Table . PUFAs and CHD/CVD: Design Type 1 Studies

Author/ Year	De-sign Type	Class	Quality (+,-,Ø)	Purpose/ Population Sample Size	Regimen	Primary Outcome Measures Results	Author's Conclusions/ *Reviewer's Comments (Italicized)*
Howard et al., 1995	**RCT**	**A**	**+**	**Purpose:** To compare chol-lowering effects of PUFA and MUFA in reciprocal, dose-dependent fashion in context of National Cholesterol Education Program Step 1 diet **Sample:** 63 moderately hypercholesterolemic men and women (77 started) **Inclusions:** African American and white; bet 20 and 55 y of age; <32% (men) or 37% (women) body fat; LDL chol bet 3.4 and 4.9 mmol/L; TG conc <4 mmol/L **Exclusions:** HX or recent (<3 mo) or chronic oral hypolipidemic TX including FO or fiber supplements; HX of chronic use of systematic antibiotics,	**Run-in Period:** 6 wk; baseline diet (37% TE from fat with 15% SFA, 3% PUFA and 19% MUFA) **TX/Duration:** Randomly assigned into 4 groups that followed reduced fat diets in following orders: 1) 1-2-3-4 2) 2-1-4-3 3) 3-4-1-2 4) 4-3-2-1 30 wk **Dose/Form:** Diets differed only in content of butter, specifically mixed oil blends and mayonnaises and margarines prepared from oil blends to achieve indicated distribution of FA: 1) Diet 1: 3% PUFA, 17% MUFA 2) Diet 2: 6% PUFA, 14%, MUFA 3) Diet 3: 10% PUFA, 10% MUFA	**Outcome Measures:** Lipids Immune function **Results:** Progressive decr in TC (*P*=0.028) and LDL (*P*=0.184) across 4 diets, with greatest decr observed in diet with highest content of PUFA and least decr seen in diet with highest content of MUFA Small, but sig decr in HDL (0.08-0.10 mmol/L) with no trend bet PUFA and MUFA diets Trend bet 4 diets in TG elevations (*P*=0.029), with smallest increment occurring in diets high in PUFA NS diff in apolipoprotein B or A-1 bet 4 diets Subj who responded more to highest PUFA diet also responded most to highest MUFA diet (*r*=0.420, *P*=0.006), although lesser degrees of chol lowering achieved with MUFA-substituted compared with PUFA-substituted diet in most subj	**Author's Conclusions:** "In conclusion, in an NCEP Step 1 diet containing 30% total fat, with all other known cholesterol-influencing dietary factors held constant, the substitution of polyunsaturated fatty acid for mono-unsaturated fatty acid from 3% to 14% resulted in a progressive decline in total cholesterol and less triacylglycerol elevations, without effect on HDL cholesterol" ***Reviewer's Comments:*** *None*

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				corticosteroid androgens or thyroid hormones; MI, CABG, PTCA or other major surgical procedure within past 6 mo; recent onset of angina or current stable angina; congestive heart failure; other sig clinical disorders; HX of eating disorders, habitually expended >1000 kcals/wk via exercise; taking >400 mg niacin/d or megadoses of vits; HX of major gastrointestinal surgery or bowel disorders requiring medical TX	4) Diet 4: 14% PUFA, 6% MUFA Oils combination of canola, coconut, corn, olive and safflower; supplemented with squalene (~4.5 mg/g oil) and mixture of plant sterols (~7 mg/g oil) **Dietary Intake During Study:** Total fat: 30% TE SFA: 10% TE Chol: 35.7 mg/MJ/d Calories: 7.6, 9.2 or 10.9 MJ/d **Dietary Intake Assessment/Frequency:** Daily food log and random 24-h food recalls **Study Visits/ Measurements:** Visits 2x/wk for food pick-up and wt measurement Fasting blood samples collected on 2 separate d last wk of each diet period	Degree of HDL lowering and TG elevations also correlated (r=0.523, P=0.001; r=0.381, P=0.0021, respectively), although greater TG elevation with high MUFA diet Magnitude of chol lowering response greater in subj with higher baseline chol and less in more obese subj **% change and absolute change not provided**	

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Kris-Etherton et al., 1993	**RCT, CO, DB**	**A**	**+**	**Purpose:** To examine effects of diets high in cocoa butter, olive oil, soybean oil and dairy butter on plasma levels of lipids, lipoproteins and apolipoproteins A-1 and B **Sample:** 33 healthy young men (19 experimental, 14 CNTL; 9 and 12, respectively, completed) **Inclusions:** Nonsmokers; normal wt and plasma chol; moderate activity levels **Exclusions:** Metabolic and endocrine disease; unusual dietary practices	**Run-in Period:** None **TX/Duration:** Subj in experimental group received each diet in randomized sequence: 1) TX 1: Cocoa butter (11.4% TE stearic acid, 13.2% TE MUFA) 2) TX 2: Olive oil (27.2% TE MUFA) 3) TX 3: Soybean oil (17.8% TE linoleic acid) 4) TX 4: Dairy butter (9.3% TE palmitic acid and 10.1% TE MUFA) CO; 26 d each Subj in CNTL group consumed habitual diet for entire study 8 mo **Dose/Form:** 81% of fat energy provided by test fats incorporated into cookies, muffins and pudding **Dietary Intake During Study:**	**Outcome Measures:** Plasma lipids Apolipoproteins A-1 and B **Results:** % change in TC for each diet relative to baseline: Cocoa butter: 2.1±4.3 (NS) Olive oil: -8.3±4.4 (P<0.05) Soybean oil: -24.0±4.1 (P<0.01) Dairy butter: 11.7±6.7 (P<0.05) LDL levels paralleled TC levels, except NS diff when olive and soybean oil diets compared Dairy butter diet hypercholesterol-emic compared with all other test diets (P<0.05, cocoa butter; P<0.01, olive and soybean oil) Olive and soybean oil diets hypocholesterolemic compared with cocoa butter diet (P<0.01) Soybean oil diet elicited most hypocholesterolemic response compared with other diets (P<0.01) NS effects of TX diets on VLDL or HDL	**Author's Conclusions:** "…it is evident that linoleic acid is significantly more potent than oleic acid in decreasing plasma cholesterol levels of young men" ***Reviewer's Comments:*** *None*

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					Total fat: 37% TE SFA (%TE): Cocoa butter: 20.9 Olive oil: 6.0 Soybean oil: 6.3 Dairy butter: 21.0 Chol: 360 mg/d Calories: 2700 to 3500 kcals/d **Dietary Intake Assessment/Frequency:** 4-d food record prior to study initiation Food and beverage consumption recorded 2x/d by nutritionists **Study Visits/ Measurements:** 3-d fecal samples collected 2 wk into each TX period **Washout Period:** Habitual diet consumed for 4 wk bet each diet period	Soybean oil diet elicited hypotriglyceridemic effect compared with cocoa butter and dairy butter diets ($P<0.05$, $P<0.01$, respectively) Soybean oil diet sig decr apolipoprotein B conc compared with other test diets ($P<0.01$)	
Zock and Katan, 1992	**RCT**	**A**	**+**	**Purpose:** To compare effects of linoleic acid and its hydrogenation	**Run-in Period:** 3-d food record completed for estimation of energy and nutrient intake	**Outcome Measures:** Serum lipoprotein Serum apolipoprotein	**Author's Conclusions:** "Based on our two studies…it can be

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				products elaidic and stearic acid on serum lipoprotein levels in humans **Sample:** 31 men and 31 women (26 men and 30 women completed) **Inclusions:** Normolipidepmic; apparently healthy **Exclusions:** HX of atherosclerosis, anemia, glycosuria, proteinuria or HTN; use of meds known to affect blood lipids	**TX/Duration:** Multiple CO - 3 experimental diets for 3 wk each in random order Subj divided into 6 groups of nearly identical number from both sexes; each group received diets in diff order **Dose/Form:** Study diets consisted of conventional solid foods: 1) CNTL: Linoleate diet – high in linoleic acid (commercially available margarine high in linoleic acid + high-linoleic acid sunflower oil) 2) TX 1: Stearate diet 3) TX 2: *Trans* diet – high in elaidic acid (high-oleic acid sunflower) **Dietary Intake During Study:** Diets formulated at 24 levels of energy intake ranging from 5.5 to 17.5 MJ (1315 to 4185 kcal)/d	**Results:** Mean change in lipids with each diet relative to linoleic acid diet: TC Stearate diet: 0.15 mmol/L (*P*=0.0081; 95% CI, 0.02 to 0.27) *Trans* diet: 0.16 mmol/L (*P*=0.0041; 95% CI, 0.04 to 0.29) LDL Stearate diet: 0.17 mmol/L (*P*=0.0008; 95% CI, 0.05 to 0.28) *Trans* diet: 0.24 mmol/L (*P*=0.0001; 95% CI, 0.12 to 0.35) HDL Stearate diet: -0.06 mmol/L (*P*< 0.0001; 95% CI, 0.03 to 0.10) *Trans* diet: -0.10 mmol/L (*P*<0.0001; 95% CI, 0.06 to 0.13) Lower HDL levels on *trans* diet than on linoleate diet in 46 of 56 subj Diff of 0.034 mmol/L in HDL bet stearate diet and *trans* diet just failed to reach sig (*P*=0.0210; 95% CI, -0.00 to 0.07)	speculated that one dietary energy % of trans fatty acids in the diet raises LDL cholesterol by about 1.2 mg/dl (0.03 mmol/l) and lowers HDL cholesterol by about 0.6 mg/dl (0.015 mmol/l) relative to oleic or linoleic acid….Replacement of 8 dietary energy % of monounsaturated *trans* fatty acids by stearic acid resulted in only minor changes in serum lipid and lipoprotein values. Our data thus do not support the idea that increasing the stearic acid content of hardened fats at the expense of *trans* fatty acids is beneficial for the serum lipid profile; either mode of hydrogenation produced fatty acids that increased LDL and decreased HDL cholesterol relative to

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					Fat: Linoleate diet: 12.0% TE linoleic acid, 2.8% TE stearic acid and 0.1% TE TFA Stearate diet: 3.9% TE linoleic acid, 11.8% TE stearic acid and 0.3% TE TFA *Trans* diet: 3.8% TE linoleic acid, 3.0% TE stearic acid and 7.7% monounsaturated TFA (largely elaidic acid) **Dietary Intake Assessment/Frequency:** None **Study Visits/ Measurements:** Hot meals served and eaten at department on wk d; all other food supplied daily as package Wt measured 2x/wk Fasting blood samples taken on d 1, 17 and 21 (period l), d 38 and 42 (period 2) and d 59 and 63 (period 3)	HDL:LDL ratio 0.55 on linoleate diet, 0.50 on the stearate diet, and 0.47 on *trans* diet; all 3 values sig diff from each other (*P*<0.0037 for each comparison) TG levels 0.09 mmol/L higher on stearate diet than on linoleate diet (*P*=0.0074; 95% CI, 0.01 to 0.17);TG values NS diff bet *trans* diet and stearate diet Mean change in apolipoprotein levels with each diet relative to linoleate diet: Apolipoprotein B Stearate diet: 3.4 mg/dL (*P*<0.0184; 95% CI, 1.7 to 5.0) *Trans* diet: 5.0 mg/dL (*P*<0.0184; 95% CI, 3.4 to 6.6) Apolipoprotein B/LDL ratio NS diff for each diet Mean apolipoprotein A-I level 2.0 mg/dL higher on linoleate diet than on *trans* diet (*P*=0.0119; 95% CI, 0.1 to 4.0) Diff in serum apolipoprotein A-I bet linoleate and stearate diet periods and bet stearate and *trans* diet periods NS	linoleic acid itself" ***Reviewer's Comments:*** *None*

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						Mean apolipoprotein A-I/HDL ratio incr from 856 mg/mmol on linoleate diet to 887 mg/mmol on stearate diet and to 904 mg/mmol on *trans* diet (*P*<0.0081 for each comparison) Apolipoprotein A-I/apolipoprotein B ratio 1.85±0.36 on linoleate diet, 1.75±0.37 on stearate diet and 1.69±0.33 on the *trans* diet (*P*<0.0012 for each comparison) As compared with linoleate diet, mean response of men on stearate diet sig greater than that of women for TC (diff in change, 0.22 mmol/L; *P*=0.0438) and for apolipoprotein B (diff in change, 3.7 mg/dL; *P*=0.0155)	
McDonald et al., 1989	**RCT**	**A**	**Ø**	**Purpose:** To evaluate changes in plasma lipids and lipoproteins of healthy men caused by dietary fats, which differed in oleic acid, linoleic acid and linolenic acid content, and effect of dietary fat source on production of thromboxane A_2 and	**Run-in Period:** 6-d; mixed fat diet (14% of TE SFA, 15% MUFA and 7% PUFA) **TX/Duration:** Approx 75% of fat in diet from test fat 4 subj randomized to each group: 1) CAN-SUN group - canola oil diet followed	**Outcome Measures:** Plasma lipids Bleeding times Thromboxane B_2 6-keto-$PGF_{1\alpha}$ Platelet aggregation BP **Results:** Sig decr in TC for both groups during experimental period 1 % change in chol values during	**Author's Conclusions:** "This study demonstrated that the hypercholesterolemic effect of a diet rich in oleic acid (20% of total energy) was equivalent to that of a diet providing a similar amount of linoleic acid (22% of total energy)….It should be

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				prostocyclin in vivo in response to standardized vascular injury **Sample:** 8 male students **Inclusions:** Male **Exclusions:** Family HX of CHD	by sunflower oil diet 2) SUN-CAN group - sunflower oil diet followed by canola oil diet 18 d each (36 d total) **Dose/Form:** Canola oil diet - 59% oleic, 21% linoleic, 10% linolenic acid; 5% of total dietary energy SFA, 20% MUFA and 10% PUFA Sunflower oil diet - 14% oleic, 73% linoleic, trace linolenic acid; 7% of total dietary energy SFA, 7% MUFA and 22% PUFA **Dietary Intake During Study:** Total fat: 36% TE Calories: ~3000 kcal/d **Dietary Intake Assessment/Frequency:** None **Study Visits/ Measurements:** Fasting blood samples collected on d 1, 7, 16, 25,	1^{st} period: TC Canola oil: -20% Sunflower oil: -15% LDL Canola oil: -25% Sunflower oil: -21% Changing dietary fat source during experimental period 2 did not result in any further changes in TC or LDL No sig diff in HDL and TG for either period Bleeding times longer and in vivo 1-keto-PGF production greater (P<0.05) on the canola oil diet compared to mixed fat diet Mean thromboxane B_2 lower (P<0.05) and 6-keto-$PGF_{1\alpha}$/thromboxane ratio higher (P<0.05) after sunflower oil diet compared to mixed fat diet	noted, however, that canola oil, the primary source of fat in the high-oleic-acid diet, also contained an appreciable amount of linoleic acid (21%) and linolenic acid (10%). The present study also found that the antithrombic effects of canola oil were similar to those of sunflower oil, the primary source of fat in the high-linoleic-acid diet" ***Reviewer's Comments:*** *Small sample size*

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					43 and 49 Bleeding times and BP measured at end of preexperimental (d 7) period and each experimental period (d 25 and 43) **Washout Period:** None **Postexperimental Period:** 6 d; mixed fat diet		
Mattson and Grundy, 1985	**RCT**	**A**	**Ø**	**Purpose:** To compare PUFA and MUFA when substituted for SFA for effects on plasma lipoproteins **Sample:** 20 pts (12 normo-triglyceridemic, 8 hypertriglyceridemic) **Inclusions:** Metabolic ward pt of Veterans Administration Medical Center in Texas or San Diego	**Run-in Period:** None **TX/Duration:** Randomized to liquid formula diet with diff FA 4 wks **Dose/Form:** 1) CNTL: SFA - palm oil 2) TX 1: MUFA - high-oleic safflower oil 3) TX 2: PUFA - high-linoleic safflower oil **Dietary Intake During Study:**	**Outcome Measures:** Plasma lipid and lipoprotein levels **Results:** Compared to SFA diet, both unsaturated FA caused sig reductions in TC and LDL ($P<0.05$), although no diff in degree of reductions bet 2 fats NS diff in TG, VLDL or HDL levels % change relative to SFA diet when pts divided according to TG levels (normotriglyceridemic vs hypertriglyceridemic): TC Normolipidemic:	**Author's Conclusions:** "The major finding of this study was that the two unsaturated fatty acids had almost identical effectiveness in reducing TC and LDL-C. The current results, furthermore, are in accord with previous studies showing that high intakes of linoleic acid frequently lower HDL-C levels; this response appeared to occur less often when

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				Exclusions: HX of MI, unstable angina pectoris, congestive heart failure, or liver, gastrointestinal tract, kidney or endocrine system disease	Liquid formula diet Total fat: 40% TE **Dietary Intake Assessment/Frequency:** None **Study Visits/ Measurements:** Fasting blood samples collected on d 17, 19, 20, 24, 26 and 27	MUFA: -12.5% (*P*=0.01) PUFA: -15.6% (*P*=0.01) Hypertriglceridemic: MUFA: -8.8% (NS) PUFA: -11.2% (*P*=0.05) LDL Normolipidemic: MUFA: -17.7% (*P*=0.01) PUFA: -17.1% (*P*=0.01) Hypertriglceridemic: MUFA: -13.5% (*P*=0.05) PUFA: -12.2% (NS) In normotriglyceridemic pts, PUFA diet caused sig decr in conc of HDL (-5.0±1.7 mg/dL, *P*<0.02), although percentage reduction (9.8±4.7%) NS; NS change on MUFA diet 4 pts with highest TC on SFA diet had ave reductions of 21% and 22% on MUFA and PUFA diets, respectively, vs 4 pts with TC levels <200 mg/dL on SFA diet had decreases of 8% and 12% on MUFA and PUFA diets, respectively	the patients were taking large quantities of oleic acid" ***Reviewer's Comments:*** *None*
Becker et al., 1983	**RCT**	**A**	**Ø**	**Purpose:** To independently compare relative effects of n-6 PUFA vs SFA on plasma	**Run-in Period:** None **TX/Duration:** Subj each consumed 3	**Outcome Measures:** Plasma lipids Lipoproteins Apoproteins	**Author's Conclusions:** "Our results lend support to the theory that the presence of

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				lipids, lipoproteins and apoproteins **Sample:** 12 healthy men **Inclusions:** Healthy; normolipidemic **Exclusions:** Clinical or biochemical evidence of cardiac, hepatic, renal or endocrine disease; smoker; use of prescription drugs	diff formula diets in random order for separate periods of 4 wk each **Dose/Form:** Chol-free liquid formula diet 40% of calories from fat substituted with 1 of following for each period: 1) CNTL: High MUFA diet (10% SFA, 80% MUFA, 10% PUFA) – high oleic safflower oil 2) TX 1: High PUFA diet (10% SFA, 40% MUFA, 50% PUFA) – corn oil and olive oil 3) TX 2: High SFA diet (50% SFA, 40% MUFA, 10% PUFA) – cocoa butter and safflower oil **Dietary Intake During Study:** Total fat: 40% TE Chol: 0 mg Calories: eucaloric Plant sterol content: 500 mg/d **Dietary Intake Assessment/Frequency:**	**Results:** Plasma conc of lipids and lipoproteins at baseline and for each diet after 4 wk: Chol Baseline: 166±29.1mg/dL MUFA: 127±13.2 mg/dL PUFA: 122.6±16.3 mg/dL SFA: 132.9±29.0 mg/dL TG Baseline: 100.8±54.2mg/dL MUFA: 74.5±34.0 mg/dL PUFA: 70.1±34.7 mg/dL SFA: 71.8±35.3 mg/dL LDL Baseline: 102.8±27.9mg/dL MUFA: 70.6±17.5 mg/dL PUFA: 64.8±14.7 mg/dL SFA: 81.4±13.1 mg/dL Plasma conc of chol, TG and LDL decr sig from baseline after all 3 dietary periods ($P<0.05$) Final chol and LDL conc sig diff ($P<0.05$) bet 3 diets HDL NS diff from baseline after diets or bet diet phases LDL:HDL ratios during 4th wk of diets lowest on PUFA (1.52),intermediate on MUFA (1.71) and highest on SFA	polyunsaturated fat has a lipid-lowering effect, while saturated fat in the diet has the opposite effect. The LDL-C to HDL-C ratio, an index of atherogenicity, can be ameliorated as well by the substitution of moderate amounts of polyunsaturated fat for saturated fat" ***Reviewer's Comments:*** *None*

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					None **Study Visits/ Measurements:** Wt measured daily and stool samples collected Blood samples obtained 3x/wk **Washout Period:** Usually <2 wk; occasionally ≥2 wk	(2.21);*P*<0.05 Final values of apoprotein B NS diff from one another, but decr sig (*P*<0.05) from baseline Final values of apoproteins A1 and CIII NS diff from baseline or bet diets **% change not provided**	