

Table 1: The effect of replacing SFA with other dietary macronutrients on cardiovascular outcomes

Study	Design	n	Mean follow-up time (years)	Outcome	Substitution	Result	Effect size (95% CI)	Covariates included in analyses
Substitution of saturated fat for MUFA								
Jakobsen 2009 [1]	Pooled analysis of prospective cohort studies	11 studies (n=344,696)	Range 4 to 10	Coronary events Coronary deaths	5% of energy from SFA → MUFA 5% of energy from SFA → MUFA	↔ ↔	HR 1.19 (1.00-1.42) HR 1.01 (0.73-1.41)	Age; BMI; year survey completed; percentage of energy from MUFA, PUFA, trans fat, protein and carbohydrates; energy intake; smoking; physical activity; education; alcohol intake; fiber intake; cholesterol intake; hypertension
Guasch-Ferré 2015 [2] [PREDIMED]	Prospective cohort	7,038	6	CVD All-cause death	5% of energy from SFA → MUFA	↓ ↔	HR 0.63 (0.43-0.94) HR 0.91 (0.65-1.26)	Age; sex; BMI; intake of subtypes of fat, protein, and carbohydrates; energy intake; smoking; physical activity; education; alcohol intake; fiber intake; cholesterol intake; hypertension; intervention group; diabetes; hyper-cholesterolemia; family history of CHD; antihypertensive medication; oral antidiabetic agents; lipid lowering drugs
Li 2015 [3] [NHS; HPFS]	Prospective cohort	127,536	Range 24-30	CHD	5% of energy from SFA → MUFA	↓	HR 0.85 (0.74-0.97)	BMI, percentage of energy from protein; energy intake; smoking; physical activity; alcohol intake; cholesterol intake; hypertension at

								baseline; hypercholesterolemia at baseline; family history of myocardial infarction and diabetes; use of vitamins and aspirin
Praagman 2016 [4] [EPIC-Netherlands]	Prospective cohort	35,597	12	IHD	5% of energy from SFA → cis-MUFA	↑	HR 1.30 (1.02-1.65)	Age, sex, BMI, waist circumference; intake of carbohydrate, cis-MUFA, PUFA, trans fat, animal protein and vegetable (per 5% of energy); energy intake (excluding alcohol); smoking, physical activity; education; alcohol intake; fiber intake (energy adjusted); cholesterol intake (energy adjusted); vitamin c (energy adjusted)
Wang 2016 [5] [NHS; HPFS]	Prospective cohort	126,233	NHS ≤ 32; HPFS ≤ 26	CVD mortality Total mortality	5% of energy from SFA → MUFA	↔ ↓	HR 0.96 (0.84-1.09) HR 0.87 (0.82-0.93)	Age; BMI, percentage of energy intake from protein, remaining fatty acids (saturated fat, PUFA, MUFA, trans-fat, ω-6 PUFAs, ω-3 PUFAs, linoleic acid, arachidonic acid, α-linolenic acid, and marine ω-3 fats); energy intake; smoking; physical activity; alcohol intake; cholesterol intake; family history of myocardial infarction, diabetes, cancer, hypertension, hypercholesterolemia; multivitamin use; vitamin E supplement; aspirin use; white race; marital status; menopausal status and hormone use in women
Zong 2016 [6] [NHS; HPFS]	Prospective cohort	115,782	NHS 25.8; HPFS 21.2	CHD	1% of energy from 12:0-18:0 SFA → MUFA	↔	HR 0.95 (0.90, 1.01)	Age; BMI; ethnicity; total energy; energy from trans fat; energy from carbohydrates of non-whole grain sources; energy from non-plant sources; smoking status; physical

								activity; alcohol intake; family history of MI; menopausal status; postmenopausal hormone use; aspirin use; multivitamin use; baseline hypertension; baseline hypercholesterolemia; PUFA intake; whole grains intake; plant proteins intake; intake of other SFA
Hooper 2015 [7] Cochrane review	Meta-analysis of randomized controlled trials	15 studies (n >59,000)	>2	CVD events	SFA → MUFA	↔	RR 1.00 (0.53-1.89)	Aggregate meta-analysis –no overall adjustment
Substitution of saturated fat for PUFA								
Mozaffarian 2010 [8]	Meta-analysis of randomized controlled trials	8 studies (n= 13,614)	Median of all trials 4.25	CHD	5% of energy from SFA → total PUFA	↓	RR 0.90 (0.83-0.97)	Aggregate meta-analysis –no overall adjustment
Jakobsen 2009 [1]	Pooled analysis of prospective cohort studies	11 studies (n=344,696)	Range 4 to 10	Coronary events	5% of energy from SFA → total PUFA	↓	HR 0.87 (0.77-0.97)	Age; BMI; year survey completed; percentage of energy from MUFA, PUFA, trans fat, protein and carbohydrates; energy intake; smoking; physical activity; education; alcohol intake; fiber intake; cholesterol intake; hypertension
				Coronary deaths	5% of energy from SFA → total PUFA	↓	HR 0.74 (0.61-0.89)	
Farvid 2014 [9]	Meta-analysis of prospective	13 studies (n=310,602)	Range 5.3 to 30	Coronary events	5% of energy from SFA → linoleic acid	↓	RR 0.91 (0.87-0.96)	Aggregate meta-analysis – analyses in the individuals studies adjusted but no overall adjustment

	cohort studies			Coronary deaths		↓	RR 0.87 (0.82-0.94)	
Li 2015 [3] [NHS; HPFS]	Prospective cohort	127,536	Range 24-30	CHD	5% of energy from SFA → total PUFA	↓	HR 0.75 (0.67-0.84)	BMI, percentage of energy from protein; energy intake; smoking; physical activity; alcohol intake; cholesterol intake; hypertension at baseline; hypercholesterolemia at baseline; family history of myocardial infarction and diabetes; use of vitamins and aspirin
Guasch-Ferré 2015 [2] [PREDIMED]	Prospective cohort	7,038	6	CVD All-cause mortality	5% of energy from SFA → PUFA	↓ ↓	HR 0.67 (0.45-0.98) HR 0.61 (0.39-0.97)	Age; sex; BMI; intake of subtypes of fat, protein, and carbohydrates; energy intake; smoking; physical activity; education; alcohol intake; fiber intake; cholesterol intake; hypertension; intervention group; diabetes; hyper-cholesterolemia; family history of CHD; antihypertensive medication; oral antidiabetic agents; lipid lowering drugs
Chen 2016 [10] [NHS; NHS II; HPFS]	Prospective cohort	134,327	NHS ≤ 32; NHS II ≤; HPFS ≤ 24	CVD CHD Stroke	5% of energy from dairy fat → total PUFA	↓ ↓ ↓	HR 0.76 (0.71-0.81) HR 0.74 (0.68-0.81) HR 0.78 (0.70-0.88)	Age, BMI, intake of protein; energy intake; smoking; physical activity; intake of fruit, vegetables, coffee; alcohol intake; baseline hypertension; baseline hyper-cholesterolemia; race; menopausal status and menopausal hormone use (NHS and NHS II); oral contraceptive use (NHS II only)

				CVD	5% of energy from dairy fat → <i>n</i> -6 PUFA	↓	HR 0.75 (0.70- 0.81)	
				CHD		↓	HR 0.75 (0.69- 0.82)	
				Stroke		↓	HR 0.76 (0.68- 0.86)	
				CVD	0.3% of energy from dairy fat → α-linolenic acid	↓	HR 0.86 (0.82- 0.90)	
				CHD		↓	HR 0.83 (0.78- 0.88)	
				Stroke		↓	HR 0.89 (0.83- 0.96)	
				CVD	0.3% of energy from dairy fat → marine n-3	↓	HR 0.89 (0.84- 0.94)	
				CHD		↓	HR 0.87 (0.81- 0.93)	
				Stroke		↔	HR 0.92 (0.84- 1.01)	
Praagman 2016 [4] [EPIC- Netherlands]	Prospective cohort	35,597	12	IHD	5% of energy from SFA → PUFA	↑	HR 1.35 (1.14- 1.61)	Age, sex, BMI, waist circumference; intake of carbohydrate, cis-MUFA, PUFA, trans fat, animal protein and vegetable (per 5% of energy); energy intake (excluding alcohol); smoking, physical activity; education; alcohol

								intake; fiber intake (energy adjusted); cholesterol intake (energy adjusted); vitamin c (energy adjusted)
Wang 2016 [5] [NHS; HPFS]	Prospective cohort	126,233	NHS ≤ 32; HPFS ≤ 26	CVD mortality	5% of energy from SFA → total PUFA	↓	HR 0.72 (0.65- 0.80)	Age; BMI, percentage of energy intake from protein, remaining fatty acids (saturated fat, PUFA, MUFA, trans-fat, ω-6 PUFAs, ω-3 PUFAs, linoleic acid, arachidonic acid, α-linolenic acid, and marine ω-3 fats); energy intake; smoking; physical activity; alcohol intake; cholesterol intake; family history of myocardial infarction, diabetes, cancer, hypertension, hyper- cholesterolemia; multivitamin use; vitamin E supplement; aspirin use; white race; marital status; menopausal status and hormone use in women
				Total mortality		↓	HR 0.73 (0.70- 0.77)	
				CVD mortality	2% of energy from SFA → <i>n</i> -6 PUFA	↓	HR 0.89 (0.85- 0.94)	
				Total mortality		↓	HR 0.93 (0.91- 0.96)	
				CVD mortality	0.3% of energy from SFA → <i>n</i> -3 PUFA	↔	HR 1.01 (0.97- 1.05)	
				Total mortality		↓	HR 0.95 (0.93- 0.96)	
Zong 2016 [6] [NHS; HPFS]	Prospective cohort	115,782	NHS 25.8; HPFS 21.2	CHD	1% of energy from 12:0-18:0 SFA → PUFA	↓	HR 0.92 (0.89, 0.96)	Age; BMI; ethnicity; total energy; energy from trans fat; energy from carbohydrates of non-whole grain sources; energy from non-plant sources; smoking status; physical activity; alcohol intake; family history of MI; menopausal status; postmenopausal hormone use; aspirin use; multivitamin use; baseline hypertension; baseline hypercholesterolemia; MUFA intake;

								whole grain intake; plant protein intake; intake of other SFA
Hooper 2015 [7] Cochrane review	Meta-analysis of randomized controlled trials	15 studies (n >59,000)	>2	CVD events	SFA → PUFA	↓	RR 0.73 (0.58-0.92)	Aggregate meta-analysis –no overall adjustment
Substitution of saturated fat for carbohydrate								
Jakobsen 2009 [1]	Pooled analysis of prospective cohort studies	11 studies (n=344,696)	Range 4 to 10	Coronary events Coronary deaths	5% of energy from SFA → total carbohydrate 5% of energy from SFA → total carbohydrate	↑ ↔	HR 1.07 (1.01-1.14) HR 0.96 (0.82-1.13)	Age; BMI; year survey completed; percentage of energy from MUFA, PUFA, trans fat, protein and carbohydrates; energy intake; smoking; physical activity; education; alcohol intake; fiber intake; cholesterol intake; hypertension
Jakobsen 2010 [11]	Prospective cohort	53,644	Median 12	MI	5% of energy from SFA → total carbohydrates	↔	HR 1.04 (0.92-1.17)	Age, sex, BMI; percentage of energy from glycemic carbohydrates, proteins, MUFA, PUFA; energy intake; smoking; physical activity; education; alcohol consumer; intake of alcohol; hypertension
					5% of energy from SFA → carbohydrates with low-GI (median GI 82)	↔	HR 0.88 (0.72-1.07)	
					5% of energy from SFA → carbohydrates with medium-GI (median GI 88)	↔	HR 0.98 (0.80-1.21)	

					5% of energy from SFA → carbohydrates with high-GI (median GI 93)	↑	HR 1.33 (1.08-1.64)	
Guasch-Ferré 2015 [2] [PREDIMED]	Prospective cohort	7,038	6	CVD All-cause death	5% of energy from SFA → total carbohydrate	↔ ↔	HR 0.83 (0.63-1.10) HR 1.04 (0.81-1.33)	Age; sex; BMI; intake of subtypes of fat, protein, and carbohydrates; energy intake; smoking; physical activity; education; alcohol intake; fiber intake; cholesterol intake; hypertension; intervention group; diabetes; hyper-cholesterolemia; family history of CHD; antihypertensive medication; oral antidiabetic agents; lipid lowering drugs
Li 2015 [3] [NHS; HPFS]	Prospective cohort	127,536	Range 24-30	CHD	5% of energy from SFA → whole grains 5% of energy from SFA → refined starches/ added sugar	↓ ↔	HR 0.91 (0.85-0.98) Not reported	BMI, percentage of energy from protein; energy intake; smoking; physical activity; alcohol intake; cholesterol intake; hypertension at baseline; hypercholesterolemia at baseline; family history of myocardial infarction and diabetes; use of vitamins and aspirin
Zong 2016 [6] [NHS; HPFS]	Prospective cohort	115,782	NHS 25.8; HPFS 21.2	CHD	1% of energy from 12:0-18:0 SFA → whole grains	↓	HR 0.94 (0.91, 0.97)	Age; BMI; ethnicity; total energy; energy from trans fat; energy from carbohydrates of non-whole grain sources; energy from non-plant sources; smoking status; physical activity; alcohol intake; family history of MI; menopausal status; postmenopausal hormone use; aspirin

								use; multivitamin use; baseline hypertension; baseline hypercholesterolemia; MUFA intake; PUFA intake; plant protein intake; intake of other SFA
Chen 2016 [10] [NHS; NHS II; HPFS]	Prospective cohort	134,327	NHS ≤ 32; NHS II ≤ 20; HPFS ≤ 24	CVD	5% of energy from dairy fat → carbohydrate from whole grains	↓	HR 0.72 (0.69-0.75)	Age, BMI, intake of protein; energy intake; smoking; physical activity; intake of fruit, vegetables, coffee; alcohol intake; baseline hypertension; baseline hyper-cholesterolemia; race; menopausal status and menopausal hormone use (NHS and NHS II); oral contraceptive use (NHS II only)
				CHD		↓	HR 0.66 (0.62-0.70)	
				Stroke		↓	HR 0.84 (0.78-0.91)	
				CVD	5% of energy from dairy fat → carbohydrate from refined starch and added sugar	↔	HR 0.97 (0.94-1.00)	
				CHD		↔	HR 0.96 (0.93-1.00)	
				Stroke		↔	HR 0.98 (0.94-1.03)	
Praagman 2016 [EPIC-NL] [4]	Prospective cohort	35,597	12	IHD	5% of energy from SFA → total carbohydrates	↑	HR (1.23 (1.09-1.40)	Age, sex, BMI, waist circumference; intake of carbohydrate, cis-MUFA, PUFA, trans fat, animal protein and vegetable (per 5% of energy); energy intake (excluding alcohol); smoking, physical activity; education; alcohol intake; fiber intake (energy adjusted);
					5% of energy from SFA → carbohydrates	↔	HR 1.14 (0.91-1.43)	

					with low GI (GI <53)			cholesterol intake (energy adjusted); vitamin c (energy adjusted)
					5% of energy from SFA → carbohydrates with medium GI	↑	HR 1.35 (1.05-1.73)	
					5% of energy from SFA → carbohydrates with high GI (GI>56)	↑	HR 1.27 (1.03-1.56)	
Hooper 2015 [7] Cochrane review	Meta-analysis of randomized controlled trials	15 studies (n >59,000)	>2	CVD events	SFA → carbohydrate	↔	RR 0.93 (0.79-1.08)	Aggregate meta-analysis –no overall adjustment
Substitution of saturated fat for protein								
Larsson 2012 [12]	Prospective cohort	34,670	Median 10.4	Stroke	5% of energy from SFA → protein	↓	13% lower risk (0-26%)	Age, BMI; intake of fat; energy intake; smoking status and smoking pack years; physical activity; education; alcohol intake; intake of cholesterol, calcium, fruits and vegetables; hypertension; diabetes; aspirin use; family history of myocardial infarction
Praagman 2016 [4] [EPIC- NL]	Prospective cohort	35,597	12	IHD	5% of energy from SFA → total protein	↑	HR 1.29 (1.08-1.54)	Age, sex, BMI, waist circumference; intake of carbohydrate, cis-MUFA, PUFA, trans fat, animal protein and vegetable (per 5% of energy); energy intake (excluding alcohol); smoking, physical activity; education; alcohol
					5% of energy from SFA → animal protein	↑	HR 1.37 (1.14-1.65)	

					5% of energy from SFA → vegetable protein	↔	HR 0.81 (0.57-1.17)	intake; fiber intake (energy adjusted); cholesterol intake (energy adjusted); vitamin c (energy adjusted)
Zong 2016 [6] [NHS; HPFS]	Prospective cohort	115,782	NHS 25.8; HPFS 21.2	CHD	1% of energy from 12:0-18:0 SFA → plant protein	↓	HR 0.93 (0.89, 0.97)	Age; BMI; ethnicity; total energy; energy from trans fat; energy from carbohydrates of non-whole grain sources; energy from non-plant sources; smoking status; physical activity; alcohol intake; family history of MI; menopausal status; postmenopausal hormone use; aspirin use; multivitamin use; baseline hypertension; baseline hypercholesterolemia; MUFA intake; whole grain intake; intake of other SFA
Hooper 2015 [7] Cochrane review	Meta-analysis of randomized controlled trials	15 studies (n >59,000)	>2	CVD events	SFA → protein	↔	RR 0.98 (0.90-1.06)	Aggregate meta-analysis –no overall adjustment

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