] However, these apolipoproteins are not routinely measured and used as a treatment target for any intervention in clinical practice.

Oil palm yields more oil per unit area than any other temperate or tropical oil crop,[5] hence it is the most widely consumed vegetable oil in the world.[6] It is sourced from the tropical plant Elaeis guineensis,[7] and the oil contains mainly saturated fatty acids including palmitic acid (44%), stearic acid (5%) and myristic acid (1%). The unsaturated fatty acids component consists mostly of monounsaturated oleic acid (39%) with a small proportion of polyunsaturated linoleic acid (10%).[8,9] Despite its eco-nomic importance as a high-yielding source of edible oils with high oxidative stability, controversies concerning palm oil consumption and its associated health risks remain because of its high saturated fat content. For example, multiple studies have suggested an association between high contents of saturated fats with detrimental atherogenic profile.[10-13] Current dietary guidelines recommend reducing intake of total saturated fat and replacing it with foods high in monounsaturated fatty acids (MUFAs) or polyunsaturated fatty acids (PUFAs) to reduce the risk of CVDs. The guidelines make recommendation based on evidence from clinical trials that high consumption of saturated fats raised blood cholesterol which would increase CVD risk. However, one recently published opinion paper questions the recommendations.[14] The authors pointed out that dif-

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ferent saturated fatty acids have different health effects. As for palm oil, emerging evidence suggests that although it contains 50% saturated fat, it behaves like a MUFA in terms of its effects on serum cholesterol levels.[15]

At least two systematic reviews found no association of intake of dietary saturated fats with an increased risk of CVD.[16,17] Specific for palm oil, evidence from one systematic review[18] could not establish whether its consumption is associated with risk of CVD or mortality. As for the effects of palm oil on CVD risk markers (TC, LDL-C, TG) one systematic review[19] that assessed the effect of substituting palm oil with other dietary fats concluded that that palm oil showed both favourable and unfavourable changes. Similarly, another earlier systematic review[20] that reviewed the effects of palm oil intake on blood lipids compared with other cooking oils concluded that palm oil seemed to have unfavourable effects on LDL-C, a well-accepted biomarker for risk of CVD. We aimed to update previous reviews and establish the evidence for the effects of palm oil consumption on serum lipid profiles compared to edible oils rich in MUFAs and PUFAs. However, unlike the previous systematic reviews, we included assessment of the confidence in evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[21-22]

METHODS

Search strategy

We identified relevant trials up to December 2019 through searches of the following electronic databases: Medline, Embase, Cochrane Central Register of Controlled Trials, Evidence-based Medicine Reviews and CINAHL from inception to December 2019. The search was supplemented by bibliographies of retrieved articles and previous reviews. Truncation operators "*" and "$" were used according to the database's requirement. Medical Subject Headings (MeSH) and free text-word were also used in the search. The search terms used were: (palm oil* OR oil*, palm OR palm olein* OR palmitic acid*) AND (lipid* OR high-density lipoprotein OR HDL OR low-density lipoprotein OR LDL OR total cholesterol OR TC OR triglyceride* OR TG OR hyperlipid* OR dyslipid* OR hypercholesterolemi* OR hypertriglyceridemi* OR cholesterol level* OR apolipoprotein* OR apo*).

Selection of trials

Studies were eligible for inclusion if (a) the studies were parallel group randomised controlled trials (RCTs) or crossover studies (b) the intervention included palm oil or palm olein in the diet; (c) the comparators were vegetable oils rich in MUFAs or PUFAs or both (d) the intervention period lasted more than two weeks (e) the outcome assessed included at least one of the following biomarkers (TC, LDL-C, HDL-C, TG, Apo A1 and Apo B).

We excluded (a) observational studies (b) studies in which the intervention arm used palm stearin, palm kernel oil and crude red palm oil (c) trials which used palm oil in combination with other vegetable oil or specially formulated palm oil (d) studies which compared palm oil with other saturated fat-rich vegetable oil (e.g., coconut oil). Current evidence conclusively shows that industrially produced trans fatty acids increases incidence of cardiovascular disease and mortality. Thus, we also excluded trials, which compared palm oil with trans fatty acids (e.g., partially hydrogenated oils).

Two independent reviewers independently examined the titles and abstracts of the articles identified from the searches to assess the relevance of the studies according to the pre-determined inclusion criteria. We obtained potentially eligible studies in full text and then assessed them against the inclusion criteria.

Data extraction

Data from trials deemed eligible for inclusion were extracted using a uniform data extraction form. In case of any disagreement between the two reviewers, we consulted a third review author. For each outcome of interest, we extracted the mean end points and the variability data (SD) for both intervention and control group. We combined effects for MUFA and PUFA trials separately in the meta-analysis because it has been shown that MUFA have less plasma cholesterol-lowering effect than PUFA.[11] We also presented separate analysis for cross-over and parallel studies because of the potential biases notably associated with the crossover trials.[23] For crossover studies with more than one group, we considered endpoint data for each of the group.

Risk of bias

Two review authors independently assessed the risk of bias of included studies addressing seven specific domains, using the Cochrane Collaboration's tool for assessing risk of bias of each study.[23] For crossover design, we applied three additional critical domains.[24]

Assessment of summary effects

Results for all outcomes were expressed as a mean difference (MD) with 95% confidence intervals, calculated from either end of treatment values or change from baseline values. We pooled that data in a meta-analysis to determine the effect of palm oil consumption on TC, LDL-C, HDL-C, TG, Apo A1 and Apo B using RevMan software version 5.3. We standardised units for Apo A1 and Apo B to μmol/L while for serum lipids to mmol/L. For trials with more than one group per arm, the groups within the arm were combined and compared collectively.[23] Statistical significance was set at $p<0.05$ for all outcomes.

Assessment of heterogeneity

We considered clinical and methodological heterogeneity: that is how trials' characteristics (e.g. health condition of participants, types of comparator oils, geographical location) varied between studies. This assessment was complemented by evaluating statistical heterogeneity using I^2 test.[25] I^2 is the percentage of total variation across studies due to heterogeneity. Where statistical heterogeneity was greater than 0%, we planned to use a random effects model. We planned to explore the heterogeneity by conducting subgroup analyses because we expected high levels of clinical and methodological heterogeneity. We prespecified that the following study characteristics might explain some heterogeneity: gender, participant's health

condition (healthy, hypercholesterolemic), geographical location (Western, Asian, and Australian regions), and type of oil as comparators, and percentage of energy derived from fats. We did not conduct the subgroup analysis if the number of included studies was less than 10.

Assessment of publication bias

If ≥10 studies were available we explored the possibility of publication bias through visual inspection of the funnel plot and conducting Egger's regression test (significant at $p< 0.10$).[26] We performed sensitivity analyses to explore the effect of studies with high risk of bias by conducting a meta-analysis both with and without the studies assessed as being at a high risk of bias. A study whose removal either pushed the significance level of the overall association from $p<0.05$ to $p\geq0.05$ (or vice versa), or altered the effect size by 10% or more, we considered it as an influential outlier.

Quality of evidence

GRADE approach was used to assess the confidence in the effect estimates for each outcome in terms of publication bias, study limitations, consistency of effect, imprecision, and indirectness.[23] GRADEpro Guideline Development Tool software (version 2017) was used to generate the "Summary of findings" table. Different quality grade of evidence (high, moderate, low, or very low quality) indicates the different level of confidence in the effect's estimate.[23]

RESULTS

From electronic databases search and other sources, we identified 769 potential articles (Figure 1). Out of these, after removing the duplicates and studies not meeting the inclusion criteria, we retrieved full texts of 26 articles. A further five trials were excluded (Supplementary table 1). Out of the remaining 21 studies, two studies[32,33] involved two distinct subjects in their trials, thus the total number of studies included in our review were 23 studies. However, two trials were excluded from the meta-analysis because of insufficient statistical data.[34,35]

Characteristics of included studies

We included 23 studies (from 21 trials) involving 706 participants (Table 1). Of the 23 studies, 20 studies were RCTs with a crossover design while 3 studies used parallel design. The included studies were published between 1985 and 2016 and the duration of trials ranged from 3 weeks up to 15 weeks, while the washout period ranged from 0 to 6 weeks. The primary outcome measures of TC,

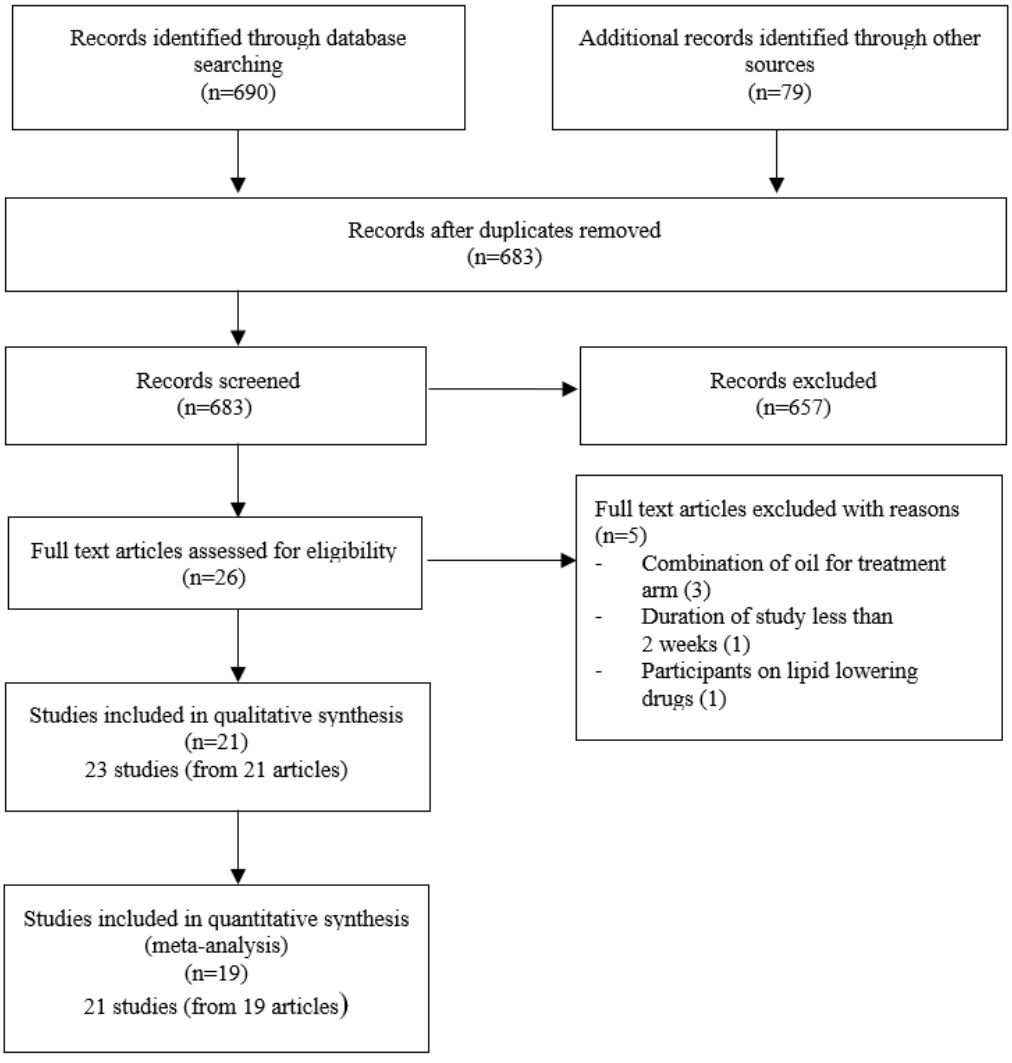

Figure 1. PRISMA flowchart of studies selection.

Table 1. Characteristics of included study

Study (Country)	Design (washout)	Participants health status Number of male: number of female for analysis (total number of dropouts) Mean age (years)±SD/Range	Intervention Type of diet (major fatty acids) (percentage of total energy from fat; percentage of total energy from test fat)	Comparator Type of diet (major fatty acids) (percentage of total energy from fat; percentage of total energy from test fat)	Duration (weeks)	Funding
Iggman et al, 2014[37] (Sweden)	Randomised, double-blinded, parallel groups	Healthy 27M:12F (0) 26.9±4.2	Palm oil (palmitic acid) (51%; NA)	Sunflower oil (linoleic acid) (51%; NA)	7	Swedish Research Council
Ng et al, 1991[38] (Malaysia)	Randomised, double-blinded, parallel groups	Healthy 39M:14F (2) Range: 22-41	Palm oil (palmitic acid) (30%; 23%)	Corn oil (linoleic acid) (30%; 23%)	5	MPOB
Zhang et al, 1997; Exp I[29] (China)	Randomised, parallel groups	Healthy 90M:0F (0) Range: 18-25	Palm oil (palmitic acid) (30%; 18-20%)	a) Soybean oil (linoleic acid) (30%; 18-20%) b) Peanut oil (oleic acid) (30%; 18-20%)	6	MPOB
Bonanome & Grundy, 1988[39] (United States)	Randomised, crossover groups (No washout)	Healthy and Hypercholesterolemic 11M:0F (0) 64±4	Palm oil (palmitic acid) (40%; 40%)	Safflower oil (oleic acid) (40%; NA)	3	NR
Cater & Denke, 2001[40] (United States)	Randomised, single-blinded, crossover groups (≥1week washout)	Mild Hypercholesterolemia 7M:0F (0) Range: 55-75	Palm oil (palmitic acid) (53%; 43%)	Sunflower oil (oleic acid) (53%; 43%)	3	NIH
Cater et al, 1997[41] (United States)	Randomised, crossover groups (≥1 week washout)	Mild Hypercholesterolemia 9M:0F (0) Range: 55-75	Palm oil (palmitic acid) (53%; 43%)	Sunflower oil (oleic acid) (53%; 43%)	3	NIH
Choudhury et al, 1995[42] (Australia)	Randomised, crossover groups (No washout)	Healthy 10M:11F (3) Range: 19-44	Palm olein (palmitic acid) (30%; 17% as test fat)	Olive Oil (oleic acid) (31%; 17%)	4	University of Sydney Nutrition Research Foundation; MPOB
Choudhury et al, 1997[43] (Australia)	Randomised, double-blinded crossover groups (No washout)	Healthy 24M:18F (5) 37±3	Palm oil (palmitic acid) (NA; NA)	Sunflower oil (oleic acid) (NA; NA)	4 weeks Palm oil; 3 weeks Sunflower oil	GRDC; Meadow Lea Foods, Australia
Denke & Grundy, 1992[34] (United States)	Randomised, crossover groups (≥1week washout)	Patients from Metabolic Ward 14M:0F (0) 63±5	Palm oil (palmitic acid) (40%; NA)	Sunflower oil (oleic acid) (40%; NA)	3	Southwestern Medical Foundation; Moss Heart Foundation; VAMC; NHLBI

M: male; F: female; SD: standard deviation; NA: not available; NR: not reported; GRDC: Grains Research and Development Australia; MPOB: Malaysian Palm Oil Board; NIH: National Institute of Health; NHLBI: National Heart Lung Blood Institute; USDA: United States Department of Agriculture; VAMC: Veteran's Affairs Medical Centre.

Table 1. Characteristics of included study (cont.)

Study (Country)	Design (washout)	Participants health status Number of male: number of female for analysis (total number of dropouts) Mean age (years)±SD/Range	Intervention Type of diet (major fatty acids) (percentage of total energy from fat; percentage of total energy from test fat)	Comparator Type of diet (major fatty acids) (percentage of total energy from fat; percentage of total energy from test fat)	Duration (weeks)	Funding
Ghafoorunissa et al, 1995; Exp I[28] (India)	Crossover groups, (6 weeks washout)	Healthy 12M:0F (0) 35±3.8	Palm oil (palmitic acid) (27%; 18%)	Groundnut oil (linoleic acid) (27%; 18)	8	MPOB
Ghafoorunissa et al, 1995; Exp II[28] (India)	Crossover groups, (No washout)	Normocholesterolemic and hypercholesterolemic 12M: 12F (0) 41±5.6	Palm oil (palmitic acid) (32%; 20%)	Groundnut oil (Linoleic acid) (32%; 20%)	8	MPOB
Karupaiah et al, 2016[30] (Malaysia)	Randomised, double-blinded, crossover groups (2 weeks washout)	Healthy 16M:18F (0) 23.4±7.0	Palm olein based mayonnaise (palmitic acid) (NA; 25%)	Soybean oil-based mayonnaise (linoleic acid) (NA; 25%)	4	Kewpie Corporation, Japan
Mattson & Grundy, 1985[44] (United States)	Crossover, (No washout)	Normocholesterolemic and hypercholesterolemic 20M:0F (0) 58.7±6.1	Palm oil (palmitic acid) (40%; NA)	a) High oleic safflower oil (oleic acid) (40%; NA) b) High linoleic safflower oil (linoleic acid) (40%; NA)	4	NIH Moss Heart Foundation
Mensink, 2008[45] (Netherlands)	Randomised, double-blinded, crossover groups (1-week washout)	Healthy 11M:33F (0) 41±16.4	Palm olein (palmitic acid) (40%; 15%)	Rapeseed oil (oleic acid) c) (40%; 15%)	3	Cargill Refined Oils Europe, Netherlands
Noakes et al, 1996[46] (Australia)	Double-blinded, crossover groups (No washout)	Normocholesterolemic and hypercholesterolemic patients 9M:14F (4) 53±9.0	Palm oil (palmitic acid) (35%; 20%)	Sunflower oil (oleic acid) (35% 20%)	3	Meadow Lea Foods, Sydney
Ng et al,1992[35] (Malaysia)	Randomised, crossover groups, (No washout)	Healthy 20M:13F Range: 22-41	Palm olein (palmitic acid) (34%; 23%)	Olive oil (oleic acid) (34%; 23%)	6	MPOB
Sundram et al, 1995[31] (Malaysia)	Double-blinded, crossover groups (No washout)	Healthy 23M:0F (1) 22±4.0	Palm olein (palmitic acid) (31%; 20%)	Canola oils (oleic acid) d) (31%; 20%)	4	NR

M: male; F: female; SD: standard deviation; NA: not available; NR: not reported; GRDC: Grains Research and Development Australia; MPOB: Malaysian Palm Oil Board; NIH: National Institute of Health; NHLBI: National Heart Lung Blood Institute; USDA: United States Department of Agriculture; VAMC: Veteran's Affairs Medical Centre.

Table 1. Characteristics of included study (cont.)

Study (Country)	Design (washout)	Participants health status Number of male: number of female for analysis (total number of dropouts) Mean age (years)±SD/Range	Intervention Type of diet (major fatty acids) (percentage of total energy from fat; percentage of total energy from test fat)	Comparator Type of diet (major fatty acids) (percentage of total energy from fat; percentage of total energy from test fat)	Duration (weeks)	Funding
Tholstrup et al, 2011[36] (Denmark)	Randomised, double-blinded, crossover groups (No washout)	Healthy 43M:0F (2) 29.6±10.3	Palm olein (palmitic acid) (35.8 %; 17%)	Olive oil (oleic acid) (35%; 17%)	3	NR
Utarwuthipong et al, 2009[47] (Thailand)	Randomised, crossover groups (No washout)	Hyperlipidemic 0M:16F (0) Range: 44-67	Palm oil (palmitic acid) (30%; 20%)	a) Soybean oil (linoleic acid) (30%; 20%) b) Rice bran oil (oleic acid) (30%; 20%)	10	Mahidol University
Vega-Lopez et al, 2006[32] (United States)	Randomised, crossover groups (No washout)	Mild hypercholesterolemia 5M:10F (0) 63.9±5.7	Palm oil (palmitic acid) (30%; 20%)	a) Soybean oil (linoleic acid) (28%; 20%) b) Canola oil (oleic acid) (32%; 20%)	5	NIH. USDA
Voon et al, 2011[33] (Malaysia)	Randomised, crossover groups (No washout)	Healthy 9M:36F (0) 30.1±8.3	Palm oil (palmitic acid) (30%; NA)	Olive oil (oleic acid) (31%; NA)	5	MPOB
Wood et al, 1993[48] (United States)	Crossover groups, (6 weeks washout)	Healthy 29M:0F (1) 41±8	Refined palm oil (palmitic acid) (40%; 24%)	Refined sunflower oil (linoleic acid) (40%; 24%)	6	MPOB
Zhang et al,1997; Exp II[29] (China)	Crossover groups, (No washout)	Hypercholesterolemia 31M:20F (0) Range: 32-68	Palm oil (palmitic acid) (30%; 18-20%)	Peanut oil (oleic acid) (30%; 19-20%)	6	MPOB

M: male; F: female; SD: standard deviation; NA: not available; NR: not reported; GRDC: Grains Research and Development Australia; MPOB: Malaysian Palm Oil Board; NIH: National Institute of Health; NHLBI: National Heart Lung Blood Institute; USDA: United States Department of Agriculture; VAMC: Veteran's Affairs Medical Centre.

LDL-C HDL-C and TG were reported in all studies. However, for Apo A1 and Apo B only five studies reported the levels.[36-40] About half of the total studies included healthy volunteers and one study[41] included patients from the metabolic ward.

For the intervention arm, all studies used diets rich in palm oil. For the control arm, diets rich in MUFAs consisted mainly of oil rich in oleic acid while diets rich in PUFAs were primarily oils rich in linoleic acid. For the comparison of palm oil versus diet rich in MUFAs, sixteen crossover studies and one parallel study involving 425 subjects were included for quantitative synthesis (Table 2). Meanwhile, only five crossover trials and three RCTs involving 266 subjects compared palm oil versus diets rich in PUFAs (Table 3).

Risk of bias assessment

Figure 2 and Supplementary Figure 1 show the assessment of trial's quality using the Cochrane 'Risk of bias' tool with the addition of three domains for the assessment of crossover studies. The three domains were appropriate crossover design, carry-over effects and randomised order of receiving treatment.

Appropriate crossover design was given based on three criteria; the condition of the participants was stable, the intervention did not provide permanent change, information on washout period.[24] We judged eight trials had low risk of bias for appropriateness of crossover de-

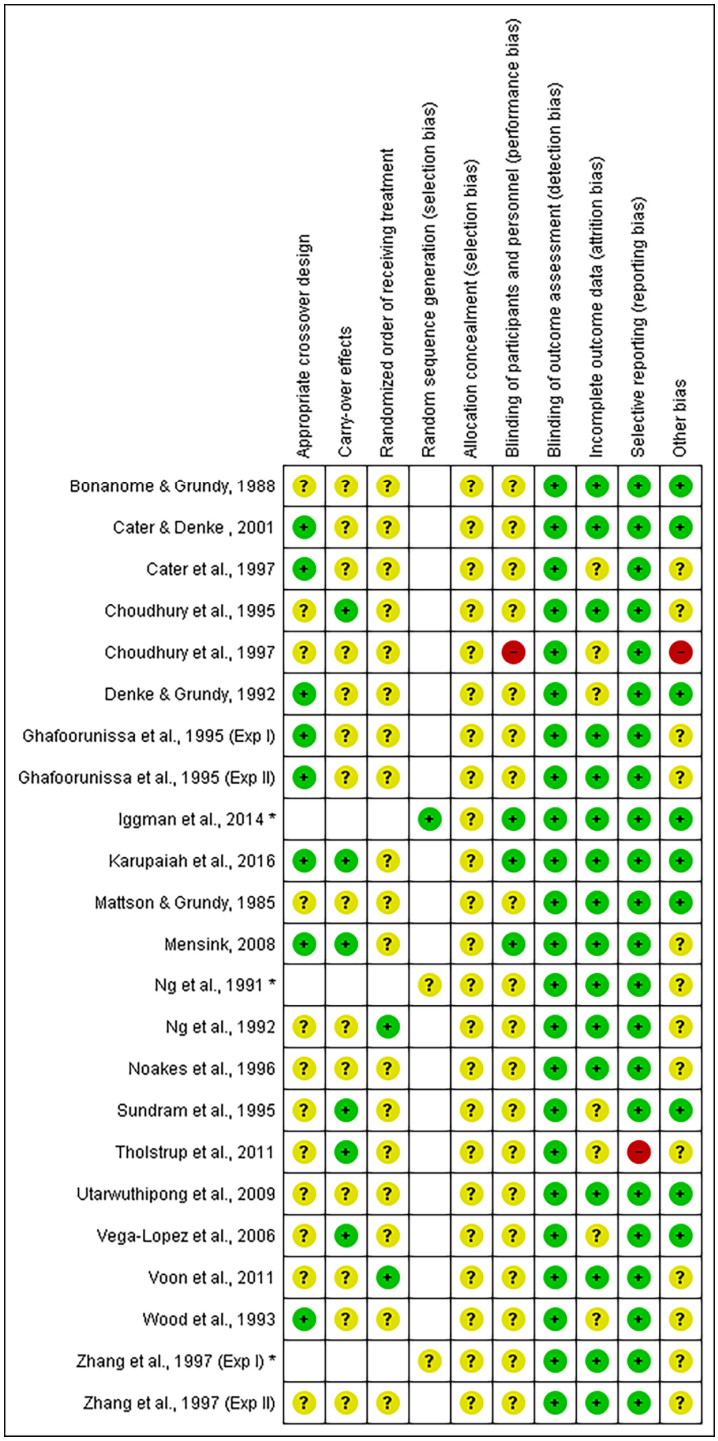

Figure 2. Risk of bias summary.

Table 2. Summary of comparison between palm oil and MUFA diets

	Crossover study					Parallel study				
Outcome	Studies, n	Participants, n	Effect estimate	*p* value	I^2, %	Studies, n	Participants, n	Effect estimate	*p* value	I^2, %
TC (mmol/L)	16	365	0.31 (0.11, 0.51)	<0.01*	62	1	60	-0.12 (-0.38, 0.14)	0.37	NA
LDL-C (mmol/L)	16	365	0.24 (0.06, 0.42)	<0.01*	60	1	60	-0.28 (-0.53, -0.03)	0.03*	NA
HDL-C (mmol/L)	16	365	0.03 (-0.01, 0.07)	0.11	0	1	60	0.18 (0.09, 0.27)	<0.01*	NA
TG (mmol/L)	16	365	0.08 (-0.06, 0.09)	0.75	0	1	60	0.08 (-0.18, 0.34)	0.54	NA
Apo A1 (µmol/L)	3	83	1.34 (-0.80, 3.49)	0.22	0	0	-	-	-	-
Apo B (µmol/L)	3	83	0.10 (-0.06, 0.27)	0.22	0	0	-	-	-	-

MUFA: monounsaturated fatty acid; TC: total cholesterol; LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein; TG: triglycerides; Apo A1: apolipoprotein A1; Apo B; apolipoprotein B; NA: not applicable.
*Significant at $p<0.05$.

Table 3. Summary of comparison between palm oil and PUFA diets

	Crossover study					Parallel study				
Outcome	Studies, n	Participants, n	Effect estimate	*p* value	I^2, %	Studies, n	Participants, n	Effect estimate	*p* value	I^2, %
TC (mmol/L)	5	114	0.37 (0.17, 0.58)	<0.01*	0	3	152	0.32 (-0.22, 0.86)	0.25	82
LDL-C (mmol/L)	5	114	0.26 (0.06, 0.45)	0.01*	0	3	152	0.54 (-0.45, 1.52)	0.29	96
HDL-C (mmol/L)	5	114	0.08 (0.01, 0.15)	0.02*	0	3	152	0.08 (0.00, 0.16)	0.04*	0
TG (mmol/L)	5	114	0.02 (-0.15, 0.20)	0.79	0	2	113	-0.03 (-0.18, 0.13)	0.72	0
Apo A1 (µmol/L)	2	49	0.99 (-2.51, 4.48)	0.58	52	1	38	-2.14 (-6.67, 2.39)	0.35	NA
Apo B (µmol/L)	2	49	0.09 (-0.14, 0.33)	0.43	31	1	38	0.08 (-0.09, 0.25)	0.35	NA

PUFA: polyunsaturated fatty acid; TC: total cholesterol; LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein; TG: triglycerides; Apo A1: apolipoprotein A1; Apo B; apolipoprotein B; NA: not applicable.
*Significant at $p<0.05$.

sign.[32,37,41,44,45,49,52] For the domain of carry-over effects only six studies[34,37,38,39,46,49] were deemed to have low risk of bias as the authors of these trials examined the possibilities of carry-over effect while we judged the rest as unclear. For the domain of randomised treatment order, only two studies[35,40] were considered having a low risk of bias as the method of randomisation was adequately reported. All trials were considered having unclear risk of bias for allocation concealment as the method of concealment was not provided.

Three trials[36,37,49] had low risk of bias for blinding for participants and personnel while one trial,[47] was judged to have a high risk of bias. In this trial, the researchers packed the potato crisps that was part of the dietary intervention in two distinct bags, thus a possibility of blinding being broken.

For the domain of incomplete outcome data, seven trials[34,38,39,41,45,47,52] were judged to have unclear risk of bias. These trials either did not offer reasons for dropouts or provide information whether all participants completed the study. One trial[34] was judged to have a high risk of bias for the domain of selective reporting as 11 randomised participants that had a baseline total cholesterol level of more than 5.2 mmol/L were excluded from statistical analysis. About half of the included studies were financially supported by a palm oil related organisation or a private body that supplied the comparator oil. We judged the risk of bias for financial and commercial conflict of interest for these studies to be unclear.

Effects of palm oil on lipid levels

Comparison of palm oil with diets rich in monounsaturated fatty acids

The effects of palm oil were compared with several edible oils rich in MUFAs and PUFAs. MUFA diets mainly involved oleic acid while PUFA diets, linoleic acid. The comparisons were presented as follows;

One parallel and sixteen crossover trials compared palm oil with MUFAs (Supplementary figure 3-8). Only three crossover trials reported outcome data for Apo A1 and Apo B.[38-40] In crossover studies, palm oil compared to oil rich in MUFAs showed significant difference in levels of TC and LDL-C favouring MUFAs but the effects on HDL-C, TG, Apo A1 and Apo B were not significantly different between the groups (Table 2). For a parallel study design involving one trial, there was a significant difference in LDL-C, and HDL-C between the two groups (Table 2).

Comparison of palm oil with oils rich in polyunsaturated fatty acids

Three parallel and five crossover designs compared palm oil with PUFA diets (Supplementary Figure 9-14). Three studies[36,37,39] reported data for Apo A1 and Apo B. Five crossover studies which compared palm oil versus oils rich in PUFA shows there was a significant difference in TC, LDL-C, and HDL-C between the two groups (Table 3). For parallel study design, there was a significant increase in only HDL-C level (Table 3).

Subgroup analysis

We performed subgroup analyses to examine how estimated effects varies across trials' characteristics (Supplementary table 2). We only provided the findings of the effect of palm oil on LDL-C and TC outcomes because these two biomarkers are well-accepted risk factors for atherosclerosis. Overall, we found trials from Western countries and Australia gave a higher pooled estimate of increased LDL-C and TC compared to trials from Asia (Supplementary table 2). Meanwhile, trials using a higher percentage of total energy derived from fat also showed a higher estimate of LDL-C and TC levels. For other subgroup analyses, we did not detect any other significant differences between the effect of palm oil compared to oil rich in MUFAs. We did not perform subgroup analyses for the comparison of oil palm with diet rich in PUFA, as the number of studies were too few.

Publication bias

We examined data for LDL-C and TC only because they are considered as a risk factor for atherosclerosis. The visual inspection of the funnel plot for the effect of palm oil versus MUFA on LDL-C and TC (Supplementary figure 2) and the Egger's test shows the presence of publication bias. For comparison of palm oil with PUFA, since only eight trials were involved, we did not explore the possibility of publication bias as suggested by Sterne et al.[26]

Grades of recommendation, assessment, development and evaluation

Comparison of palm oil versus MUFAs

The quality of the evidence obtained from the pooled result of our meta-analysis was assessed using the GRADE approach. As recommended by Higgins et al[23] for 16 crossover studies, the quality of evidence for all outcomes was rated down from high to moderate due to studies limitations such as unclear risk and high risk of bias. The quality of outcomes for TC and LDL-C were further rated down from moderate to low due to publication bias (Table 4). Similarly, for the one parallel study, the quality of the evidence was rated down two levels for TC and TG (Table 4).

Comparison of palm oil versus PUFAs

For the three RCTs with parallel design, the quality of evidence started high.[20] We rated the quality of evidence down two levels for TC and LDL-C (Table 5) due to imprecision of the estimates and substantial heterogeneity across the three trials. The quality of evidence remained high for HDL-C. The quality of evidence of crossover studies, for all outcomes was rated down one level because of the study limitations and for TG, Apo A1 and Apo B, the quality was further rated down one level due to imprecision of the estimate (Table 5).

DISCUSSION

In this systematic review and synthesis of evidence from RCTs comparing palm oil, with oil rich in MUFAs or PUFAs we found a marginal increase in the levels of TC, LDL-C and HDL-C with palm oil. To our knowledge, this is the third systematic review and meta-analysis of clinical trials assessing the effects of palm oil on lipid profiles since 2014.

Table 4. Summary of findings: palm oil compared with MUFAs[†]

	Crossover study					Parallel study				
Outcome	Studies, n	Participants, n	Effect estimate	*p* value	Quality of evidence (GRADE) [‡]	Studies, n	Participants, n	Effect estimate	*p* value	Quality of evidence (GRADE) [‡]
TC (mmol/L)	16	365	0.31 (0.11, 0.51)	<0.01*	⊕⊕⊖⊖ Low[1,3]	1	60	-0.12 (-0.38, 0.14)	0.37	⊕⊕⊖⊖ Low[1,2]
LDL-C (mmol/L)	16	365	0.24 (0.06, 0.42)	<0.01*	⊕⊕⊖⊖ Low[1,3]	1	60	-0.28 (-0.53, -0.03)	0.03*	⊕⊕⊕⊖ Moderate[1]
HDL-C (mmol/L)	16	365	0.03 (-0.01, 0.07)	0.11	⊕⊕⊖⊖ Low[1,2]	1	60	0.18 (0.09, 0.27)	<0.01	⊕⊕⊕⊖ Moderate[1]
TG (mmol/L)	16	365	0.01 (-0.06, 0.09)	0.75	⊕⊕⊖⊖ Low[1,2]	1	60	0.08 (-0.18, 0.34)	0.54	⊕⊕⊖⊖ Low[1,2]
Apo A1 (µmol/L)	3	83	1.34 (-0.80, 3.49)	0.22	⊕⊕⊖⊖ Low[1,2]	-	-	-	-	-
Apo B (µmol/L)	3	83	0.10 (-0.06, 0.27)	0.22	⊕⊕⊖⊖ Low[1,2]	-	-	-	-	-

MUFAs: monounsaturated fatty acids; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; Apo A1: apolipoprotein A1; Apo B; apolipoprotein B.

[†]Statistical methods used are Mean Difference (generic inverse variance method, Random, 95% Confidence interval)

[‡]GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate

[1] Downgraded due to studies limitations

[2] Downgraded due to imprecision (95% confidence interval of the pooled effect includes no effect and negative effect)

[3] Downgraded due to publication bias

*Significant at $p<0.05$.

Table 5. Summary of findings: palm oil compared with PUFAs[†]

	Crossover study					Parallel study				
Outcome	Studies, n	Participants, n	Effect estimate	*p* value	Quality of evidence (GRADE)[‡]	Studies, n	Participants, n	Effect estimate	*p* value	Quality of evidence (GRADE)[‡]
TC (mmol/L)	5	114	0.37 (0.17, 0.58)	<0.01*	⊕⊕⊕⊖ Moderate[1]	3	152	0.32 (-0.22, 0.86)	0.25	⊕⊕⊖⊖ Low[2,3]
LDL-C (mmol/L)	5	114	0.26 (0.06, 0.45)	0.01*	⊕⊕⊕⊖ Moderate[1]	3	152	0.54 (-0.45, 1.52)	0.29	⊕⊕⊖⊖ Low[2,3]
HDL-C (mmol/L)	5	114	0.08 (0.01, 0.15)	0.02*	⊕⊕⊕⊖ Moderate[1]	3	152	0.08 (0.00, 0.16)	0.04*	⊕⊕⊕⊕ High
TG (mmol/L)	5	114	0.02 (-0.15, 0.20)	0.79	⊕⊕⊖⊖ Low[1,2]	2	113	-0.03 (-0.18, 0.13)	0.72	⊕⊕⊕⊖ Moderate[2]
Apo A1 (µmol/L)	2	49	0.99 (-2.51, 4.48)	0.12	⊕⊕⊖⊖ Low[1,2]	1	38	-2.14 (-6.67, 2.39)	0.35	⊕⊕⊕⊖ Moderate[2]
Apo B (µmol/L)	2	49	0.09 (-0.14, 0.33)	0.15	⊕⊕⊖⊖ Low[1,2]	1	38	0.08 (-0.09, 0.25)	0.44	⊕⊕⊕⊖ Moderate[2]

PUFAs: polyunsaturated fatty acids; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; Apo A1: apolipoprotein A1; Apo B; apolipoprotein B.

[†]Statistical methods used are Mean Difference (generic inverse variance method, Random, 95% Confidence interval)

[‡]GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate

[1] Downgraded due to studies limitations

[2] Downgraded due to imprecision (95% confidence interval of the pooled effect includes no effect and negative effect)

[3] Downgraded due to publication bias

*Significant at $p<0.05$.

Findings of our updated meta-analysis that focused on the comparison of palm oil with MUFA and PUFA concur with the two previous reviews[19,20] and the most recent RCT[53] that palm oil increases lipid levels namely TC, LDL-C and HDL-C. However, unlike two previous reviews,[19,20] we assessed the quality of the evidence using GRADE approach to indicate the level of confidence in the effects' estimate. We found that the level of confidence for raised LDL-C, which is a well-accepted biomarker for risk of atherosclerosis and CVD, was low. Thus, this means that the estimated effect (raised LDL-C) may probably be markedly different from the true effect. The findings from our systematic review show that further research is necessary to make a firm conclusion that diets rich in palm oil compared to diets rich in MUFA or PUFA has an unfavourable impact on biomarker for CVDs. Several reasons contribute to the uncertainty; the main reason being high heterogeneities among trials. For example, we assessed whether trials from different geographical locations influenced the estimated effects for LDL-C. The test for subgroup differences indicates that trials from Western countries gave a statistically significant higher pooled estimate compared to that from Australia while trials from Asia have the lowest estimated effect. Similarly, heterogeneities were also significant for percentage of total energy derived from fat (p=0.005).

Other reasons that contribute to the uncertainty of the evidence are the unclear risk of bias found in several studies, publication bias and imprecise effects estimate. Palmitic acid (C16:0) in palm oil appears to produce less detrimental effect on blood lipids compared to saturated fatty acids derived from lauric acid (C12:0) to myristic acid (C14:0) rich diets.[54] We did not compare palm oil with trans-fatty acid because current evidence has established that dietary trans-fatty acids are highly atherogenic compared to all dietary saturated fats and dramatically increase risk for cardiovascular diseases.[55] There is a new compelling argument that although palm oil is 50% saturated, it behaves more like a monounsaturated fat[40] and does not adversely affect blood lipid profiles and cardiovascular risks; contradictory to the publicity about its health risk. In addition, conflicting results[56,57] and opinions[14] have recently emerged regarding the benefit of substituting saturated fatty acids with PUFAs on major cardiovascular outcomes.

It has been well established that the different classes of fatty acid show different effects on serum lipid profiles. Clinical and animal studies have shown MUFAs and PUFAs decrease serum cholesterol levels.[58,59] Evidence suggests that the reduction of serum LDL-C level is by three primary mechanisms. One, they increase LDL receptor synthesis and subsequently, the number of receptors available for LDL-C uptake.[60] Two, MUFAs and PUFAs promote cholesterol elimination as bile acid.[61] Three, they reduce the transcription of lipogenic genes which decrease TG and very-low-density lipoprotein (VLDL) and subsequently serum LDL-C.[62]

This study has several strengths. First, we used GRADE approach to assess the confidence in the estimate of the effects of palm oil. The GRADE approach is useful and has the potential for the development of guidelines.[23] Second, the quantitative analysis focused on comparison of studies with similar designs and similar control to minimise methodological heterogeneity. We presented pooled data from the two different designs (parallel, crossover) separately in the same meta-analysis because according to Higgins et al[23] the differences in the trial designs may bias the effect estimate of the intervention. We also separated the meta-analysis for PUFA and MUFA as MUFA have been reported to have less plasma cholesterol-lowering effect than PUFA.[11] Third, similar to another systematic review[19] we synthesised quantitatively results for Apo A1 and Apo B, as these biomarkers have been suggested to be better predictors of CVD risk.[63]

However, this review had several limitations. First, the search of grey literature was not comprehensive, so it is possible we could have missed trials not indexed in the databases even though we attempted to identify all relevant trials by searching through electronic databases using comprehensive search strategies. There was also a possibility that we failed to identify trials published in non-English language. The omissions could have affected the number of studies included in the review and thus the effect estimates. Second, considerable heterogeneity observed in most analyses remains unexplained as we found only geographical locations and total energy intake to explain the heterogeneity. Third, poor reporting in several included trials interferes with the assessment of risk of bias for many domains. Fourth, relates to the unavailability of relevant data for quantitative synthesis. For example, in our analysis, two trials[34,35] were excluded from the meta-analysis because of insufficient statistical data.

Conclusion

In conclusion, we found that palm oil compared to MUFAs or PUFAs increases marginally the levels of TC and LDL-C and HDL-C. However, the quality of the evidence is mostly of low to moderate, so the estimated effects might be markedly different from the true effects due to several factors; limitations of included studies, heterogeneities and possibility of publication bias. Thus, there is still uncertainty in the current recommendations to replace saturated fats (including palm oil) with MUFA or PUFA rich diets as highlighted by one recent opinion paper.[14] Further high quality randomised controlled trials are needed to substantiate that palm oil adversely affects blood lipid profiles particularly LDL-C. Ideally, future studies should involve a larger sample size and authors should improve the trials reporting.

AUTHOR DISCLOSURES

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