Palm oil and blood lipid–related markers of cardiovascular disease: a systematic review and meta-analysis of dietary intervention trials[1–3]

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ABSTRACT

Background: Palm oil (PO) may be an unhealthy fat because of its high saturated fatty acid content.

Objective: The objective was to assess the effect of substituting PO for other primary dietary fats on blood lipid–related markers of coronary heart disease (CHD) and cardiovascular disease (CVD).

Design: We performed a systematic review and meta-analysis of dietary intervention trials. Studies were eligible if they included original data comparing PO-rich diets with other fat-rich diets and analyzed at least one of the following CHD/CVD biomarkers: total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, TC/HDL cholesterol, LDL cholesterol/HDL cholesterol, triacylglycerols, apolipoprotein A-I and B, very-low-density lipoprotein cholesterol, and lipoprotein(a).

Results: Fifty-one studies were included. Intervention times ranged from 2 to 16 wk, and different fat substitutions ranged from 4% to 43%. Comparison of PO diets with diets rich in stearic acid, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) showed significantly higher TC, LDL cholesterol, apolipoprotein B, HDL cholesterol, and apolipoprotein A-I, whereas most of the same biomarkers were significantly lower when compared with diets rich in myristic/lauric acid. Comparison of PO-rich diets with diets rich in *trans* fatty acids showed significantly higher concentrations of HDL cholesterol and apolipoprotein A-I and significantly lower apolipoprotein B, triacylglycerols, and TC/HDL cholesterol. Stratified and meta-regression analyses showed that the higher concentrations of TC and LDL cholesterol, when PO was substituted for MUFAs and PUFAs, were not significant in young people and in subjects with diets with a lower percentage of energy from fat.

Conclusions: Both favorable and unfavorable changes in CHD/CVD risk markers occurred when PO was substituted for the primary dietary fats, whereas only favorable changes occurred when PO was substituted for *trans* fatty acids. Additional studies are needed to provide guidance for policymaking. *Am J Clin Nutr* 2014;99:1331–50.

INTRODUCTION

Diets high in animal fats and low in unsaturated fats have been associated with an increased risk of coronary heart disease (CHD)[4] and cardiovascular disease (CVD) in animal and human studies (1–4). In the past few decades, recommendations indicating that animal fats, which are rich in SFAs, should be substituted with PUFAs have been the main focus of several dietary guidelines targeted toward reducing CHD and CVD morbidity and mortality (5). These recommendations were put forward because dietary SFAs increase blood total cholesterol (TC) and LDL cholesterol, which are known risk factors for CHD and CVD (6). However, not all studies have supported the relation between SFAs and CHD or CVD (7–11), and research on individual dietary fats has shown that different SFAs can exert different effects on cholesterolemia (12) and not only the type of fatty acid, but also the triacylglycerol structure, plays a role (13). In addition, conflicting results have recently emerged regarding the benefit of substituting SFAs with PUFAs on major cardiovascular outcomes (14–16).

Overall, during the past several years, a more complex picture concerning the risk factors for CVD has been developed. In addition to the major traditional serum/plasma markers of CHD risk (ie, TC, LDL cholesterol, HDL cholesterol, and triacylglycerols), other lipid-related biomarkers, such as apolipoprotein A-I and -B, which are the main protein components of HDL cholesterol and LDL cholesterol, respectively, and lipoprotein(a), have been suggested to be valid, if not better, risk predictors (17–20).

Palm oil (PO), a vegetable oil obtained from the fruit of the palm tree (*Elaeis guineensis*), is composed of ∼50% palmitic acid, 40% oleic acid, and 10% linoleic acid. Palmitic acid, in addition to being the most abundant constituent of PO, is the main SFA that naturally occurs in animal and vegetable fats and is the main component of human milk fats (21). Over the past few years, PO use has significantly increased, despite debates over whether it is a potential unhealthy fat because of its relatively high palmitic

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[2] Supported by the Università Bocconi (Milan, Italy) and Soremartec Italia s.r.l.

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[4] Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; PO, palm oil; TC, total cholesterol; WMD, weighted mean difference.

Received December 4, 2013. Accepted for publication March 20, 2014.
First published online April 9, 2014; doi: 10.3945/ajcn.113.081190.

Supplemental Material can be found at:
http://ajcn.nutrition.org/content/suppl/2014/05/13/ajcn.113.081190.DCSupplemental.html

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acid content. However, according to a previous review (22), few studies have investigated the specific effect of palmitic acid or PO on CHD or CVD outcomes (23–27); most of the studies examined intermediate biomarkers of CVD risk.

In this study, we systematically reviewed and performed a meta-analysis of interventional studies that assessed the effect of substituting PO for the other primary dietary fats or oils on traditional and emerging biomarkers of CHD and CVD risk.

METHODS

Search strategy and study selection

The systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (28). We identified relevant articles published up to 30 May 2013, through literature searches in the PubMed/MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed), Embase (http://embase.com), and Cochrane Library (http://www.thecochranelibrary.com/) databases. Combinations of the following keywords were used: "palm oil"[all fields] OR "palmitic acid"[MeSH terms] OR "palm olein"[all fields] AND (cardiovascular disease*[MeSH Terms] "coronary heart disease*"[all fields] OR "cerebrovascular disease*[all fields] OR "acute myocardial infarction"[all fields] OR cholesterol[MeSH Terms] OR lipoprotein*[MeSH Terms]) for the search in PubMed/Medline; "palm oil"/exp/mj OR "palmitic acid"/exp/mj OR "palm olein" OR palm olein AND ("cholesterol"/exp/mj OR lipoprotein* OR apolipoprotein* OR apo*) for the search in EMBASE; and "palm oil" OR "palmitic acid" OR "palm olein" OR palm olein:ti, ab, kw AND "trials" for the search in the Cochrane Library.

We retrieved and assessed potentially relevant articles and checked the reference lists of all articles of interest to identify additional relevant publications. Studies were considered eligible if *1*) they included original data from a controlled dietary intervention trial comparing PO- or palm olein–rich diets with a control diet rich in other oils/fatty acids; *2*) the intervention lasted ≥2 wk (29); *3*) after the intervention diet, the investigators provided estimates of mean values for at least one of the biomarkers of interest [ie, TC, LDL cholesterol, HDL cholesterol, TC/HDL cholesterol ratio, LDL cholesterol/HDL cholesterol ratio, triacylglycerols, apolipoprotein A-I, apolipoprotein B, VLDL cholesterol, and lipoprotein(a)] and a corresponding measure of dispersion; *4*) they were conducted in humans; and *5*) they were published in English. When multiple reports were published on the same population or subpopulation, we included only the most recent and informative report in the meta-analysis. We did not assign quality scores to the studies, and no study was excluded a priori because of weakness of design or data quality. Abstracts and full-text articles were screened for inclusion by 2 independent reviewers (EF and CB), and disagreements were resolved by consensus.

Data collection

For each study selected, we abstracted information on authors, publication year, country, characteristics of the subjects (sex, age, baseline values for BMI and for the markers of interest, and morbidities), number of subjects involved, study design (randomized, crossover, or parallel trial), use of run-in or washout periods, duration of the intervention, type of intervention (including the fatty acid composition, the percentage of energy from fats provided by the intervention diet, and the percentage of energy exchanged by the specific test fat), the subjects' body weight variations after the intervention diet, and source of funding. In addition, for each marker of interest, we extracted the mean within-subjects difference in serum concentrations between the intervention groups and the corresponding SE or SD. If this difference was not available, we extracted the separate means in the intervention groups, with corresponding SEs, SDs, or 95% CIs.

Statistical analysis

Because the studies considered included a significant variety of intervention diets, we classified them into the following 7 groups: *1*) diets rich in PO, red PO, palm olein, or palmitic acid (interesterified at the sn-1,3 position of the glycerol molecule); *2*) diets rich in stearic acid; *3*) diets rich in myristic and/or lauric acid; *4*) diets rich in MUFAs (mainly oleic acid); *5*) diets rich in PUFAs (mainly linoleic acid with a variable low amount of α-linoleic acid); *6*) diets rich in partially hydrogenated *trans* fatty acids; and *7*) diets rich in interesterified PO or fats with palmitic acid in the sn-2 position (*see* Supplemental Table 1 under "Supplemental data" in the online issue). Principal component analysis was applied to the fatty acid composition data of the test diets to verify the robustness of our classification by using Simca-P 8.0 software (Umetrics AB). For studies in which more than one intervention diet fell into the same defined diet group, we combined the intervention groups into a single group (30).

For the analyses, TC, HDL cholesterol, LDL cholesterol, triacylglycerols, and VLDL cholesterol values were converted into milligrams per deciliter; apolipoprotein A-I, apolipoprotein B, and lipoprotein(a) values were converted into milligrams per liter. For each marker, we calculated the weighted mean difference (WMD) in blood concentrations between the PO intervention diet and each of the other intervention diets by using both fixed-effects models and random-effects models. However, to be more conservative, only the results from the latter models were presented to account for the heterogeneity of the effect estimates (31). We assessed the heterogeneity between studies by using the chi-square test, defining significant heterogeneity as a P value <0.10 (31), and we quantified the heterogeneity by using the I^2 statistic (32), which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance. Subgroup analyses were conducted on a priori defined covariates, such as age group, sex, baseline TC, study design, percentage of total dietary energy provided by fat, percentage of energy exchanged by the test fat, country, and source of funding. Meta-regression analyses were also performed to assess the potential modifying effects of these covariates. Moreover, sensitivity analyses were conducted to test the robustness of the results by including only studies on healthy subjects, crossover studies, studies that randomly assigned diets to participants, studies with a washout period between interventions, and studies reporting no meaningful weight change in subjects.

For TC, we provided forest plots, in which a square was plotted for each study with a center projection that corresponds to the

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study-specific mean difference on the underlying scale. The area of the square is proportional to the inverse of the variance of the mean difference and thus provides a measure of the amount of statistical information available. A diamond was used to plot the summary WMD and the corresponding 95% CI. Publication bias was evaluated by visual inspection of funnel plots and quantified by Egger's and Begg's tests (33, 34). STATA software (version 11.2; StataCorp) was used for the statistical analyses.

RESULTS

From the original literature search, we identified 902 records (376 from PubMed, 239 from EMBASE, and 287 from the Cochrane Library). After excluding duplicate records in the various databases, we screened 725 citations. Of these, 106 were considered of interest based on their title and abstract, and their full texts were retrieved for detailed evaluation. Two additional studies were identified from the reference sections of the retrieved articles. Fifty-three articles were subsequently excluded from the meta-analysis for not meeting the inclusion criteria. Overall, a total of 51 studies, corresponding to 49 articles, were considered in the current review/meta-analysis (**Figure 1**). The main characteristics of the studies considered are provided in **Table 1**. The studies included a total of 1526 volunteers (1007 men and 519 women) aged between 16 and 70 y. Ten studies were conducted in Malaysia (35–44); 8 in Australia (45–52); 7 in the United States (53–59); 5 in Denmark (60–64); 4 in the Netherlands (40, 65–68); 3 each in China (69, 70) and Spain (71–73); 2 in Finland (74, 75); 2 in India (76); 2 in Norway (77, 78); and 1 each in Canada (79), France (80), Scotland (81), South Africa (82), and Thailand (83). Ten studies were conducted in women only (58, 71, 73–75, 77, 78, 80, 83, 84), 22 in men only (36, 39, 47–51, 53–57, 61–64, 69, 70, 79, 81, 85), and 19 in both sexes (35, 37, 38, 41, 42, 44–46, 52, 59, 60, 65–69, 72, 76, 82), of which 5 studies (65–68, 76) also provided the results stratified by sex. Sixteen studies were conducted in young people and/or students (average age ≤30 y) (35–39, 41, 62–64, 69, 70, 74, 75, 78, 79, 85), 8 were conducted in the elderly (average age ≥60 y) (53–55, 57, 59, 71, 73, 83), and the remaining studies were conducted in adult subjects of mixed ages. Most studies included healthy volunteers, with the exception of 2 studies that were conducted in subjects with specific pathologic conditions (hyperfibrinogenemia and non-insulin-dependent diabetes mellitus) (60, 82) and 1 study that was conducted in patients at the Veterans' Affairs Medical Center (55). Thirty studies were conducted in normocholesterolemic subjects (35, 36, 38, 39, 41, 42, 44, 45, 47, 56, 58, 61–64, 66–70, 74–77, 79–82, 85), 9 in mild/hypercholesterolemic subjects (37, 46, 54, 55, 60, 65, 72, 78, 84), and 12 in hypercholesterolemic subjects (48–53, 57, 59, 69, 71, 73, 83). The intervention duration ranged from 2 wk (79) to 16 wk (76). Almost all the studies assigned the diets randomly to the volunteers and had a crossover design, whereas 5 had a parallel design (37, 69, 70, 81, 82) and 1 had a sequential design (73). Of the crossover studies, 22 specified that there was a washout period between the intervention diets (35, 36, 44, 47, 54–56, 58, 60, 62–66, 73–79,

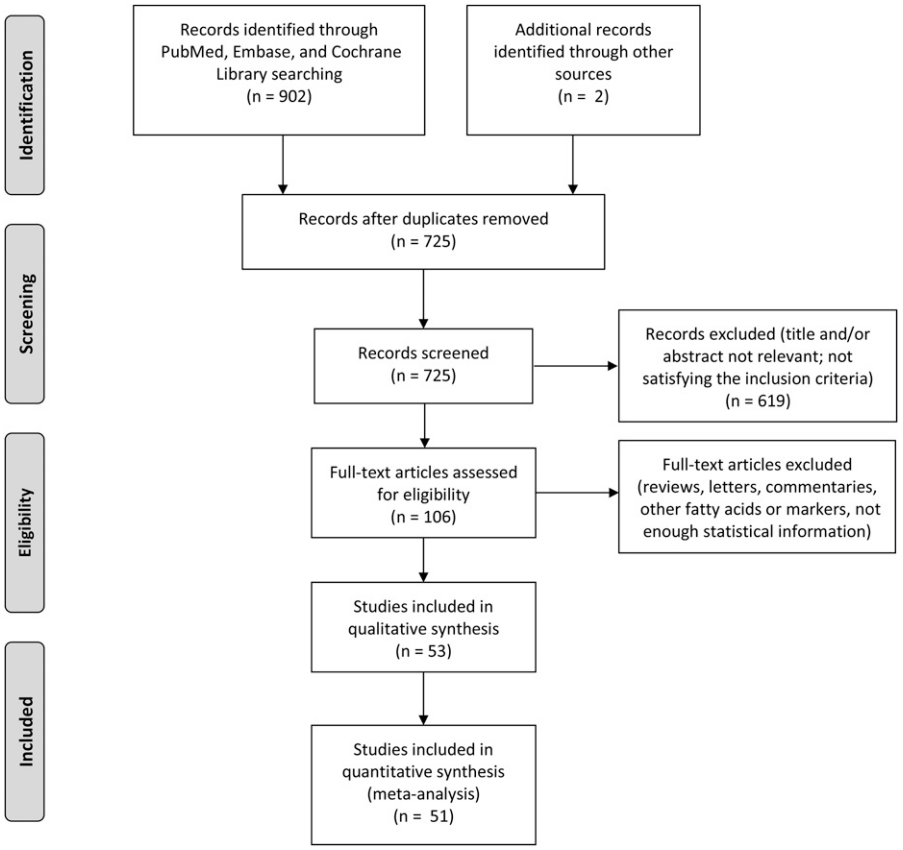

FIGURE 1. Flowchart of the selection of studies for the systematic review/meta-analysis. PubMed, http://www.ncbi.nlm.nih.gov/pubmed; Embase, http://embase.com; and Cochrane, http://www.thecochranelibrary.com/.

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TABLE 1
Main characteristics of the studies included in the review/meta-analysis[1]

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
			y					*wk*	
Baudet, 1984 (80)	France	24 F	46 ± 11	Benedictine nuns		Randomized	Peanut oil	21.4 diet	CETIOM
		12		Normocholesterolemic	TC: 188.33 ± 25.16 mg/dL	Crossover	Sunflower oil		COI
		12		Hypercholesterolemic	TC: 266.25 ± 20.57 mg/dL		Palm oil		CNIEL
							Milk fat		Society Lesieur-Cotelle
							30% of total E as fat		
							20% E as test fat		
Mattson, 1985 (57)	USA	20 M	59 ± 6	VAMC patients	Weight: 51–116 kg	Randomized	Palm oil	4 diet	VAMC
					TC: 263 ± 50 mg/dL	Crossover	High–oleic acid safflower oil		NIH
					TGs: 111–496 mg/dL		High–linoleic acid safflower oil		Moss Heart Foundation
							40% of total E as fat		
Bonanome, 1988 (53)	USA	11 M	64 ± 1.2	Healthy	BMI: 24 ± 0.5 kg/m^2	Randomized	Palmitic acid	3 × 3 diet	VAMC
				Hypercholesterolemic	TC: 5.87 ± 0.23 mmol/L HDL-C: 1.11 ± 0.10 mmol/L LDL-C: 3.98 ± 0.20 mmol/L TGs: 1.64 ± 0.15 mmol/L	Crossover	Stearic acid Oleic acid 40% of total E as fat		
Marzuki, 1991 (36)	Malaysia	110 M	16–17	Healthy	Weight: 51.7 ± 0.7 kg	Crossover	Palm oil	5 × 2 diet	University of Kebangsaan
				Normocholesterolemic Students			Soybean oil 35% of total E	6 washout	
Ng, 1991 (37)	Malaysia	83	20–35	Normolipidemic	BMI: <26 kg/m^2	Randomized	Palm olein	5 × 3 diet	MPOB
Hornstra, 1991 (95)					TC: <6.20 mmol/L	Parallel	Coconut oil		
		61 M 22 F			TGs: <2.26 mmol/L		30% of total E as fat 23% E as test fat		
Nestel, 1992 (49)	Australia	27 M	46.8 ± 9.6	Mildly hypercholesterolemic	TC: 221 ± 29 mg/dL	Blind	Oleic acid	3 × 3 diet	Meadow Lea Foods, Australia
						Randomized Crossover	Elaidic acid Palmitic acid 35% of total E as fat 20% as test fat	2 control period	
Ng, 1992 (38)	Malaysia	20 M 13 F	22–41	Normolipidemic	BMI: <28 kg/m^2	Randomized Crossover	Palm oil Olive oil 30% of total E as fat 23% E as test fat	4 run-in 6 × 2 diet	PORI
Heber, 1992 (56)	USA	13 M	22–43	Healthy Normocholesterolemic		Randomized Crossover	Palm oil Coconut oil Hydrogenated soybean oil 35% of total E as fat 17.5% E as test fat	3 diet 2 washout	NIH MPOB

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TABLE 1 (*Continued*)

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
Denke, 1992 (55)	USA	14 M	63 ± 5	VAMC patients	BMI: 25.5 ± 2.5 kg/m^2	Randomized	High–oleic acid sunflower oil	3 × 3 diet	Southwestern Medical Foundation
						Crossover	High–lauric acid synthetic oil	1 washout	Moss Heart Foundation Dallas
							High–palmitic acid palm oil		VAMC
							40% of total E as fat		National Heart, Lung, and Blood Institute
Nestel, 1994 (48)	Australia	34 M	49 ± 9.8	Healthy	BMI: 25.7 ± 2.96 kg/m^2	Blind	Palmitoleic acid	1–1.5 baseline	Meadow Lea Foods, Australia
				Hypercholesterolemic		Randomized Crossover	Oleic acid Palmitic acid 37% of total E as fat 25% E as test fat	3 × 4 diet	
Sundram, 1994 (85)	Malaysia	17 M	21 ± 1.1	Healthy	BMI: 20.1 ± 1.8 kg/m^2	Double-blind	Lauric + myristic acid	3 run-in	MPOB
				Normocholesterolemic	TC: 4.24 ± 0.73 mmol/L HDL-C: 1.1 ± 0.28 mmol/L TGs: 1.00 ± 0.39 mmol/L	Randomized Crossover	Palmitic acid 30% of total E as fat 20% E as test fat	4 × 2 diet	
Zock, 1994 (68)	Netherlands	69	18–62	Healthy	TC: 3.67–7.10 mmol/L	Blind	Myristic acid	3 × 3 diet	Foundation for Nutrition and Health Sciences
		23 M	18–62	Normocholesterolemic	BMI: 17.9–32.4 kg/m^2	Randomized	Palm oil		Netherlands Postgraduate School of Human Nutrition
		36 F	18–55		BMI: 19.0–26.8 kg/m^2	Crossover	Sunflower oil 39% of total E as fat 10% E as test fat		
Tholstrup, 1994 (62)	Denmark	15 M	22–30	Healthy	BMI: 20.4–26.4 kg/m^2	Randomized	Myristic and lauric acids	3 × 3 diet	DAVRC
				Normocholesterolemic Students		Crossover	Palmitic acid Stearic acid 40% of total E as fat 36% E as test fat	4.3–6.8 washout	DTRC
Tholstrup, 1994 (63)	Denmark	12 M	21–26	Healthy	BMI: 20.25–25.7 kg/m^2	Randomized	Palmitic acid	3 × 2 diet	DAVRC
				Normocholesterolemic		Crossover	Myristic acid 40% of total E as fat 36% as test fat	5 usual diet	DTRC Danish Agricultural Ministry
Ghafoorunissa, 1995 (76)	India	12 M	29–39	Healthy	BMI: 18–27 kg/m^2	Crossover	Groundnut oil	8 × 2 diet	PORI
				Normocholesterolemic			Palm olein 27% of total E as fat 18% E as test fat	6 washout	
Ghafoorunissa, 1995 (76)	India	24	33–52	Healthy		Crossover	Groundnut oil	16 × 2 diet	PORI
		12 M 12 F	30–52 33–39	Normocholesterolemic	BMI: 17–26 kg/m^2 BMI: 16–30 kg/m^2		Palm olein 32% of total E as fat 20% as test fat		

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TABLE 1 (*Continued*)

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
Sundram, 1995 (39)	Malaysia	23 M	22 ± 4	Healthy	TC: 174 ± 23 mg/dL	Randomized	America Health Association blend (50% soybean oil, 40% palm oil, 10% canola oil)	4 × 2 diet	MPOB
				Normocholesterolemic Members of the Royal Malaysian Army	BMI: 21.3 ± 1.7 kg/m^2 HDL-C: 45 ± 10 mg/dL LDL-C: 105 ± 46 mg/dL TGs: 88 ± 27 mg/dL	Crossover	Canola oil Palm olein 31% of total E as fat 20% E as test fat	3 control	
Tholstrup, 1995 (64)	Denmark	15 M	22–30	Healthy	BMI: 20.4–26.4 kg/m^2	Randomized	Myristic and lauric acids	3 × 2 diet	DAVRC
				Normocholesterolemic	TC: 4.00 ± 0.12 mmol/L HDL-C: 0.97 ± 0.04 mmol/L LDL-C: 2.87 ± 0.12 mmol/L TGs: 0.79 ± 0.08 mmol/L	Crossover	Stearic acid Palmitic acid (palm oil) 40% of total E as fat 36% as test fat	6.3–8.6 washout	DTRC Danish Agricultural Ministry
Zock, 1995 (67)	Netherlands	60	19–67	Healthy	TC: 2.80–6.98 mmol/L	Randomized	Palm oil esterified in sn-1,3 positions	3 × 2 diet	Foundation for Nutrition and Health Science
		23 M		Normocholesterolemic	HDL-C: 0.76–2.42 mmol/L	Crossover	Modified palm oil esterified in sn-2 position		Netherland Postgraduate School of Human Nutrition
		37 F			TGs: 0.41–2.24 mmol/L BMI: 18.5–30.9 kg/m^2 BMI: 18.1–29.7 kg/m^2		40% of total E as fat		
Schwab, 1995 (75)	Finland	15 F	23.9 ± 1.2	Healthy	BMI: 21.4 ± 0.5 kg/m^2	Randomized	Palmitic acid by palm oil	2 baseline	FNR
				Normocholesterolemic	TC: 4.86 ± 0.7 mmol/L HDL-C: 1.55 ± 0.07 mmol/L LDL-C: 2.86 ± 0.12 mmol/L TGs: 0.93 ± 0.10 mmol/L	Crossover	Lauric acid by coconut oil 38% of total E as fat 4% E as test fat	4 × 2 diet	FCF FHRF Academy of Finland
Choudhury, 1995 (45)	Australia	21	19–44	Healthy		Randomized	Palm olein	0.5 preexperiment	University of Sidney
		10 M 11 F		Normocholesterolemic	BMI: 24.2 ± 1.2 kg/m^2 BMI: 23.9 ± 3.2 kg/m^2	Crossover	Olive oil 30% of total E from fat 17% as test fat	4 × 2 diet	Nutrition Research Foundation MPOB
Nestel, 1995 (50)	Australia	27 M	49 ± 8	Healthy Moderately hypercholesterolemic	BMI: 26.3 ± 2.5 kg/m^2 TC: 6.00 ± 0.78 mmol/L	Double-blind Randomized Crossover	High–palm oil margarine Interesterified high–palm oil margarine High–linoleic acid moderate *trans* fatty acid margarine 30–35% of total E as fat 20% E as test fat	2 baseline 3 × 3 diet	Meadow Lea Foods, Australia
Noakes, 1996 (52)	Australia	9 M	53 ± 9	Healthy	BMI: 24.7 ± 2.9 kg/m^2	Double-blind	Palm oil	2 baseline	Meadow Lea Foods, Australia
		14 F		Mildly hypercholesterolemic	TC: 6.1 ± 0.6 mmol/L TGs: 1.2 ± 0.4 mmol/L	Randomized Crossover	High–oleic acid sunflower oil Oil test blend 35–40% total E as fat 20% E as test fat	3 diet	

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TABLE 1 (*Continued*)

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
Temme, 1996 (66)	Netherlands	32	41 (20–60)	Healthy	BMI: 19–31 kg/m^2	Randomized	Lauric acid	6 × 3 diet	Dutch Dairy Foundation on Nutrition and Health
		14 M 18 F		Normocholesterolemic	TC: 3.41–6.48 mmol/L HDL-C: 0.86–2.48 mmol/L TGs: 0.26–2.53 mmol/L	Crossover	Palmitic acid Oleic acid 40% total E as fat 28% E as test fat	2 or 3 washout	
Schwab, 1996 (74)	Finland	12 F	23.5 ± 0.9	Healthy	BMI: 22.1 ± 0.7 kg/m^2	Randomized	Palmitic acid	2 × 2 run-in diet	FNR
				Normocholesterolemic	TC: 4.21 ± 0.17 mmol/L LDL-C: 2.40 ± 0.13 mmol/L HDL-C: 1.44 ± 0.06 mmol/L TGs: 0.96 ± 0.14 mmol/L	Crossover	Stearic acid 37–38% of total E as fat 36% E as test fat	4 × 2 diet	FCF FHRF Academy of Finland
Choudhury, 1997 (46)	Australia	42	22–71	Normocholesterolemic	BMI: 18–33 kg/m^2	Double-blind	Palm oil crisps	1 regimen	Australian Grains Research Development Corporation
		24 M		Hypercholesterolemic	TC: 5.51 ± 1.56 mmol/L	Randomized	High–oleic acid sunflower crisps	4 palm oil	Meadow Lea Foods, Australia
		18 F			LDL-C: 3.72 ± 1.34 mmol/L HDL-C: 1.16 ± 0.39 mmol/L TGs: 1.38 ± 0.86 mmol/L LDL-C/HDL-C: 3.58 ± 1.83	Crossover	30% of total E as fat 17% E as test fat	3 high–oleic acid sunflower	
Cater, 1997 (54)	USA	9 M	55–75	Mild hypercholesterolemic	BMI: 27 ± 5 kg/m^2 TC: 5.69 ± 0.54 mmol/L TGs: 1.52 ± 0.77 mmol/L	Randomized Crossover	Palm oil High–oleic acid sunflower oil Medium-chain TG oil 53% of total E as fat 43% E as test fat	3 diet 1 washout	NIH
Zhang, 1997 (69)	China	51	32–68	Hypercholesterolemic	TC: 5.5–7.0 mmol/L	Randomized	Palm oil	3 baseline	MPOB
		31 M 20 F				Crossover	Peanut oil 30% of total E as fat 18–20% as test fat	6 diet	
Zhang, 1997 (69)	China	120 M	18–25	Healthy	BMI: 18.5–25 kg/m^2	Randomized	Palm oil	3 run-in	MPOB
				Normocholesterolemic	TC: 2.8–5.0 mmol/L	Parallel	Soybean oil Peanut oil Lard 30% of total E as fat 23% as test fat	6 × 4 diet	
Sundram, 1997 (41)	Malaysia	29	29.4 ± 4.6	Healthy	BMI: 22.7 ± 2.59 kg/m^2	Double-blind	Habitual diet (26.4% E as fat)	2 habitual	MPOB
		20 M		Normolipidemic	TC: 5.10 ± 0.78 mmol/L	Randomized	*trans*-Rich hydrogenated soybean oil	4 diet	
		9 F			LDL-C: 3.68 ± 0.80 mmol/L HDL-C: 1.02 ± 0.20 mmol/L	Crossover	High oleic acid (mixture of rapeseed, sunflower, and palmitic oil) High palmitic acid (palm olein)		

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TABLE 1 (*Continued*)

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
					TGs: 1.02 ± 0.50 mmol/L		High lauric + myristic acid (mixture of coconut, palm kernel, and corn oil) 31% of total E as fat 21% as test fat		
Storm, 1997 (60)	Denmark	15	53 ± 9	Non-insulin-dependent diabetes mellitus patients	BMI: 29.7 ± 5.0 kg/m^2	Randomized	High fat (45% E), stearic acid–rich (13%)	2 run-in	Danish Medical Research Council
		8 M			TC: 5.7 ± 1.4 mmol/L	Crossover	High fat (45% E), palmitic acid–rich (16%)	3 × 3 diet	Danish Diabetes Association
		7 F			LDL-C: 3.5 ± 1.2 mmol/L		Low-fat (30% E)/high carbohydrate (50% E)	2 washout	The NovoFoundation
					HDL-C: 1.2 ± 0.3 mmol/L				Institute of Experimental Clinical Medicine
					TGs: 2.2 ± 1.5 mmol/L				Aarhus University
Cuesta, 1998 (71)	Spain	14 F	63 ± 11	Religious community	BMI: 23.2 ± 3.4 kg/m^2	Crossover	Oleic acid–rich sunflower oil	4 × 2 diet	Spanish Comision Interministerial de Ciencia y Tecnologia
					TC: 6.41 ± 1.15 mmol/L LDL-C: 3.78 ± 0.8 mmol/L HDL-C: 1.88 ± 0.40 mmol/L TGs: 0.83 ± 0.19 mmol/L apo A-I: 1.56 ± 0.21 g/L apo B: 1.08 ± 0.21 g/L LDL-C/HDL-C: 2.07 ± 0.48		Palm olein 46% of total E as fat 31% E as test fat		
Muller, 1998 (78)	Norway	27 F	27 ± 5.8	Mild hypercholesterolemic	BMI: 26.5 ± 4.1 kg/m^2	Latin-square	PALM-margarine (hard *trans*-free margarine rich in palm oil	2.4 × 3 diet	Nordic Industrial Fund
					TC: 5.30 ± 0.93 mmol/L	Crossover	*trans*-Margarine (hard margarine rich in partially hydrogenated soybean oil)	1 washout	Norwegian Food Company Mills DA
					LDL-C: 3.26 ± 0.87 mmol/L		PUFA-margarine (soft margarine rich in PUFAs)		
					HDL-C: 1.58 ± 0.40 mmol/L TGs: 1.03 ± 0.50 mmol/L apo A-I: 1.89 ± 0.233 g/L apo B: 1.24 ± 0.28 g/L LDL-C/HDL-C: 2.27 ± 0.98		30% of total E as fat 26% E as test fat		
Nestel, 1998 (51)	Australia	15 M+F	51 ± 7	Hypercholesterolemic	BMI: 26.2 ± 3.9 kg/m^2	Blind	Palmitic acid	2 run-in	Cultor Food Sciences USA
					TC: 6.13 ± 0.80 mmol/L	Randomized Crossover	Stearic acid 40% of total E as fat 25% E as test fat	5 × 2 diet	Meadow Lea Foods, Australia

(*Continued*)

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TABLE 1 (*Continued*)

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
Mutalib, 1999 (81)	Scotland	53 M	Not specified	Healthy		Parallel	Palm fat	8 diet	Not specified
				Normocholesterolemic		Randomized	Hydrogenated soya fat Hydrogenated rapeseed fat 40% E as total fat 26% E as test fat		
Kelly, 2002 (47)	Australia	9 M	39 ± 10	Healthy Normocholesterolemic	BMI: 25 ± 2.5 kg/m^2	Single-blind Randomized Crossover	Stearic acid Palmitic acid 30% of total E as fat 10% E as test fat	3 diet 1 washout	Effem Foods, Pty Ltd, Australia
Sanchez-Muniz, 2002 (73)	Spain	14 F	62.9 ± 11.2	Postmenopause	BMI: 23.2 ± 3.4 kg/m^2	Sequential	Palm olein	4 diet	Spanish Comision Interministerial de Ciencia y Tecnologia
				Hypercholesterolemic	TC: 6.41 ± 1.15 mmol/L TGs: 0.83 ± 0.19 mmol/L TC/HDL-C: 3.47 ± 0.54		Sunflower oil 46% of total E as fat 28% E as test fat		
Montoya, 2002 (72)	Spain	41		Religious community		Crossover	SFA (17.3% E from palm oil)	4 SFA diet	Fondo de Investigacione Sanitarias
		24 M	45.1 ± 16.2	Priests	BMI: 26.6 ± 4.6 3 kg/m^2		MUFA (20.9% E from oleic acid)	5 MUFA diet	
		17 F	45.8 ± 9.5	Nuns (10 postmenopause)	BMI: 23.1 ± 3 kg/m^2		PUFA n−6 (12.8% E from sunflower oil, linoleic acid)	5 PUFA diet	
				Mild hypercholesterolemic			PUFA n−3 (1.6% E from fish oil) 35% of total E as fat	5 PUFA diet	
French, 2002 (35)	Malaysia	6	25 ± 1.7	Healthy	BMI: 21.3 ± 0.6 kg/m^2	Crossover	Palmitic acid	3 × 8 diet	MPOB
		3 M		Normocholesterolemic			Palmitic acid + linoleic acid	1 washout	Natural Sciences and Engineering Research Council of Canada
		3 F					30% of total E as fat 20% E as test fat)		Dairy Farmers of Canada Alberta Agricultural Research Institute
Zhang, 2003 (70)	China	42 M	18–32	Healthy	BMI: 21.4 ± 1.9 kg/m^2 (red-palm-oil group)	Parallel	Red palm oil	3 control	Not specified
				Normocholesterolemic Soldiers	TC: 3.52 ± 0.52 mmol/L HDL-C: 1.16 ± 0.20 mmol/L TGs: 0.81 ± 0.32 mmol/L apo A-I: 1.42 ± 0.15 g/L apo B: 0.78 ± 0.05 g/L BMI: 21.9 ± 1.6 kg/m^2 (soybean-oil group) TC: 3.49 ± 0.57 mmol/L HDL-C: 1.17 ± 0.19 mmol/L TGs: 0.80 ± 0.40 mmol/L apo A-I: 1.37 ± 0.15 g/L apo B: 0.77 ± 0.08 g/L BMI: 23.89 ± 0.8 kg/m^2		Soybean oil 28% of E as total fat 60% of total fat as test fat	6 diet	

(*Continued*)

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TABLE 1 (*Continued*)

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
Sundram, 2003 (84)	Malaysia	10 F	Not specified	Healthy	TC: 5.37 ± 0.35 mmol/L	Randomized	High palmitic acid	3 control	Natural Sciences and Engineering Research Council of Canada
				Normocholesterolemic	LDL-C: 3.35 ± 0.27 mmol/L HDL-C: 1.44 ± 0.09 mmol/L	Crossover	High *trans* fatty acid 30% of total E as fat 20% as test fat	4 diet	MPOB
Scholtz, 2004 (82)	South Africa	56		Hyperfibrinogenemic		Single-blind	Palm olein	4 run-in	MPOB
		36 M	48.8		BMI: 29.0 kg/m^2 TC: 5.1 mmol/L HDL: 0.9 mmol/L LDL-C: 3.3 mmol/L TGs: 1.9 mmol/L	Randomized Parallel	Red palm oil Sunflower oil 35% of total E as fat 12% E as test fat	4 diet	
		20 F	47.4		BMI: 28.1 kg/m^2 TC: 5.1 mmol/L LDL-C: 3.1 mmol/L HDL-C: 1.3 mmol/L TGs: 1.5 mmol/L				
Pedersen, 2005 (77)	Norway	27 F	19–42	Healthy	BMI: 20–36 kg/m^2	Latin-square	PALM-margarine (*trans*-free-containing palm oil)	2.4 × 3 diet	Nordic Industrial Fund
				Normocholesterolemic		Crossover	*trans*-margarine (high *trans* fatty acids from soybean oil)		Norwegian Food Company Mills DA
				Students			PUFA-margarine (high in PUFAs, mainly from sunflower oil) 34% of total E as fat 28% E as test fat		
Vega-Lopez, 2006 (59)	USA	15	63.9 ± 5.7	Moderately hypercholesterolemic	TC: 253 ± 30 mg/dL	Randomized	Partially hydrogenated soybean oil	7 × 6 diet	NIH
		10 F		Postmenopause	LDL-C: 177 ± 30 mg/dL HDL-C: 54 ± 11 mg/dL TGs: 111 ± 38 mg/dL apo A-I: 174 ± 15 mg/dL apo B: 138 ± 23 mg/dL TC/HDL-C: 4.85 ± 1.11	Crossover	Soybean oil Palm oil Canola oil 30% of total E as fat 20% E as test fat		USDA
		5 M			BMI: 25.6 ± 2.7 kg/m^2 BMI: 26.2 ± 2.3 kg/m^2				
Sundram, 2007 (42)	Malaysia	32	30 ± 8	Healthy	BMI: 22 ± 4 kg/m^2	Randomized	Palm olein (12% E as palmitic acid)	4 × 3 diet	MPOB
		21 F		Normocholesterolemic	TC: 5.05 ± 0.53 mmol/L	Crossover	*trans*-Rich partially hydrogenated soybean oil (3.2% E *trans* fatty acid)		
		11 M			LDL-C: 3.17 ± 0.51 mmol/L HDL-C: 1.48 ± 0.25 mmol/L TGs: 0.89 ± 0.30 mmol/L		Interesterified stearic acid (12% E from stearic acid) 31% of total E as fat 21% as test fat		
Forsythe, 2007 (79)	Canada	8 M	21–28	Healthy		Crossover	High–palmitic acid sn-2 (8% E) and low linoleic acid (3% E)	2 × 4 diet	MPOB

(Continued)

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TABLE 1 (*Continued*)

First author, year (ref)	Country	No. of subjects and sex	Age	Subjects' characteristics	Baseline values	Study design	Diet-enriched fat and energy level	Duration of intervention	Funding
				Normocholesterolemic			High–palmitic acid sn-1,3 (8% E) and low linoleic acid (3% E) High–palmitic acid sn-2 (8% E) and high linoleic acid (7–9% E) High-palmitic acid sn-1,3 (8% E) and high-linoleic acid (7–9% E) 30% of total E as fat 14% E as test fat	2 washout	Natural Sciences and Engineering Research Council of Canada
Mensink, 2008 (65)	Netherlands	44		Healthy	BMI: 24.0 ± 1.8 kg/m^2	Double-blind	High–palmitic acid *trans*-free	3 × 2 diet	Cargill Refined Oils Europe
		11 M	41 ± 11	Normocholesterolemic	TC: 5.40 ± 0.64 mmol/L	Randomized	High–oleic acid low-*trans*	1 washout	
					LDL-C: 3.47 ± 0.66 mmol/L	Crossover	40% of total E as fat		
					HDL-C: 1.20 ± 0.23 mmol/L		15% E as test fat		
					TGs: 1.62 ± 0.75 mmol/L				
					BMI: 23.8 ± 3.3 kg/m^2				
		33 F	41 ± 18		TC: 5.31 ± 0.67 mmol/L				
					LDL-C: 3.05 ± 0.62 mmol/L				
					HDL-C: 1.54 ± 0.43 mmol/L				
					TGs: 1.56 ± 0.67 mmol/L				
Utarwuthipong, 2009 (83)	Thailand	16 F	44–67	Hypercholesterolemic	BMI: <25 kg/m^2	Randomized	Palm oil	1 control period	Ministry of University Affairs
					TC: 266.7 ± 27.3 mg/dL	Crossover	Soybean oil	10 × 4 diet	Faculty of Graduate Studies, Thailand
					LDL-C: 184.0 ± 26.6 mg/dL		Rice bran oil/palm oil mixture (3:1)		
					HDL-C: 56.9 ± 13.8 mg/dL		30% of total E as fat		
					TGs: 128.8 ± 46.0 mg/dL		20% as test fat		
Teng, 2010 (44)	Malaysia	41	28.8 ± 9.1	Healthy	BMI: 21.9 ± 3.9 kg/m^2	Single-blind	Palm stearin	5 × 3 diet;	MPOB
		8 M		Normocholesterolemic	TC: 4.6 ± 0.6 mmol/L	Randomized	High–oleic acid palm olein	1 washout	
		33 F			LDL-C: 2.8 ± 0.5 mmol/L	Crossover	Partially hydrogenated soybean oil		
					HDL-C: 1.6 ± 0.3 mmol/L		30–35% of total E as fat		
					TGs: 0.8 ± 0.2 mmol/L		20–25% E as test fat		
Tholstrup, 2011 (61)	Denmark	32 M	29.6 ± 10.3	Healthy	BMI: 22.9 ± 2.5 kg/m^2	Double-blind	Palm olein	3 × 3 diet	MPOB
				Normocholesterolemic	TC/HDL-C: 3.79 ± 0.96	Randomized Crossover	Olive oil Lard 40% of total E as fat 17% E as test fat		

[1] apo, apoliprotein; CETIOM, Centre Technique Interprofessionnel des Oleagineux Metropolitains; COI, the Conseil Oleicole International; CNIEL, the Centre Interprofessionnel de l'Economie Laitiere; DAVRC, Danish Agricultural and Veterinary Research Council; DTRC, Danish Technical Research Council; E, energy; FCF, Finnish Cultural Foundation; FHRF, Finnish Heart Research Foundation; FNR, Foundation for Nutrition Research of Finland; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; MPOB, Malaysian Palm Oil Board; PORI, Palm Oil Research Institute of Malaysia; ref, reference; TC, total cholesterol; TG, triacylglycerol; VAMC, Veterans Administration Medical Center.

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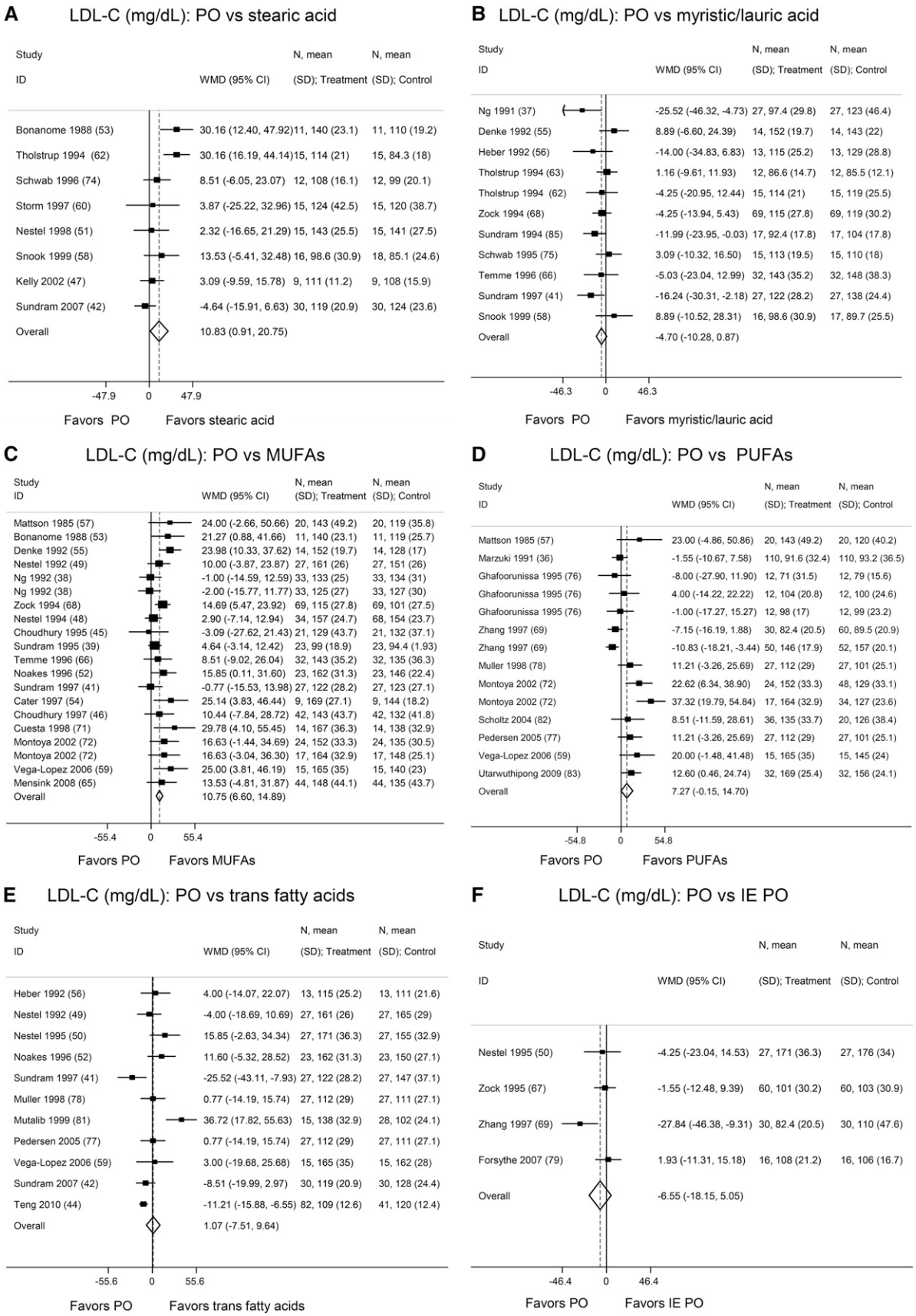

FIGURE 2. WMD in LDL-C after PO substitution for stearic acid (A), myristic/lauric acids (B), MUFAs (C), PUFAs (D), partially hydrogenated *trans* fatty acids (E), and IE PO (F). WMD was calculated from a random-effects model. ID, identifier; IE, interesterified; LDL-C, LDL cholesterol; PO, palm oil; WMD, weighted mean difference.

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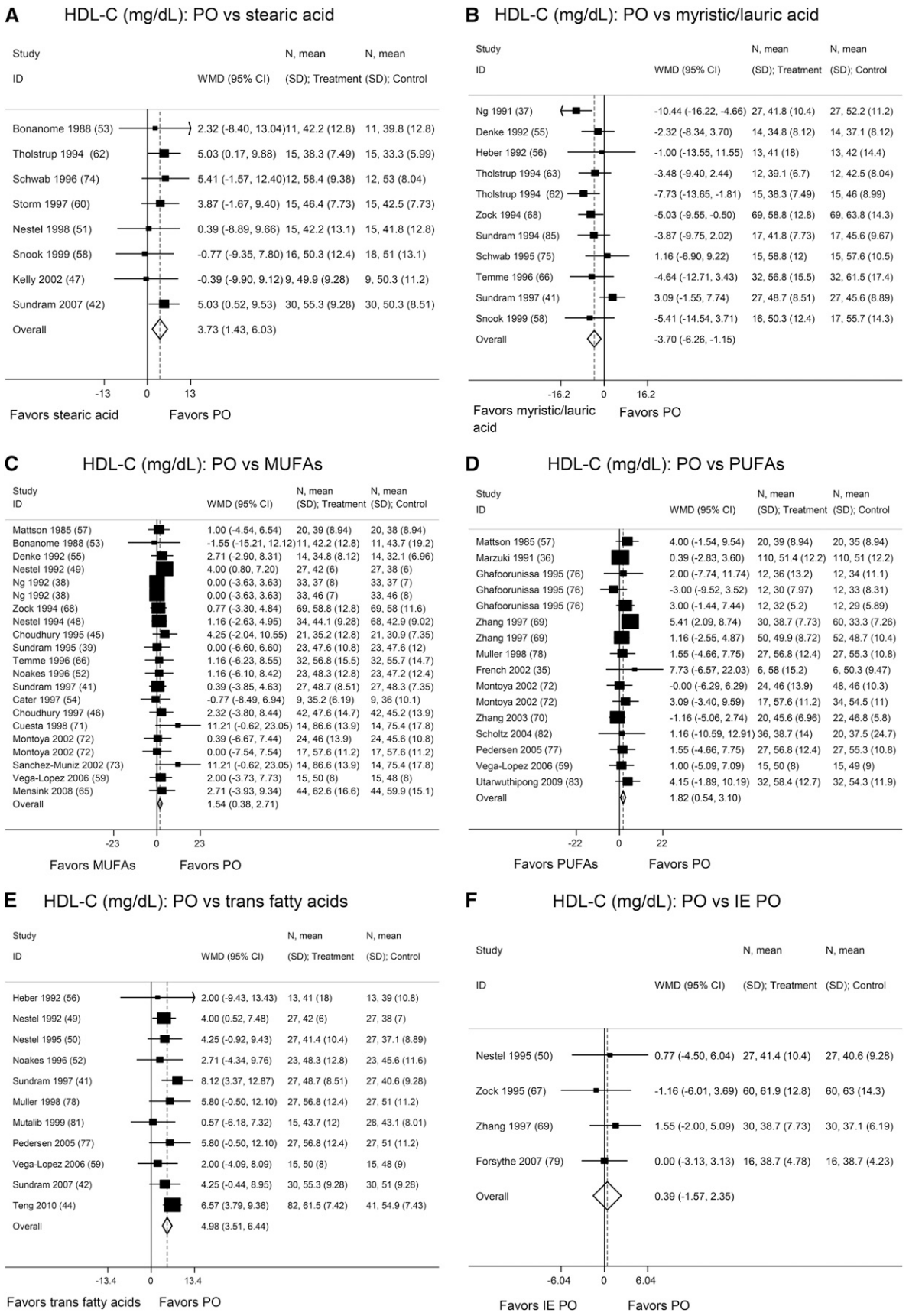

FIGURE 3. WMD in HDL-C after PO substitution for stearic acid (A), myristic/lauric acids (B), MUFAs (C), PUFAs (D), partially hydrogenated *trans* fatty acids (E), and IE PO (F). WMD was calculated from a random-effects model. HDL-C, HDL cholesterol; ID, identifier; IE, interesterified; PO, palm oil; WMD, weighted mean difference.

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TABLE 2
WMDs, and corresponding 95% CIs, in selected blood lipid–related markers of cardiovascular disease after palm oil substitution for stearic acid[1]

Blood marker	No. of studies	No. treated/ control subjects	WMD (95% CI)[2]	*P*-heterogeneity[3]	I^2
					%
TC (mg/dL)	8	123/125	14.15 (4.11, 24.19)*	0.02	57.72
LDL-C (mg/dL)	8	123/125	10.83 (0.91, 20.75)*	0.003	67.45
VLDL-C (mg/dL)	4	68/68	−0.35 (−1.74, 1.05)	0.783	0.00
apo B (mg/L)	3	43/45	97.08 (29.98, 164.18)*	0.631	0.00
HDL-C (mg/dL)	8	123/125	3.73 (1.43, 6.03)*	0.869	0.00
apo A-I (mg/L)	3	43/45	142.45 (64.05, 220.84)*	0.66	0.00
TGs (mg/dL)	7	114/116	5.02 (−3.03, 13.07)	0.973	0.00
TC/HDL-C	3	54/54	−0.12 (−0.4, 0.16)	0.293	18.43
LDL-C/HDL-C	4	71/71	0.56 (0.3, 0.82)*	0.493	0.00
Lp(a) (mg/L)	1	15/15	−29 (−119.1, 61.1)	—	—

[1] apo, apolipoprotein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triacylglycerol; VLDL-C, VLDL cholesterol; WMD, weighted mean difference.
[2] Calculated from a random-effects model. *Significant result, $P < 0.05$.
[3] Calculated by using chi-square statistic.

84), whereas 27 had no washout periods or did not mention a washout period. The energy from fat in the intervention diets ranged between 28% and 53%. All the intervention diets replaced isoenergetic amounts of the test fat, which represented 4–43% of the energy intake from fat. Six studies did not specify whether the subjects' body weight was constant during the intervention (59, 69, 70, 72, 73, 80), whereas 4 studies found a significant change in body weight at the end of the study (36, 77, 78, 82); in the remaining studies, no appreciable change in body weight was observed. Nineteen studies were conducted with the support of the Malaysian Palm Oil Board (35, 37–39, 41, 42, 44, 45, 56, 61, 69, 70, 76, 79, 82, 84, 85), 12 with the support of private companies (46–52, 65, 66, 77, 78, 80), and 19 with the support of national/public research institutions (36, 53–55, 57–60, 62–64, 67, 71–75, 83, 86); in 1 study, the funding source was not specified (81).

The changes in blood LDL cholesterol and HDL cholesterol, respectively, after PO substitution for other primary fats (in each study and overall) are shown in **Figures 2** and **3**. A summary of the results of the meta-analysis of intervention studies that examined the effect of PO compared with stearic acid on various markers of CVD is shown in **Table 2**. Significantly higher serum concentrations of TC (WMD = 14.15), LDL cholesterol (WMD = 10.83), apolipoprotein B (WMD = 97.08), HDL cholesterol (WMD = 3.73), apolipoprotein A-I (WMD = 142.45), and LDL cholesterol/HDL cholesterol (WMD = 0.56) were observed. No differences were found for VLDL cholesterol, triacylglycerols, or TC/HDL cholesterol, whereas only one study evaluated lipoprotein(a) and reported a nonsignificant reduction (WMD = −29.0). No significant heterogeneity was observed between studies, except for TC and LDL cholesterol.

The corresponding figures for intervention studies comparing PO with myristic/lauric acid are shown in **Table 3**. Significantly lower serum concentrations were found for TC (WMD = −8.77), HDL cholesterol (WMD = −3.70), and apolipoprotein A-I (WMD = −52.21); the lower LDL cholesterol (WMD = −4.70)

TABLE 3
WMDs, and corresponding 95% CIs, in selected blood lipid–related markers of cardiovascular disease after palm oil substitution for myristic and lauric acids[1]

Blood marker	No. of studies	No. of treated/ control subjects	WMD (95% CI)[2]	*P*-heterogeneity[3]	I^2
					%
TC (mg/dL)	11	257/258	−8.77 (−15, −2.53)*	0.117	35.26
LDL-C (mg/dL)	11	257/258	−4.7 (−10.28, 0.87)	0.102	37.13
VLDL-C (mg/dL)	6	100/100	−0.31 (−1.71, 1.09)	0.866	0.00
apo B (mg/L)	9	216/217	−25.15 (−58.77, 8.48)	0.231	23.84
HDL-C (mg/dL)	11	257/258	−3.7 (−6.26, −1.15)*	0.063	42.95
apo A-I (mg/L)	9	216/217	−52.21 (−95.46, −8.96)*	0.366	8.32
TGs (mg/dL)	11	257/250	0.18 (−5.71, 6.06)	0.99	0.00
TC/HDL-C	—	—	—	—	—
LDL-C/HDL-C	5	98/98	−0.06 (−0.38, 0.26)	0.104	47.88
Lp(a) (mg/L)	2	42/42	−8.49 (−54.29, 37.3)	0.72	0.00

[1] apo, apolipoprotein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triacylglycerol; VLDL-C, VLDL cholesterol; WMD, weighted mean difference.
[2] Calculated from a random-effects model. *Significant result, $P < 0.05$.
[3] Calculated by using chi-square statistic.

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TABLE 4
WMDs, and corresponding 95% CIs, in selected blood lipid–related markers of cardiovascular disease after palm oil substitution for MUFAs[1]

Blood marker	No. of studies	No. of treated/ control subjects	WMD (95% CI)[2]	*P*-heterogeneity[3]	I^2
					%
TC (mg/dL)	21	546/580	13.77 (8.85, 18.69)*	0.043	37.6
LDL-C (mg/dL)	20	532/566	10.75 (6.60, 14.89)*	0.096	30.6
VLDL-C (mg/dL)	9	160/160	0.01 (−1.36, 1.37)	0.743	0.00
apo B (mg/L)	8	221/221	60.97 (24.01, 97.93)*	0.6	0.00
HDL-C (mg/dL)	21	546/580	1.54 (0.38, 2.71)*	0.936	0.00
apo A-I (mg/L)	9	235/235	22.72 (−15.54, 60.98)	0.787	0.00
TGs (mg/dL)	20	523/557	1.57 (−3.11, 6.25)	1.00	0.00
TC/HDL-C	5	119/119	0.02 (−0.1, 0.14)	0.918	0.00
LDL-C/HDL-C	8	206/206	0.07 (−0.1, 0.25)	0.933	0.00
Lp(a) (mg/L)	3	77/77	−1 (−44.84, 42.84)	0.934	0.00

[1] apo, apolipoprotein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triacylglycerol; VLDL-C, VLDL cholesterol; WMD, weighted mean difference.
[2] Calculated from a random-effects model. *Significant result, $P < 0.05$.
[3] Calculated by using chi-square statistic.

was of borderline significance. No difference was found for VLDL cholesterol, apolipoprotein B, TC/HDL cholesterol, LDL cholesterol/HDL cholesterol, triacylglycerols, or lipoprotein(a). Study estimates were significantly heterogeneous only for HDL cholesterol.

When PO was substituted for MUFAs (**Table 4**), significantly higher blood concentrations of TC (WMD = 13.77), LDL cholesterol (WMD = 10.75), apolipoprotein B (WMD = 60.97), and HDL cholesterol (WMD = 1.54) were found, whereas no meaningful differences were observed for all other markers considered. No heterogeneity was observed between studies, except for TC.

Higher concentrations in TC (WMD = 9.36), apolipoprotein B (WMD = 50.73), HDL cholesterol (WMD = 1.82), and apolipoprotein A-I (WMD = 76.74) were found when PO was substituted for PUFAs (**Table 5**). No differences were found for the other markers considered. Significant heterogeneity between studies was observed for TC, LDL cholesterol, and triacylglycerols.

When PO was substituted for *trans* fatty acids (**Table 6**), higher concentrations of HDL cholesterol (WMD = 4.98) and apolipoprotein A-I (WMD = 103.92) were observed, whereas significantly lower concentrations were found for apolipoprotein B (WMD = −57.83), triacylglycerols (WMD = −3.02), and TC/HDL cholesterol (WMD = −0.45). However, the results for apo B and triacylglycerols occurred because one single large study provided most of the information (44); when that study was excluded, the WMDs were −1.92 (−9.93, 6.09) and −48.59 (−103.34, 6.16), respectively (data not shown). No meaningful differences were observed for TC, LDL cholesterol, or the other markers considered. Significant heterogeneity between studies was observed for TC, LDL cholesterol, and LDL cholesterol/HDL cholesterol. In a few studies, PO was substituted for interesterified PO, and no meaningful differences were observed for TC or any other blood biomarkers (data not shown).

In sensitivity analyses, we found no relevant differences in most of our results when we limited the analyses to studies

TABLE 5
WMDs, and corresponding 95% CIs, in selected blood lipid–related markers of cardiovascular disease after palm oil substitution for PUFAs[1]

Blood marker	No. of studies	No. of treated/ control subjects	WMD (95% CI)[2]	*P*-heterogeneity[3]	I^2
					%
TC (mg/dL)	16	468/551	9.36 (2.39, 16.34)*	<0.001	75.5
LDL-C (mg/dL)	14	424/481	7.27 (−0.15, 14.70)	<0.001	74.2
VLDL-C (mg/dL)	4	76/117	1.34 (−0.57, 3.25)	0.471	0.00
apo B (mg/L)	7	240/283	50.73 (20.61, 80.85)*	0.743	0.00
HDL-C (mg/dL)	16	450/509	1.82 (0.54, 3.10)*	0.649	0.00
apo A-I (mg/L)	7	240/283	76.74 (40.19, 113.29)*	0.639	0.00
TGs (mg/dL)	15	438/491	1.17 (−8.58, 10.93)	0.001	60.0
TC/HDL-C	5	241/257	−0.19 (−0.43, 0.06)	0.27	22.71
LDL-C/HDL-C	2	54/54	0.21(−0.05, 0.47)	1	0.00
Lp(a) (mg/L)	2	54/54	−17.0 (−138.9, 104.9)	1	0.00

[1] apo, apolipoprotein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triacylglycerol; VLDL-C, VLDL cholesterol; WMD, weighted mean difference.
[2] Calculated from a random-effects model. *Significant result, $P < 0.05$.
[3] Calculated by using chi-square statistic.

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TABLE 6
WMDs, and corresponding 95% CIs, in selected blood lipid-related markers of cardiovascular disease after palm oil substitution for partially hydrogenated *trans* fatty acids[1]

Blood marker	No. of studies	No. of treated/ control subjects	WMD (95% CI)[2]	*P*-heterogeneity[3]	I^2
					%
TC (mg/dL)	11	313/285	3.52 (−3.54, 10.58)	0.003	62.76
LDL-C (mg/dL)	11	313/285	1.07 (−7.51, 9.64)	<0.001	76.31
VLDL-C (mg/dL)	3	72/72	1.13 (−1.04, 3.3)	0.65	0.00
apo B (mg/L)	6	191/150	−57.83 (−98.44, −17.22)*	0.418	0.00
HDL-C (mg/dL)	11	313/285	4.98 (3.51, 6.44)*	0.748	0.00
apo A-I (mg/L)	6	191/150	103.92 (57.78, 150.07)*	0.852	0.00
TGs (mg/dL)	11	313/285	−3.02 (−5.09, −0.96)*	0.97	0.00
TC/HDL-C	3	127/86	−0.45 (−0.58, −0.31)*	0.599	0.00
LDL-C/HDL-C	7	159/172	−0.28 (−0.7, 0.14)	<0.001	87.72
Lp(a) (mg/L)	4	108/108	−33.99 (−81.26, 13.28)	0.996	0.00

[1] apo, apolipoprotein; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); TC, total cholesterol; TG, triacylglycerol; VLDL-C, VLDL cholesterol; WMD, weighted mean difference.
[2] Calculated from a random-effects model. *Significant result, $P < 0.05$.
[3] Calculated by using chi-square statistic.

conducted in healthy subjects, crossover studies, randomized studies, crossover studies with a washout period, and those in which no significant change in the subjects' weight was observed. The only results that were inconsistent with those from the overall analyses were the lack of significant associations in the analyses restricted to studies reporting a washout period between dietary interventions for TC when substituting PO for myristic/lauric acid (WMD = −4.39; −11.52, 2.74) or PUFAs (WMD = 0.44; −8.28, 9.15), for LDL cholesterol when substituting PO for myristic/lauric acid (WMD = 0.83; −4.95, 6.61) or PUFAs (WMD = −0.26; −9.55, 9.03), and for HDL cholesterol when substituting PO for PUFAs (WMD = 1.10; −0.95, 3.16) (data not shown).

Subgroup analyses and meta-regression models showed no meaningful variations in the results across the strata of sex and percentage of substituted energy from the test fat (<15%, 15–19%, 20–29%, or ≥30%) for TC, LDL cholesterol, and HDL cholesterol; however, significantly stronger differences in TC and LDL cholesterol (but not HDL cholesterol) were found in the elderly population (**Figure 4**) and in studies with intervention diets characterized by a high percentage of total energy derived from fat (**Figure 5**). Some differences were also observed in relation to baseline cholesterol concentration (normocholesterolemic, mild/hypercholesterolemic, and hypercholesterolemic subjects): the effect on TC and LDL cholesterol observed when PO was substituted for MUFAs and PUFAs was reduced in normocholesterolemic subjects. Finally, larger differences were observed in studies conducted in geographic countries other than Asia (Europe, United States, Canada, and other countries) and in studies supported by national/public research institutions.

Some evidence of publication bias was observed for TC and LDL cholesterol when PO was compared with MUFAs, PUFAs, or *trans* fatty acids. No publication bias was observed for TC and LDL cholesterol when PO was compared with stearic or myristic/lauric acids or for HDL cholesterol in any substitution.

DISCUSSION

The results of this meta-analysis show that when PO was substituted for the primary dietary fats, both unfavorable and favorable changes occurred in terms of CHD/CVD lipid-related biomarkers. In particular, substitution of PO for stearic acid induced higher concentrations of several biomarkers, both unfavorable (TC, LDL cholesterol, apolipoprotein B, and LDL cholesterol/HDL cholesterol ratio) and favorable (HDL cholesterol and apolipoprotein A-I), whereas substitution for myristic/lauric acid resulted in lower concentrations of almost all the same biomarkers. In both the substitutions, nonsignificant changes in the TC/LDL cholesterol ratio occurred. These results agree with those reported in other studies (12, 87, 88), which shows that the major dietary saturated fats (palmitic, stearic, lauric, and myristic acids) have differential effects on the lipid profile: lauric and myristic acids increase all the cholesterol fractions more than does palmitic acid, and palmitic acid increases all the cholesterol fractions more than does stearic acid.

When PO was substituted for oleic acid (MUFA) or linoleic acid (PUFA), again, both unfavorable and favorable markers of

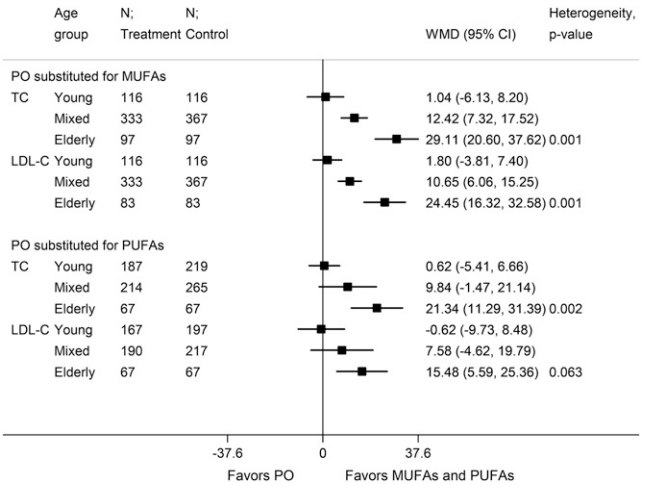

FIGURE 4. WMD in blood TC and LDL-C after PO substitution for MUFAs and PUFAs, stratified by age. WMD was calculated from a random-effects model. LDL-C, LDL cholesterol; PO, palm oil; TC, total cholesterol; WMD, weighted mean difference.

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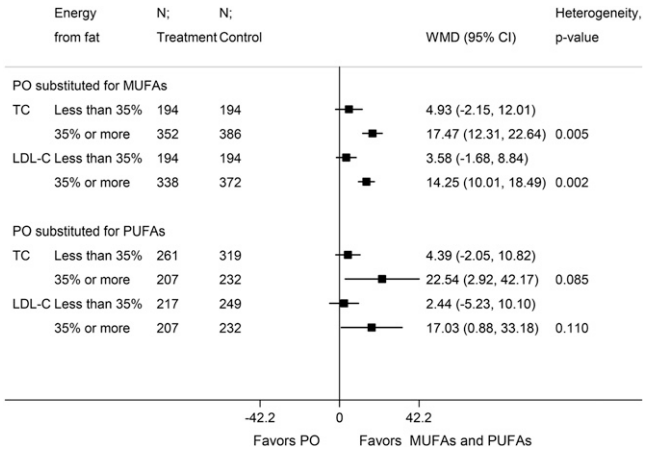

FIGURE 5. WMD in blood TC and LDL-C after PO substitution for MUFAs and PUFAs, stratified by percentage of total energy derived from fat in the intervention diets. WMD was calculated from a random-effects model. LDL-C, LDL cholesterol; PO, palm oil; TC, total cholesterol; WMD, weighted mean difference.

CHD/CVD were found. However, in both cases, no changes in TC/HDL cholesterol or LDL cholesterol/HDL cholesterol ratios were observed. These results differ somewhat from those obtained in a previous meta-analysis, in which a significantly lower TC/HDL cholesterol ratio was observed when SFAs were substituted for MUFAs (88).

When PO was substituted for hydrogenated *trans* fatty acids, all the significant changes observed were favorable in terms of CHD/CVD risk (ie, lower apolipoprotein B, TC/HDL ratio, and triacylglycerols and higher HDL cholesterol and apolipoprotein A-I). These results confirm those reported in the scientific literature regarding the physiologic effects of *trans* fatty acids when compared with saturated or unsaturated fats (89).

Finally, when PO, which contains palmitic acid mainly esterified in the sn-1,3 position of the glycerol molecule, was substituted for interesterified PO or other fats containing palmitic acid esterified in the sn-2 position, no differences were observed in any of the markers investigated. These results should be interpreted with caution because of the limited number of studies that have examined interesterified PO (50, 67, 79), and they require further investigation because the risk of deleterious effects on blood lipoproteins cannot be excluded based on a review of the recent literature (90).

The results concerning apolipoprotein A-I and B confirm that these markers reflect variations in HDL cholesterol and LDL cholesterol, respectively. Because apolipoprotein A-I and B have opposite effects in terms of CHD/CVD risk, the apolipoprotein B/apolipoprotein A-I ratio has been proposed as a better predictor of risk than the individual apolipoprotein values. In fact, in the INTERHEART study, McQueen et al (19) showed that the apolipoprotein B/apolipoprotein A-I ratio accounted for a worldwide population attributable risk of myocardial infarction of 54% compared with 37% and 32% for the LDL cholesterol/HDL cholesterol and TC/HDL ratios, respectively. Unfortunately because only a few studies reported the apolipoprotein B/apolipoprotein A-I ratio (36, 39, 41, 85), it was not possible to conduct a meta-analysis for this biomarker. However, in the individual studies, the apolipoprotein B/apolipoprotein A-I ratio did not change significantly when PO was substituted for the other dietary fats (36, 39, 41, 85).

Finally, lipoprotein(a) did not show a significant change in any of the PO substitutions. Despite the limited number of studies reporting this biomarker, this result is consistent with our knowledge on the strict genetic control of serum lipoprotein(a) concentrations (91).

Subgroup analyses showed that the unfavorable effects of a PO diet on TC and LDL cholesterol compared with MUFA and PUFA diets were dependent on age because such effects disappeared when young people (≤30 y of age) were considered (Figure 4). The same trend was observed for baseline cholesterol: in normocholesterolemic subjects, the unfavorable effect of PO on TC and LDL cholesterol was lower than that of MUFAs and PUFAs. Effect modifications were also observed in relation to the total amount of energy provided from fat (ie, intervention diets with less total energy derived from fat showed less evident variations in TC and LDL cholesterol) (Figure 5). Finally, effect modifications were observed in relation to country and funding source (ie, changes in TC and LDL cholesterol were less evident in studies conducted in Asia than in those conducted in the USA or Europe, and changes were less evident in studies funded by the Malaysian Palm Oil Board than in those funded by other private or public institutions). All these variables were closely related because most of the studies conducted in Asia were funded at least partially by the Malaysian Palm Oil Board, involved young normocholesterolemic subjects, and involved intervention diets that were less rich in fat, reflecting the lower fat-derived energy generally found in the traditional Asian diet. Moreover, it should be taken into account that other dietary components that may largely vary among different dietary patterns, such as calcium, dietary fiber, sterols/stanols or polyphenols, might represent substantial confounders to the effect exerted by dietary fats on the blood lipids markers considered here (92). Thus, these results show that age-related physiologic conditions and overall dietary habits are important determining factors for the effects induced by the primary dietary fats on TC and LDL cholesterol. In addition, these results suggest that effects that may be relevant only for specific subgroups, or only in the framework of dietary patterns characterized by a high proportion of fat (as is the case in some Western countries), should not be generalized. Advice regarding dietary habit modification for nontarget populations, especially when involving macronutrients, can be self-defeating because of compensating behaviors that are not easily predictable, such as those observed when hydrogenated fats were substituted for saturated animal fats (89).

One of the major limitations of the current study was the high heterogeneity of the diets, which often contained the same fatty acids, even if in different proportions, in both the intervention and control diets, reflecting the actual composition of the primary dietary fats. However, we tried to compensate for this limitation with an accurate classification of the diets based on the different proportions in the individual fatty acids (*see* Supplemental Table 1 under "Supplemental data" in the online issue).

Another limitation of this meta-analysis was the quality of the studies included. We considered all studies that met the eligibility criteria and we did not assess the quality of the studies because of the lack of a validated quality scoring system for crossover studies. However, sensitivity analyses that excluded studies with no washout period or with no subject body weight control (as a proxy of low quality) provided results that were consistent with the overall results. Moreover, we mainly considered crossover

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studies, which generally provide poor reporting of statistical information necessary for the conduction of meta-analyses (93). There was also some heterogeneity in the results depending on the various markers considered, although we conducted various stratified analyses to understand potential sources of heterogeneity. There was also some evidence of publication bias: studies showing higher concentrations of TC and LDL cholesterol after PO substitution for MUFAs, PUFAs, and *trans*-hydrogenated fats were more likely to be published than were those reporting negative results. This result is consistent with the significant interest in recent decades in developing a dietary strategy to reduce CHD/CVD mortality, which includes a recommendation to replace SFAs (5).

In conclusion, this meta-analysis indicates that PO may produce both favorable and unfavorable changes compared with the other primary dietary SFAs, MUFAs, and PUFAs, and almost no changes were observed in TC/HDL cholesterol and LDL cholesterol/HDL cholesterol ratios. Moreover, the modifying effect of fat-rich diets and subjects' age on both the changes in TC and LDL cholesterol associated with PO and the more favorable lipid profile of PO compared with hydrogenated *trans* fatty acids on biomarkers of CVD/CHD risk further suggests that the net advantages and disadvantages derived from PO replacement with other fat sources should be carefully evaluated.

A recent article based on simulation models concluded that a 20% tax on PO in India would reduce CVD mortality but would also affect food security and have distributional consequences across sexes and between urban and rural populations (94). Our results do not support a link between PO substitution and reduction of CVD mortality, as assumed by the simulation model. Rather, our results suggest the need for further comparative research and urge caution in formulating policies that promote specific fats over others for the general population and across countries. Robust evidence of the health effects and socioeconomic consequences is needed to offer guidance for policymaking.

The authors' responsibilities were as follows—EF, CB, FB, CA, and GF: designed the research; EF and CB: conducted the library search and wrote the manuscript; EF: extracted and controlled the data and assumes primary responsibility for the final content; CB: controlled and analyzed the data; and FB, CA, and GF: contributed to the manuscript writing. All of the authors read and approved the final manuscript. None of the authors, or their close relatives, has a financial interest in or serves as an employee, officer, member, owner, trustee, or agent for an organization that has a financial interest in the outcome of this study. EF and CB received funding for the submitted work from Università Bocconi, which has no financial interest in the outcome of this study. GF received funding for the submitted work, and CA and FB received funding in the previous 3 y and outside the submitted work from Soremartec Italia s.r.l—a company that has a financial interest in products containing PO. EF received funding in the previous 3 y and outside the submitted work from the Associazione delle Industrie del Dolce e della Pasta Italiane, which might have an interest in the outcome of the study. The funders had no role in the study design, implementation, analysis, or interpretation of the data.

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