

Substituting macronutrients and all-cause mortality: a network meta-analysis of prospective observational studies

Data supplement

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Supplemental figure 1: Risk of bias of each study for each domain and all-cause mortality

	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Argos 2013								
Bajracharya 2023								
Budhathoki 2019								
Chen 2020								
Das 2022								
Dehghan 2017								
Dominguez 2018								
Fontana 2021								
Friden 2023								
Guasch-Ferre 2015								
Guasch-Ferre 2019 (NHS)								
Guasch-Ferre 2019 (HPFS)								
Hernandez-Alonso 2016								
Ho 2020								
Huang 2020								
Kelemen 2005								
Kwon 2021								
Laake 2012								
Laguna 2021								
Levine 2014								





Supplemental figure 1 continued

	D1	D2	D3	D4	D5	D6	D7	Overall
Li 2022b	-	X	+	+	+	+	+	X
Mao 2020	-	-	+	+	-	+	+	-
Merono 2022	-	-	+	+	X	+	+	X
Nagata 2012	-	-	+	+	-	+	+	-
Ricci 2018	-	X	+	+	-	+	+	X
Song 2016 (NHS)	-	-	+	+	-	+	+	-
Song 2016 (HPFS)	-	-	+	+	-	+	+	-
Sun 2021	-	-	+	+	+	+	+	-
Virtanen 2019	-	-	+	+	+	+	+	-
Wang 2016 (NHS)	-	-	+	+	-	+	+	-
Wang 2016 (HPFS)	-	-	+	+	-	+	+	-
Wu 2020	-	-	+	+	-	+	+	-
Zeng 2022	-	X	+	+	-	+	+	X
Zhao 2023	-	-	+	+	+	+	+	-
Zhou 2022a	-	-	+	+	-	+	+	-
Zhuang 2019a	-	-	+	+	-	+	+	-
Zhuang 2019b	-	-	+	+	-	+	+	-
Wakai 2014	-	-	+	+	-	+	+	-

Domains:

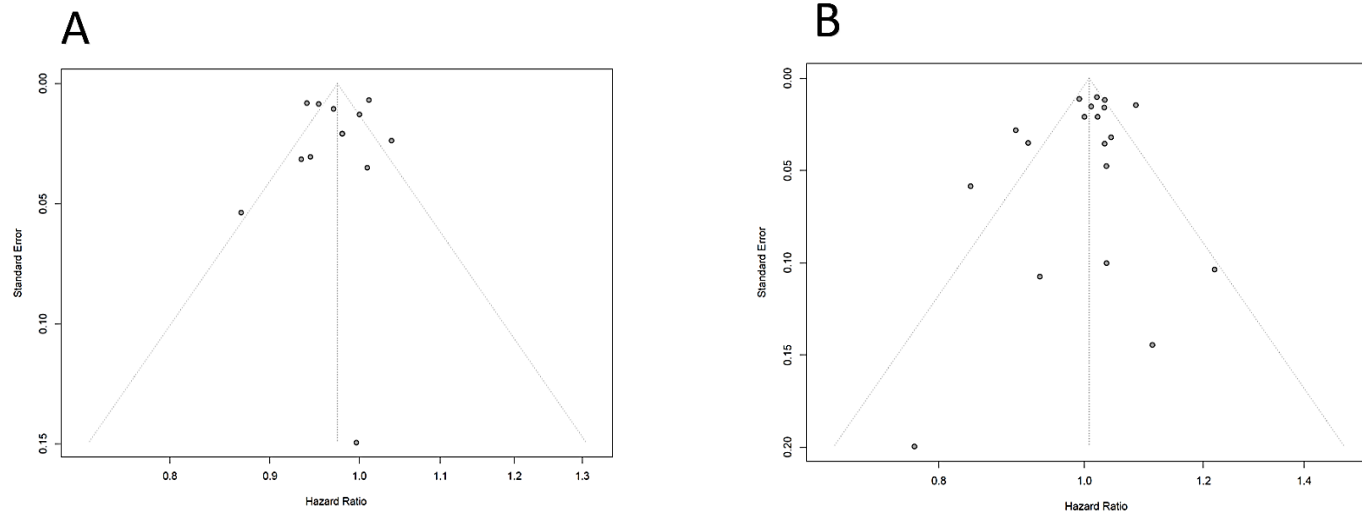
- Domain 1: Risk of bias due to confounding
- Domain 2: Risk of bias arising from measurement of the exposures
- Domain 3: Risk of bias in selection of participants into the study / into the analysis
- Domain 4: Risk of bias due to post-exposure interventions
- Domain 5: Risk of bias due to missing data
- Domain 6: Risk of bias arising from measurement of the outcomes
- Domain 7: Risk of bias in selection of the reported results

Judgement:

-  Low risk of bias
-  Some concerns
-  High risk of bias
-  No judgement due to triage in first domain

D1-7 domain 1-7; HPFS Health Professional Follow up Study; NHS Nurses' Health Study

Supplemental figure 2: Funnel plots for the overall macronutrient network (5% isocaloric energy substitution) for the outcome all-cause mortality^a



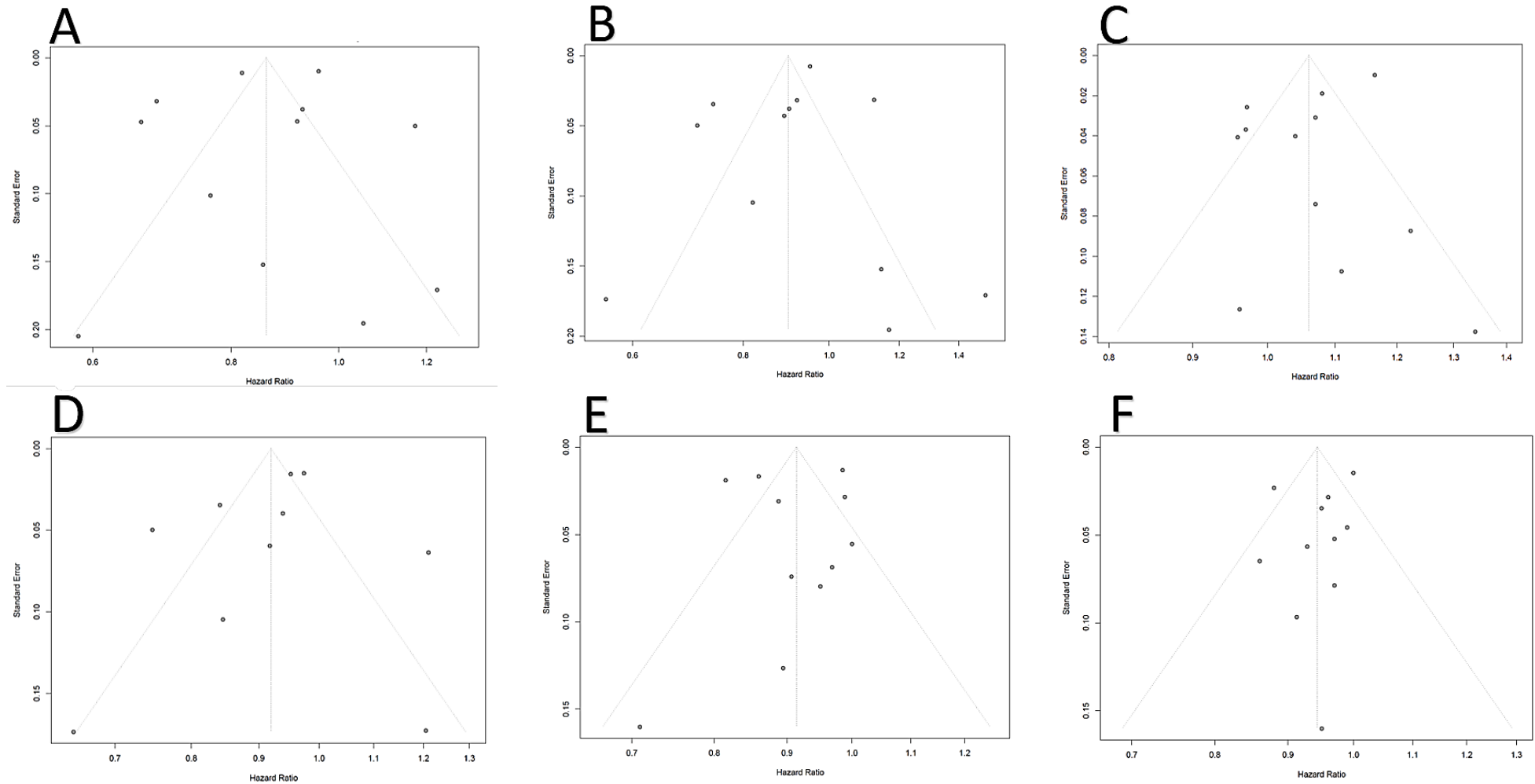
^a At least 10 studies are required to conduct a funnel plot.

A: Funnel plot showing standard error against the hazard ratio for the substitution of carbohydrates with fat. P-value for Eggers linear regression test: p-value = 0.82

B: Funnel plot showing standard error against the hazard ratio for the substitution of protein with carbohydrates. P-value for Eggers linear regression test: p-value = 0.34

Results of Egger's regression test indicated no evidence of publication bias for all-cause mortality for any of the substitutions presented.

Supplemental figure 3: Funnel plots for the fatty acid expanded network (5% isocaloric energy substitution) for the outcome all-cause mortality^a



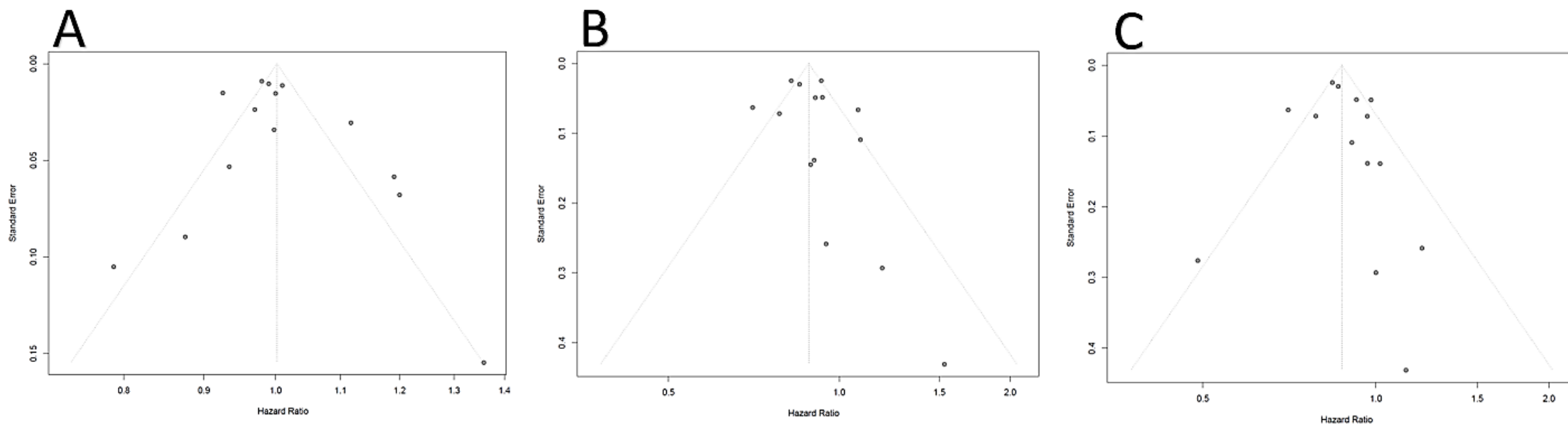
CHO carbohydrates; MUFA monounsaturated fatty acids; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids

^a At least 10 studies are required to conduct a funnel plot.

A: Funnel plot showing standard error against the hazard ratio for the substitution of SFA with PUFA. P-value for Eggers linear regression test: p-value = 0.67

B: Funnel plot showing standard error against the hazard ratio for the substitution of CHO with PUFA. P-value for Eggers linear regression test: p-value = 0.46
C: Funnel plot showing standard error against the hazard ratio for the substitution of CHO with SFA. P-value for Eggers linear regression test: p-value = 0.11
D: Funnel plot showing standard error against the hazard ratio for the substitution of MUFA with PUFA. P-value for Eggers linear regression test: p-value = 0.44
E: Funnel plot showing standard error against the hazard ratio for the substitution of SFA with MUFA. P-value for Eggers linear regression test: p-value = 0.88
F: Funnel plot showing standard error against the hazard ratio for the substitution of CHO with MUFA. P-value for Eggers linear regression test: p-value = 0.33
Results of Egger's regression test indicated no evidence of publication bias for all-cause mortality for any of the substitutions presented.

Supplemental figure 4: Funnel plots for the protein-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality^a



AP animal protein; CHO carbohydrates; PP plant protein

^a At least 10 studies are required to conduct a funnel plot.

A: Funnel plot showing standard error against the hazard ratio for the substitution of CHO with AP. P-value for Eggers linear regression test: p-value = 0.42

B: Funnel plot showing standard error against the hazard ratio for the substitution of CHO with PP. P-value for Eggers linear regression test: p-value = 0.38

C: Funnel plot showing standard error against the hazard ratio for the substitution of AP with PP. P-value for Eggers linear regression test: p-value = 0.54

Results of Egger's regression test indicated no evidence of publication bias for all-cause mortality for any of the substitutions presented.

Supplemental table 1: Eligibility criteria by the PICOS statement

	Inclusion criteria	Exclusion criteria
P (population)	Adults (aged ≥ 18 years), generally healthy population: $>2/3$ of the study population without a particular condition i.e., stable coronary heart disease, chronic kidney disease, diabetes, cancer	Studies involving exclusively infants, children, adolescents, or pregnant women
I (intervention/exposure) C (comparison)	<u>Substitution analyses:</u> Network 1: Overall macronutrient network: FAT, PRO, CHO; Network 2: Fatty acids expanded network: SFA, MUFA, PUFA, TFA, CHO, PRO; Network 3: MUFA-origin network: plant MUFA, animal MUFA, SFA, PUFA, CHO, PRO; Network 4: PUFA-origin network: n-3 PUFA, n-6 PUFA, SFA, MUFA, TFA, CHO, PRO; Network 5: Fat-origin subnetwork: AF, PF, CHO, PRO; Network 6: Protein-origin subnetwork: AP, PP, SFA, MUFA, PUFA, TFA, CHO; Network 7: Carbohydrate-origin subnetwork ^a : high-quality carbohydrates / Polysaccharides, low-quality carbohydrates / Mono-/Disaccharides, SFA, MUFA, PUFA, TFA, PRO;	a. Supplements or only one particular bioactive plant compound b. Substitution of food groups or foods b. No substitution analysis
O (outcome)	- All-cause mortality (present publication) - Cardiovascular disease, coronary heart disease, stroke (incidence and/or mortality) - Type 2 Diabetes - Cancer (incidence and/or mortality) - Adiposity (obesity, overweight, changes in body weight/ waist circumference) - Age related outcomes (dementia, cognitive decline, frailty, sarcopenia) - Other outcomes (hypertension, atrial fibrillation, heart failure, chronic kidney disease)	Biomarkers of cardiometabolic risk (e.g., fasting glucose, blood lipids, etc)
S (study design)	Prospective observational studies (e.g., prospective observational study, nested case-control study, case-cohort study, follow up of RCTs)	In vitro/animal experiments, cross-sectional and retrospective case-control studies

AF animal fat; animal MUFA monounsaturated fatty acids of animal origin; AP animal protein; CHO carbohydrates; MUFA monounsaturated fatty acids; n-3 PUFA n-3 polyunsaturated fatty acids; n-6 PUFA n-6 polyunsaturated fatty acids; PF plant fat; PICOS Population, Intervention, Comparison, Outcome Study design; plant MUFA monounsaturated fatty acids of plant origin; PP plant protein; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

^a originally planned network: glucose, fructose, sucrose, starch, fat, protein; Modified in line with the WHO report (1).

Supplemental table 2: General characteristics of the included prospective observational studies for the outcome all-cause mortality

Author, year	Cohort name, country	Disease status	Follow up (years)	Sex	Mean age (years)	Mean BMI (kg/m ²)	Number of participants	Number of cases	Outcome assessment	Exposure assessment	Multiple dietary assessment
Argos, 2013 (2)	HEALS, Bangladesh	General healthy	9	M/W	36.9	19.7	17 244	818	Report of close relatives or neighbors of deceased participants, verbal autopsy questionnaire; verbal autopsies were reviewed by a panel of local expert physicians	Validated (through food diaries) FFQ at baseline	No
Bajracharya, 2023 (3)	EPIC-Heidelberg, Germany	General healthy	22.7	M/W	51.4	25.8	24 106	4 029	Record linkages with registries for vital status	Validated (through 24h recalls) FFQ at baseline	No
Budhathoki, 2019 (4)	JPHC, Japan	General healthy	18	M/W	55.7	23.5	70 696	12 381	Residential registry	Validated (through 14- or 28-day dietary records) FFQ, repeated every 5 years	Yes, but only single FFQ was used

Chen, 2020 (5)	Rotterdam, Netherlands	General healthy	13	M/W	63.7	26.6	7 786	3 589	Clinical follow-up data collection, municipal records, information from medical records at general practitioner's offices, hospitals and nursing homes	Validated (through 24 h food records and 24-h urinary urea excretion samples) FFQ at baseline	No
Das, 2022 (6)	CHAMP, Australia	General healthy, older population	3.7	M	81.1	27.2	794	162	Data from three population databases held by the Centre for Health Record Linkage, all-cause mortality was assessed as a result of cancer and CVD	Validated (through 4-day weighed food record), standardized DHQ, administered by research dietitians at baseline	No
Dehghan, 2017 (7)	PURE, Multiple Countries	General healthy	7.4	M/W	50.3	NR	135 335	5 796	Standardized case-report forms were used to record data on mortality	Validated (through 24h recalls), country-specific (or region-specific in India) FFQ at baseline	No

Dominguez, 2018 (8)	SUN, Spain	General healthy	9.5	M/W	53.9	25.3	18 540	255	Uninterrupted and dynamic follow-up, every six months National Death Index data were checked	Validated (through 4-day records) FFQ at baseline	Yes, every two years, but only baseline FFQ was used for the current analysis
Fontana, 2021 (9)	EPIC-Italy, Italy	General healthy	15.2	M/W	50.7	26.0	45 009	2 449	Municipal registries, date of death was obtained from the official mortality indices	Validated (through 24h recall), center-specific FFQ at baseline	No
Fridén, 2023 (10)	ULSAM, Sweden	General healthy, older population	13.7	M	71.0	NR	1 133	774	Cause of death registry	Validated (through biomarkers) 7-day dietary record at baseline, with the use of a validated (through 7-day weighed food record) pre-coded menu book from the Swedish National Food Agency	No

Guasch-Ferré, 2015 (11)	PREDIMED, Spain	High CVD risk, 50% T2D	6	M/W	67.0	29.9	7 038	414	Yearly questionnaires and examinations for all participants, family physicians, yearly review of medical records, yearly consultation of the National Death Index	Validated (3-day diet records) FFQ, done by face to face interview with a registered dietitian, annually	Yes, annually; updated intakes were used in models
Guasch-Ferré, 2019 (published and unpublished data) (12)	NHS, USA	General healthy	22	W	67.8	26.5	63 412	12 774	Linkage with vital records of states and of the National Death Index, reports from next of kin and postal authorities	Validated (through dietary records) FFQ, at baseline and every 4 years	Yes, every four years
	HPFS, USA			M	67.7	23.9	29 966	7 898			
Hernández-Alonso, 2016 (13)	PREDIMED, Spain	High CVD risk, 50% T2D	4.8	M/W	67.0	30.0	7 216	323	Yearly questionnaires and examinations for all participants, family physicians, yearly review of medical records, yearly consultation of the National Death Index	Validated (3-day diet records) FFQ, done by face to face interview with a registered dietitian, annually	Yes, annually
Ho, 2020 (published and unpublished data) (14)	UKB, United Kingdom	General healthy	13.2	M/W	56.0	25.1	208 294	12 611	Death certificates held within NHS Information Centre and NHS Central Register Scotland	Validated (through 24h hour recall administered by interviewer) Oxford WebQ web based 24h recall	Yes, up to four times

Huang, 2020 (15)	NIH-AARP, USA	General healthy	15.5	M/W	62.0	27.0	416 104	77 614	Linkage with Social Security Administration Death Master File	Validated (by 24h recall), self-administered FFQ at baseline	No
Kelemen, 2005 (16)	IWHS, USA	General healthy	15	W	75.8	25.8	29 017	3 978	Linkage with National Death Index	Validated (through 24h recalls) FFQ at baseline	No
Kwon, 2021 (17)	KoGES, Korea	General healthy	8.15	M/W	53.8	24.0	194 295	3 866	Publicly accessible files in the KoGES linked National Death Index	Validated (through dietary records) FFQ at baseline	No
Laake, 2012 (18)	NCS, Norway	General healthy	25.8	M/W	41.0	24.6	71 464	11 890	Linkage with Statistics Norway using the unique identification number	Validated (through 24h recall) FFQ	Yes, three times, at first screening only 59% of participants received a FFQ
Laguna, 2021 (19)	PREDIMED, Spain	High CVD risk, 50% T2D	6	M/W	67.0	30.0	7 056	409	Yearly questionnaires and examinations for all participants, family physicians, yearly review of medical records, yearly consultation of the National Death Index	Validated (3-day diet records) FFQ, done by face to face interview with a registered dietitian, annually	Yes, annually

Levine, 2014 (20)	NHANES III, USA	General healthy	18	M/W	65.0	27.2	6 381	2 578	Linkage with the National Death Index	24h recall, via automated, microcomputer-based coding system	No
Li, 2022 (21)	NHANES, USA	Prediabetes	7.4	M/W	55.3	29.8	9 793	1 352	Linkage with national death index	zone 24-h recall conducted in person in the NHANES Mobile Examination Center or via telephone	Mixed (no: NHANES 1999 to 2002; yes: 2003 to 2014)
Mao, 2020 (22)	CHNS, China	General healthy	14	M/W	41.2	22.4	14 305	1 006	Based on report of household members in each survey and denoted in CHNS database	3-day 24h dietary recalls at individual level in combination with weighing inventory at household level	Yes
Merono, 2022 (23)	InCHIANTI, Italy	General healthy, older population	12	M/W	75.0	27.0	1 139	811	Mortality General Registry from the Tuscany Region, as well as death certificates	Validated (through 24h recalls) Italian FFQ, assessed by trained interviewers	Yes (three to four times)
Nagata, 2012 (24)	Takahama, Japan	General healthy	16	M/W	54.1	22.3	28 356	4 616	National Vital Statistics	Validated (3-day dietary records and 24h recalls) FFQ at baseline	No
Ricci, 2018 (25)	NHANES, USA	General healthy	6.1	M/W	46.2	27.4	18 372	1 118	Linkage with national death index	zone 24-h recall conducted in person in the NHANES Mobile Examination Center or via telephone	Mixed (no: NHANES 1999 to 2002; yes: 2003 to 2014)

Shan, 2020 (26)	NHANES, USA	General healthy	8	M/W	NR	NR	37 233	4 866	Linkage with national death index	≥one 24-h recall conducted in person in the NHANES Mobile Examination Center or via telephone	Mixed (no: NHANES 1999 to 2002; yes: 2003 to 2014)
Song, 2016 (27)	NHS, USA	General healthy	27	W	49.0	25.9	131 342	36 115	Linkage with vital records of states and of the National Death Index, reports from next of kin and postal authorities	Validated (through dietary records) FFQ at baseline and every 4 years	Yes, every four years
	HPFS, USA			M							
Sun, 2021 (28)	WHI, USA	General healthy	18.1	W	62.8	27.7	102 521	25 976	Death certificates, medical records, autopsy reports, or linkage to the National Death Index	Validated (through 24h dietary recalls and a 4-day food record), self-administered FFQ at baseline	No
Virtanen, 2019 (29)	KIHD, Finland	General healthy	22.3	M	53.1	26.9	2 641	1 225	Linkage to national causes of death register, with social security number	Instructed food record of 4 days at baseline	No
Wakai, 2014 (30)	JACC, Japan	General healthy	19.3	M/W	56.1	22.8	58 672	11 656	Population registries from involved municipalities	Validated (through 3-day weighed diet records) FFQ at baseline	No
Wang, 2016 (31)	NHS, USA	General Healthy	27.3	W	46.5	24.2	126 233	33 304	Linkage with vital records of states and of the	Validated (through dietary records)	Yes, every four years
	HPFS,			M	53.2	25.4					

	USA								National Death Index, reports from next of kin and postal authorities	FFQ at baseline and every 4 years	
Wu, 2020 (32)	CHNS, China	General healthy	14	M/W	40.8	22.1	14 305	1 006	Based on report of household members in each survey and denoted in CHNS database	3-day 24h dietary recalls at individual level in combination with weighing inventory at household level	Yes
Zeng, 2022 (33)	NHANES, USA	General healthy	7.1	M/W	46.0	28.7	35 692	3 854	Linkage with national death index	≥one 24-h recall conducted in person in the NHANES Mobile Examination Center or via telephone	Mixed (no: NHANES 1999 to 2002; yes: 2003 to 2014)
Zhao, 2023 (34)	NIH-AARP, USA	General healthy	23.5	M/W	61.2	26.7	371 159	165 698	Linkage with Social Security Administration Death Master File	Validated (through 24h recall), self-administered FFQ at baseline	No
Zhou, 2022 (35)	CHNS, China	General healthy	9	M/W	44.0	22.8	17 310	1 324	Based on report of household members in each survey and denoted in CHNS database	3-day 24h dietary recalls at individual level in combination with weighing inventory at household level	Yes
Zhuang, 2019a (36)	NIH-AARP, USA	General healthy	16	M/W	62.8	26.3	521 120	129 328	Linkage with Social Security Administration Death Master File	Validated (through 24h recall), self-administered FFQ at baseline	No
Zhuang, 2019b (37)	CHNS, China	General healthy	14	M/W	41.3	22.5	14 383	1 011	Based on report of household members in each	3-day 24h dietary recalls at individual level in	Yes

									survey and denoted in CHNS database	combination with weighing inventory at household level	
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AF animal fat; animal MUFA monounsaturated fatty acids of animal origin; A-oil animal oil; AP animal protein; BMI body mass index; CHAMP Concord Health Ageing in Men Project; CHNS Chinese Health and Nutrition Survey; CHO carbohydrates; CI confidence interval; d day; EPIC European Prospective Investigation into Cancer and Nutrition; FFQ food frequency questionnaire; g/d grams/day; HEALS Health Effects of Arsenic Longitudinal Study; HPFS Health Professionals Follow-Up Study; HR hazard ratio; HRT hormone replacement therapy; InCHIANTI Invecchiare in Chianti aging in the Chianti area; IWHS Iowa Women's Health Study; JACC Japan Collaborative Cohort; JPHC Japan Public Health Center-based Prospective Cohort; kcal kilocalories; KIHD Kuopio Ischaemic Heart Disease Risk Factor Study; KoGES Korean Genome and Epidemiology Study; M men; MMSE Mini-Mental State Examination; MUFA monounsaturated fatty acids; n-3 PUFA n-3 polyunsaturated fatty acids; n-6 PUFA n-6 polyunsaturated fatty acids; NCS Norwegian Counties Study; NHANES National Health and Nutrition Examination Survey; NHANES III National Health and Nutrition Examination Survey III; NHS Nurses Health Study; NIH-AARP National Institutes of Health - American Association of Retired Persons Diet and Health Study; NR not reported; PHFO partially hydrogenated fish oil; PHVO partially hydrogenated vegetable oil; plant MUFA monounsaturated fatty acids of plant origin; P-oil oil from plant origin; PP plant protein; PREDIMED PREvención con Dieta MEDiterránea; PRO protein; PUFA polyunsaturated fatty acids; PURE Prospective Urban Rural Epidemiology; rTFA ruminant trans-fatty acids; SD standard deviation; SFA saturated fatty acids; SUN Seguimiento Universidad de Navarra; T2D type 2 diabetes; TFA trans-fatty acids; UKB United Kingdom Biobank; ULSAM Uppsala Longitudinal Study of Adult Men; W women; WHI Women's Health Initiative; WHR waist-to-hip ratio; WHS The Women's Health Study;

Supplemental table 3: (Macro)nutrient replacement including unit, effect estimates with 95% CI (as reported by authors), and adjustment factors of the included studies for the outcome all-cause mortality

Author, year	Cohort, country	↓ Nutrient ^a	↑ Replacement ^a	Unit	Hazard ratio (95% CI)	Adjustment factors ^b
Argos, 2013 (2)	HEALS, Bangladesh	CHO	PRO	10.2%	1.00 (reference)	Age, sex, energy, BMI, smoking, formal education, years of education and cohort, height, water arsenic concentration
				12.1%	0.96 (0.79, 1.17)	
				26.0%	1.09 (0.88, 1.34)	
		FAT	PRO	10.2%	1.00 (reference)	
				12.1%	0.96 (0.79, 1.16)	
				26.0%	1.07 (0.85, 1.35)	
		CHO	FAT	4.8%	1.00 (reference)	
				8.6%	1.11 (0.92, 1.35)	
				23.4%	1.22 (0.98, 1.51)	
Bajracharya, 2023 (3)	EPIC-Heidelberg, Germany	AP	PP	3%	0.97 (0.90, 1.06)	Age, sex, energy, BMI, smoking, alcohol, fiber intake
		AP	SFA	3%	0.91 (0.86, 0.96)	
		AP	MUFA	3%	0.89 (0.82, 0.97)	
		AP	PUFA	3%	1.01 (0.94, 1.08)	
		AP	Mono-/Disaccharides	3%	0.93 (0.90, 0.97)	
		AP	Other CHO	3%	0.94 (0.91, 0.98)	
		PP	SFA	3%	0.93 (0.85, 1.01)	
		PP	MUFA	3%	0.91 (0.82, 1.02)	
		PP	PUFA	3%	1.03 (0.93, 1.14)	
		PP	Mono-/Disaccharides	3%	0.95 (0.88, 1.03)	
		PP	Other CHO	3%	0.96 (0.88, 1.05)	
		SFA	MUFA	3%	0.98 (0.88, 1.09)	
		SFA	PUFA	3%	1.10 (1.04, 1.17)	
		SFA	Mono-/Disaccharides	3%	1.02 (0.97, 1.07)	
		SFA	Other CHO	3%	1.03 (0.98, 1.09)	
MUFA	PUFA	3%	1.12 (1.01, 1.26)			

		MUFA	Mono- /Disaccharides	3%	1.04 (0.97, 1.11)	
		MUFA	Other CHO	3%	1.05 (0.98, 1.13)	
		PUFA	Mono- /Disaccharides	3%	0.92 (0.87, 0.98)	
		PUFA	Other CHO	3%	0.93 (0.88, 0.99)	
		Mono- /Disaccharides	Other CHO	3%	1.01 (0.99, 1.03)	
Budhathoki, 2019 (4)	JPHC, Japan	CHO	PRO	11.3%	1.00 (reference)	Age, sex, energy, BMI, smoking, alcohol, occupation status, intake of green tea, coffee, physical activity
				13.0%	0.95 (0.89, 1.01)	
				14.3%	0.93 (0.86, 1.00)	
				15.6%	0.92 (0.84, 0.99)	
				17.6%	0.99 (0.90, 1.09)	
		CHO	AP	4.3%	1.00 (reference)	
				6.1%	0.91 (0.85, 0.97)	
				7.5%	0.95 (0.88, 1.02)	
				8.9%	0.97 (0.89, 1.05)	
				11.2%	0.98 (0.88, 1.08)	
		CHO	PP	5.0%	1.00 (reference)	
				6.0%	0.89 (0.83, 0.95)	
				6.6%	0.88 (0.82, 0.95)	
				7.3%	0.84 (0.77, 0.92)	
8.4%	0.87 (0.78, 0.96)					
Chen, 2020 (5)	Rotterdam, Netherlands	CHO	PRO	5%	1.09 (1.02, 1.17)	Age, sex, energy, BMI, smoking, alcohol, education, fiber, overall diet quality score, physical activity, cohort (RS-I, -II, and -III)
		CHO	AP	5%	1.20 (1.05, 1.37)	
		CHO	PP	5%	1.09 (0.88, 1.35)	
		FAT	PRO	5%	1.08 (1.01, 1.15)	
		FAT	AP	5%	1.16 (1.02, 1.33)	
		FAT	PP	5%	1.04 (0.85, 1.27)	
Das, 2022 (6)	CHAMP, Australia	CHO	PRO	72 g/d	1.00 (reference)	Age, energy, BMI, smoking, alcohol, income, marital status, living arrangement, physical activity, number of comorbidities, self-rated health, MMSE, polypharmacy
				86 g/d	0.41 (0.19, 0.87)	
				100 g/d	0.41 (0.19, 0.90)	
				116 g/d	0.75 (0.37, 1.51)	
				133 g/d	0.69 (0.34, 1.39)	
		FAT	PRO	72 g/d	1.00 (reference)	Age, energy, BMI, smoking, alcohol, income, marital status, living arrangement, fiber, vitamin A, C, E, folate, sodium, potassium, calcium,
				86 g/d	0.42 (0.20, 0.88)	

				100 g/d	0.40 (0.18, 0.90)	magnesium, iron, zinc, MMSE, polypharmacy, self-rated health, number of comorbidities
				116 g/d	0.75 (0.36, 1.55)	
				133 g/d	0.70 (0.34, 1.45)	
Dehghan, 2017 (7)	PURE, Multiple Countries	CHO	SFA	5%	0.97 (0.90, 1.04)	Age, sex, energy, waist-to-hip ratio, smoking, education, physical activity, diabetes, urban or rural location, center was random effect and frailty models
		CHO	MUFA	5%	0.97 (0.88, 1.08)	
		CHO	PUFA	5%	0.89 (0.82, 0.97)	
		CHO	PRO	5%	0.96 (0.90, 1.02)	
Dominguez, 2018 (8)	SUN, Spain	MUFA	SFA	5%	1.41 (1.03, 1.93)	Age, sex, energy, BMI, smoking, university education, prescription of special diets at baseline, snacking between meals, physical activity, baseline hypercholesterolemia, baseline hypertension, history of depression, history of cardiovascular disease, history of cancer, history of diabetes, year of entering the cohort, hours per day spent watching television
		PUFA	SFA	5%	1.17 (0.87, 1.58)	
		CHO	SFA	5%	1.34 (1.02, 1.75)	
Fontana, 2021 (9)	EPIC-Italy, Italy	CHO	PRO	3%	0.98 (0.93, 1.04)	Age (stratified), sex (stratified), energy, BMI, WHR, smoking, alcohol, education, fiber, physical activity, center (stratified)
		CHO	AP	3%	0.96 (0.90, 1.02)	
		CHO	PP	3%	0.94 (0.79, 1.21)	
		AP	PP	3%	0.98 (0.83, 1.15)	
Fridén, 2023 (10)	ULSAM, Sweden	SFA	PUFA	100 kcal	1.27 (0.86, 1.88)	Age, energy, smoking, education, physical activity, family history of CVD, family history of type-2 diabetes, stress, sleep
		SFA	CHO	100 kcal	0.79 (0.65, 0.97)	
Guasch-Ferré, 2015 (11)	PREDIMED, Spain	CHO	TFA	0.05%	1.00 (reference)	Age, sex, energy, BMI, smoking, alcohol, education, fiber, dietary cholesterol, physical activity, baseline diabetes, hypertension, hypercholesterolemia, family history of coronary heart disease, antihypertensive medication, oral antidiabetic agents, lipid-lowering drugs, intervention group
				0.10%	1.11 (0.80, 1.54)	
				0.16%	0.86 (0.59, 1.24)	
				0.23%	1.13 (0.78, 1.64)	
				0.36%	1.29 (0.87, 1.90)	
		CHO	MUFA	5%	0.86 (0.76, 0.98)	
		CHO	PUFA	5%	0.56 (0.40, 0.79)	
		CHO	FAT	5%	0.87 (0.80, 0.95)	
		SFA	CHO	5%	1.04 (0.81, 1.33)	
		SFA	MUFA	5%	0.91 (0.65, 1.26)	
		SFA	PUFA	5%	0.61 (0.39, 0.97)	
TFA	MUFA	1%	0.99 (0.92, 1.06)			
TFA	PUFA	1%	0.92 (0.83, 1.00)			
Guasch-Ferré, 2019 (published and	NHS, USA	SFA	Plant MUFA	5%	0.86 (0.77, 0.95)	Age, energy, BMI, smoking, alcohol, fruits and vegetables, coffee intake, physical activity, baseline hypertension, baseline hypercholesterolemia, family history of myocardial infarction, family history of diabetes mellitus,
		Refined CHO	Plant MUFA	5%	0.86 (0.80, 0.92)	
		TFA	Plant MUFA	2%	0.89 (0.83, 0.97)	
		Animal MUFA	Plant MUFA	5%	0.77 (0.70, 0.84)	

unpublished data) (12)						family history of cancer, menopausal status, postmenopausal hormone use, current aspirin use, multivitamin use, ethnicity
	HPFS, USA	SFA	Plant MUFA	5%	0.81 (0.70, 0.95)	Age, energy, BMI, smoking, alcohol, fruits and vegetables, coffee intake, physical activity, baseline hypertension, baseline hypercholesterolemia, family history of myocardial infarction, family history of diabetes mellitus, family history of cancer, current aspirin use, multivitamin use, ethnicity
		Refined CHO	Plant MUFA	5%	0.88 (0.80, 0.96)	
		TFA	Plant MUFA	2%	0.93 (0.84, 1.04)	
		Animal MUFA	Plant MUFA	5%	0.77 (0.69, 0.86)	
Hernández-Alonso, 2016 (13)	PREDIMED, Spain	CHO	PRO	13.9%	1.22 (0.84, 1.77)	Age, sex, energy, BMI, smoking, alcohol, fiber, GI, physical activity, prevalence of diabetes, hypertension, hypercholesterolemia, family history of coronary heart disease, use of aspirin, antihypertensive medication, oral antidiabetic medication, insulin medication and hypocholesterolemic medication, intervention group, node
				15.4%	0.88 (0.60, 1.28)	
				16.5%	1.00 (reference)	
				17.6%	0.93 (0.63, 1.39)	
				19.5%	1.59 (1.08, 2.35)	
		FAT	PRO	13.9%	1.17 (0.80, 1.70)	
				15.4%	0.86 (0.59, 1.25)	
				16.5%	1.00 (reference)	
				17.6%	0.95 (0.64, 1.42)	
				19.5%	1.66 (1.13, 2.43)	
		CHO	AP	8.3%	1.27 (0.87, 1.84)	
				9.8%	0.88 (0.60, 1.29)	
				11.0%	1.00 (reference)	
				12.1%	1.10 (0.74, 1.63)	
				13.9%	1.86 (1.27, 2.73)	
		FAT	AP	8.3%	1.24 (0.86, 1.81)	
				9.8%	0.88 (0.60, 1.29)	
				11.0%	1.00 (reference)	
				12.1%	1.12 (0.76, 1.65)	
				13.9%	1.92 (1.31, 2.82)	
		CHO	PP	4.5%	1.04 (0.72, 1.52)	
				5.1%	0.86 (0.59, 1.25)	
				5.5%	1.00 (reference)	
				5.9%	1.01 (0.70, 1.48)	
				6.6%	1.28 (0.84, 1.94)	
		FAT	PP	4.5%	1.02 (0.70, 1.49)	
				5.1%	0.85 (0.58, 1.24)	
				5.5%	1.00 (reference)	
				5.9%	1.01 (0.70, 1.48)	
				6.6%	1.32 (0.88, 2.00)	

Ho, 2020 (published and unpublished data) (14)	UKB, United Kingdom	CHO	FAT	5%	0.95 (0.94, 0.97)	Age, sex, energy, BMI, smoking, alcohol, fiber, physical activity, systolic blood pressure, baseline diabetes, mental health disorders, deprivation index, ethnicity, height
		CHO	PRO	5%	0.92 (0.90, 0.95)	
		FAT	PRO	5%	0.97 (0.94, 1.00)	
		CHO	SFA	5%	0.97 (0.92, 1.02)	
		CHO	MUFA	5%	0.96 (0.91, 1.02)	
		CHO	PUFA	5%	0.90 (0.83, 0.97)	
		CHO	TFA	5%	0.97 (0.56, 1.65)	
		SFA	MUFA	5%	0.99 (0.90, 1.08)	
		SFA	PUFA	5%	0.93 (0.86, 1.00)	
		SFA	TFA	5%	0.99 (0.56, 1.77)	
		SFA	PRO	5%	0.95 (0.90, 1.00)	
		MUFA	PUFA	5%	0.94 (0.83, 1.06)	
		MUFA	TFA	5%	1.01 (0.59, 1.71)	
		MUFA	PRO	5%	0.96 (0.90, 1.03)	
		PUFA	TFA	5%	1.07 (0.62, 1.86)	
		PUFA	PRO	5%	1.03 (0.95, 1.11)	
		TFA	PRO	5%	0.96 (0.55, 1.66)	
		CHO	AP	5%	0.93 (0.90, 0.95)	
		CHO	PP	5%	0.91 (0.82, 1.01)	
		SFA	AP	5%	0.95 (0.91, 1.01)	
		SFA	PP	5%	0.94 (0.84, 1.04)	
		MUFA	AP	5%	0.96 (0.90, 1.03)	
		MUFA	PP	5%	0.95 (0.84, 1.06)	
		PUFA	AP	5%	1.02 (0.94, 1.11)	
		PUFA	PP	5%	1.00 (0.87, 1.15)	
		TFA	AP	5%	0.95 (0.55, 1.65)	
		TFA	PP	5%	0.93 (0.53, 1.64)	
		AP	PP	5%	0.98 (0.89, 1.08)	
		CHO	AF	5%	0.96 (0.94, 0.98)	
		CHO	PF	5%	0.95 (0.93, 0.97)	
		AF	PF	5%	0.99 (0.97, 1.01)	
		AF	PRO	5%	0.96 (0.92, 0.99)	
PF	PRO	5%	0.97 (0.94, 1.00)			
CHO	n-3 PUFA	5%	0.77 (0.58, 1.02)			
CHO	n-6 PUFA	5%	0.92 (0.85, 1.01)			
SFA	n-3 PUFA	5%	0.79 (0.60, 1.06)			

		SFA	n-6 PUFA	5%	0.95 (0.87, 1.03)	
		MUFA	n-3 PUFA	5%	0.81 (0.60, 1.08)	
		MUFA	n-6 PUFA	5%	0.96 (0.84, 1.10)	
		n-3 PUFA	n-6 PUFA	5%	1.19 (0.87, 1.63)	
		n-3 PUFA	TFA	5%	1.21 (0.67, 2.20)	
		n-3 PUFA	PRO	5%	1.20 (0.90, 1.60)	
		n-6 PUFA	TFA	5%	1.02 (0.58, 1.78)	
		n-6 PUFA	PRO	5%	1.01 (0.92, 1.10)	
		Sugar	Starch	5%	0.97 (0.95, 0.98)	
		Sugar	SFA	5%	0.95 (0.90, 1.00)	
		Sugar	MUFA	5%	0.95 (0.90, 1.01)	
		Sugar	PUFA	5%	0.89 (0.83, 0.96)	
		Sugar	TFA	5%	1.02 (0.59, 1.74)	
		Sugar	PRO	5%	0.91 (0.89, 0.94)	
		Starch	SFA	5%	0.98 (0.93, 1.03)	
		Starch	MUFA	5%	0.99 (0.93, 1.05)	
		Starch	PUFA	5%	0.92 (0.86, 1.00)	
		Starch	TFA	5%	1.05 (0.61, 1.81)	
		Starch	PRO	5%	0.95 (0.92, 0.98)	
Huang, 2020 (15) (men) ^c	NIH-AARP, USA	AP	PP	3%	0.90 (0.88, 0.93)	Age, energy, BMI, smoking, alcohol, education, fiber, vegetables, fruits, physical activity, diabetes, race or ethnic group, marital status, health status, vitamin supplement use
		CHO	PP	1-SD	0.95 (0.94, 0.97)	Additionally adjusted for median household income
		CHO	AP	1-SD	0.99 (0.98, 1.00)	Additionally adjusted for median household income
Huang, 2020 (15) (women) ^c		AP	PP	3%	0.90 (0.87, 0.93)	Age, energy, BMI, smoking, alcohol, education, fiber, vegetables, fruits, physical activity, diabetes, race or ethnic group, marital status, health status, vitamin supplement use, HRT
		CHO	PP	1-SD	0.95 (0.93, 0.97)	Additionally adjusted for median household income
		CHO	AP	1-SD	0.98 (0.97, 1.00)	Additionally adjusted for median household income
Kelemen, 2005 (16) ^d	IWHS, USA	CHO	PRO	14.1%	1.00 (reference)	Age, energy, BMI, smoking, alcohol, education, fiber, dietary cholesterol, dietary methionine, physical activity, history of hypertension, postmenopausal hormone use, multivitamin use, vitamin E supplement use, family history of cancer
				16.3%	0.95 (0.68, 1.32)	
				17.8%	0.81 (0.58, 1.13)	
				19.4%	0.84 (0.60, 1.17)	
				22.0%	0.99 (0.71, 1.38)	
		CHO	AP	8.9%	1.00 (reference)	
				11.3%	0.93 (0.67, 1.28)	

				12.9%	0.83 (0.60, 1.14)	
				14.7%	0.79 (0.57, 1.09)	
				17.5%	0.82 (0.59, 1.13)	
		CHO	PP	3.7%	1.00 (reference)	
				4.3%	0.90 (0.78, 1.04)	
				4.8%	0.95 (0.82, 1.10)	
				5.3%	0.93 (0.80, 1.08)	
				6.1%	0.95 (0.82, 1.10)	
		AP	PP	3.7%	1.00 (reference)	
				4.3%	0.93 (0.81, 1.07)	
				4.8%	0.98 (0.85, 1.13)	
				5.3%	0.98 (0.85, 1.13)	
				6.1%	0.99 (0.86, 1.14)	
Kwon, 2021 (17)	KoGES, Korea	CHO	FAT	7.4%	1.00 (reference)	
				10.2%	0.91 (0.81, 0.99)	
				12.9%	0.84 (0.75, 0.94)	
				16.0%	0.85 (0.74, 0.97)	
				19.5%	0.89 (0.74, 1.05)	
Laake, 2012 (18) (men and women) ^e	NCS, Norway	CHO	TFA from PHVO	0.08%	1.00 (reference)	Age, sex, energy, BMI, smoking, education, cholesterol, systolic blood pressure
				0.40%	1.01 (0.96, 1.07)	
				0.90%	1.04 (0.98, 1.11)	
				1.40%	0.95 (0.89, 1.02)	
				1.90%	0.96 (0.88, 1.05)	
		CHO	TFA from PHFO	0.60%	1.00 (reference)	
				1.10%	1.01 (0.95, 1.06)	
				1.60%	0.99 (0.93, 1.06)	
				2.10%	0.94 (0.87, 1.02)	
				2.60%	1.03 (0.94, 1.14)	
Laake, 2012 (18) (men) ^e		CHO	rTFA	0.32%	1.00 (reference)	Age, energy, BMI, smoking, education, cholesterol, systolic blood pressure
				0.47%	1.00 (0.93, 1.07)	
				0.62%	1.03 (0.94, 1.13)	
				0.77%	1.03 (0.91, 1.16)	
				0.92%	0.98 (0.83, 1.16)	
Laake, 2012 (18) (women) ^e		CHO	rTFA	0.32%	1.00 (reference)	Age, energy, BMI, smoking, education, cholesterol, systolic blood pressure
				0.47%	0.95 (0.87, 1.03)	
				0.62%	1.02 (0.92, 1.13)	

				0.77%	0.99 (0.86, 1.13)	
				0.92%	1.10 (0.93, 1.31)	
Laguna, 2021 (19)	PREDIMED, Spain	Liquid sugars	SFA	5%	1.00 (0.67, 1.49)	Age, sex, energy, BMI, smoking, alcohol, salt intake, red meat, processed meat, adherence to Mediterranean diet score, physical activity, history of diabetes, history of hypertension, history of dyslipidemia, recruitment center (stratified), aspirin intake, vitamin supplementation, family history of cancer, intervention group, and additionally adjusted for robust variance estimators to account for small deviations from individual randomization.
		Liquid sugars	TFA	1%	1.23 (0.54, 2.79)	
		Liquid sugars	MUFA	5%	0.73 (0.54, 1.00)	
		Liquid sugars	PUFA	5%	0.66 (0.46, 0.94)	
		Liquid sugars	Total solid sugars	5%	0.77 (0.57, 1.04)	
		Liquid sugars	Complex CHO	5%	0.83 (0.63, 1.10)	
Levine, 2014 (20) (aged: 50-65y) ^f	NHANES III, USA	CHO	PRO	1%	0.99 (0.98, 1.01)	Age, sex, energy, waist circumference, smoking, education, chronic conditions (diabetes, cancer, myocardial infarction), trying to lose weight in the last year, diet changed in the last year, reported intake representative of typical diet, race/ethnicity
		FAT	PRO	1%	1.00 (0.99, 1.01)	
Levine, 2014 (20) (aged: >66y) ^f		CHO	PRO	1%	1.00 (0.99, 1.01)	Age, sex, energy, waist circumference, smoking, education, chronic conditions (diabetes, cancer, myocardial infarction), trying to lose weight in the last year, diet changed in the last year, reported intake representative of typical diet, race/ethnicity
		FAT	PRO	1%	1.00 (0.99, 1.00)	
Li, 2022 (21)	NHANES, USA	Low-quality CHO	High-quality CHO	5%	0.85 (0.73, 0.99)	Age, sex, energy, BMI, smoking, alcohol, education, physical activity, cholesterol intake, self-reported hypertension, hypercholesterolemia, cardiovascular disease, cancer, race/ethnicity, marital status, family income : poverty ratio
		Low-quality CHO	PP	3%	0.70 (0.46, 1.07)	
		Low-quality CHO	AP	3%	0.81 (0.61, 1.07)	
		Low-quality CHO	UFA	3%	0.86 (0.77, 0.97)	
		Low-quality CHO	SFA	3%	1.12 (0.92, 1.36)	
		SFA	High-quality CHO	5%	0.71 (0.51, 0.99)	
		SFA	Low-quality CHO	5%	0.83 (0.60, 1.15)	
		SFA	PP	3%	0.63 (0.40, 0.98)	
		SFA	AP	3%	0.72 (0.50, 1.04)	
		Mao, 2020 (22)	CHNS, China	SFA	MUFA	
SFA	Plant MUFA			5%	0.85 (0.75, 0.95)	
SFA	Animal MUFA			5%	1.11 (0.99, 1.26)	
CHO	MUFA			7.8%	1.00 (reference)	
				11.1%	0.89 (0.71, 1.13)	
				14.6%	0.94 (0.70, 1.24)	

				18.4%	0.79 (0.57, 1.09)	
		CHO	Plant MUFA	3.4%	1.00 (reference)	
				5.1%	0.67 (0.55, 0.81)	
				7.1%	0.71 (0.58, 0.86)	
				9.4%	0.72 (0.58, 0.89)	
		CHO	Animal MUFA	2.1%	1.00 (reference)	
				4.8%	0.96 (0.77, 1.21)	
				7.5%	1.12 (0.84, 1.49)	
				10.3%	1.38 (0.97, 1.95)	
Merono, 2022 (23)	InCHIANTI, Italy	CHO	PRO	13.3%	1.00 (reference)	
				14.7%	0.92 (0.74, 1.14)	
				15.7%	0.95 (0.77, 1.18)	
				16.9%	0.88 (0.70, 1.10)	
				18.7%	0.79 (0.62, 1.00)	
		CHO	AP	7.2%	1.00 (reference)	
				8.8%	0.91 (0.74, 1.13)	
				9.9%	0.86 (0.67, 1.09)	
				11.2%	0.76 (0.59, 0.97)	
				13.3%	0.77 (0.59, 1.01)	
		CHO	PP	4.4%	1.00 (reference)	
				5.3%	1.05 (0.83, 1.33)	
				5.7%	1.04 (0.82, 1.32)	
				6.3%	0.98 (0.76, 1.27)	
7.1%	0.99 (0.74, 1.34)					
Nagata, 2012 (24) (men) ^c	Takahama, Japan	CHO	FAT	16.3%	1.00 (reference)	
				20.1%	0.88 (0.77, 1.00)	
				22.7%	0.92 (0.80, 1.05)	
				25.5%	0.85 (0.73, 0.99)	
				29.6%	0.83 (0.70, 0.99)	
		CHO	SFA	4.2%	1.00 (reference)	
				5.4%	0.95 (0.83, 1.08)	
				6.2%	0.93 (0.80, 1.07)	
				7.1%	0.99 (0.85, 1.16)	
				8.7%	0.89 (0.74, 1.08)	
		CHO	MUFA	5.3%	1.00 (reference)	

				6.7%	0.97 (0.85, 1.11)	Age, energy, BMI, smoking, alcohol, education, fruit, vegetables, dietary fiber, physical activity, histories of diabetes and hypertension, marital status, height
				7.7%	0.94 (0.80, 1.09)	
				8.8%	0.87 (0.72, 1.05)	
				10.4%	1.02 (0.81, 1.28)	
		CHO	PUFA	4.2%	1.00 (reference)	
				5.1%	0.84 (0.73, 0.97)	
				5.8%	0.82 (0.71, 0.96)	
				6.6%	0.85 (0.72, 1.01)	
				7.7%	0.77 (0.62, 0.95)	
		CHO	Long-chain n-3 PUFA	0.15%	1.00 (reference)	
				0.22%	1.00 (0.88, 1.14)	
				0.28%	0.97 (0.84, 1.11)	
				0.37%	0.95 (0.82, 1.11)	
				0.56%	1.02 (0.85, 1.22)	
		CHO	FAT	16.9%	1.00 (reference)	
				21.0%	1.02 (0.89, 1.16)	
				23.7%	1.05 (0.91, 1.21)	
				26.2%	1.10 (0.94, 1.30)	
				29.6%	1.10 (0.91, 1.34)	
		CHO	SFA	4.4%	1.00 (reference)	
5.7%	0.95 (0.83, 1.10)					
6.6%	1.04 (0.89, 1.21)					
7.4%	1.09 (0.93, 1.29)					
8.8%	1.22 (0.99, 1.49)					
CHO	MUFA	5.4%	1.00 (reference)			
		6.9%	0.92 (0.80, 1.06)			
		7.9%	1.02 (0.87, 1.21)			
		8.9%	0.95 (0.77, 1.16)			
		10.4%	1.00 (0.78, 1.29)			
CHO	PUFA	4.4%	1.00 (reference)			
		5.4%	0.92 (0.80, 1.06)			
		6.0%	0.99 (0.84, 1.17)			
		6.7%	0.98 (0.81, 1.18)			
		7.8%	0.96 (0.76, 1.20)			
CHO	Long-chain n-3 PUFA	0.13%	1.00 (reference)			
		0.20%	1.02 (0.89, 1.17)			

				0.25%	1.02 (0.88, 1.17)	
				0.32%	0.91 (0.78, 1.07)	
				0.47%	0.98 (0.82, 1.18)	
Ricci, 2018 (25)	NHANES, USA	SFA	MUFA	10%	0.97 (0.93, 1.00)	Age, sex, energy, BMI, smoking, alcohol, education, fiber, sedentariness (subjects who declared having more than 8 h/d of sedentary activity or who do not declared moderate or vigorous physical activity), blood pressure (systolic and diastolic blood pressure as continuous data), ethnicity
		SFA	PUFA	10%	0.92 (0.90, 0.95)	
		MUFA	PUFA	10%	0.96 (0.92, 1.00)	
Shan, 2020 (26)	NHANES, USA	AP	PP	5%	0.49 (0.32, 0.74)	NR
Song, 2016 (27)	NHS, USA	CHO	AP	10%	1.02 (0.98, 1.07)	Age, sex, energy, BMI, smoking, alcohol, glycemic index, whole grains, fiber, fruits, and vegetables, physical activity, history of hypertension diagnosis, multivitamin use, calendar time
		CHO	PP	3%	0.96 (0.91, 1.02)	
	HPFS, USA	CHO	AP	10%	1.00 (0.94, 1.06)	
		CHO	PP	3%	0.81 (0.75, 0.87)	
Sun, 2021 (28)	WHI, USA	CHO	AP	5%	0.99 (0.97, 1.01)	Age, energy, BMI, smoking, alcohol, education, income, fiber, glycemic load, physical activity, baseline diabetes mellitus status, baseline high blood cholesterol status, family history of heart attack/stroke, race/ethnicity, Observational Study/Clinical Trials, unopposed estrogen use, estrogen + progesterone use
		CHO	PP	5%	0.86 (0.80, 0.93)	
		AP	PP	5%	0.86 (0.81, 0.91)	
Virtanen, 2019 (29)	KIHD, Finland	CHO	PRO	5 g/d	1.03 (1.01, 1.05)	Age, energy, BMI, smoking, alcohol, education, income, fiber, physical activity, diagnosis of type 2 diabetes, cardiovascular disease, cancer, hypertension or use of cardiac, hypercholesterolemia, hypertension, or diabetes medications, examination year, marital status
		CHO	AP	5 g/d	1.03 (1.01, 1.05)	
		CHO	PP	5 g/d	1.03 (0.93, 1.13)	
Wakai, 2014 (30) (men) ^c	JACC, Japan	CHO	FAT	10.8%	1.00 (reference)	Age, energy, BMI, smoking, alcohol, education, vegetable intake, fruit intake, daily walking habits, geographic area, sleep duration
				13.9%	1.01 (0.92, 1.11)	
				16.3%	0.99 (0.89, 1.09)	
				18.8%	0.94 (0.84, 1.06)	
				23.3%	1.02 (0.89, 1.17)	
		PRO	FAT	10.8%	1.00 (reference)	
				13.9%	1.02 (0.93, 1.11)	
				16.3%	0.99 (0.91, 1.09)	
				18.8%	0.95 (0.86, 1.05)	
				23.3%	1.02 (0.90, 1.16)	
Wakai, 2014 (30) (women) ^c		CHO	FAT	13.7%	1.00 (reference)	Age, energy, BMI, smoking, alcohol, education, vegetable intake, fruit intake, daily walking habits, geographic area, sleep duration
				17.6%	1.04 (0.95, 1.14)	
				20.1%	1.03 (0.92, 1.14)	
				22.6%	0.91 (0.81, 1.02)	

				26.8%	0.98 (0.86, 1.12)	
		PRO	FAT	13.7%	1.00 (reference)	
				17.6%	1.02 (0.93, 1.13)	
				20.1%	1.00 (0.89, 1.13)	
				22.6%	0.88 (0.76, 1.02)	
				26.8%	0.94 (0.78, 1.14)	
Wang, 2016 (31)	NHS/HPFS USA	SFA	MUFA	5%	0.87 (0.82, 0.93)	Age, energy, BMI, smoking, alcohol, dietary cholesterol, physical activity, history of hypertension, history of hypercholesterolemia, white race, marital status, multivitamin use (yes vs no), vitamin E supplement use, current aspirin use, family history of myocardial infarction, family history of diabetes, family history of cancer, menopausal status and hormone use in women
		SFA	PUFA	5%	0.73 (0.70, 0.77)	
		SFA	TFA	2%	1.16 (1.09, 1.24)	
		SFA	n-6 PUFA	2%	0.93 (0.91, 0.96)	
		SFA	n-3 PUFA	0.3%	0.95 (0.93, 0.96)	
	NHS, USA	CHO	FAT	5%	0.94 (0.93, 0.96)	
		CHO	SFA	5%	1.08 (1.04, 1.12)	
		CHO	PUFA	5%	0.74 (0.69, 0.79)	
		CHO	MUFA	5%	0.88 (0.84, 0.92)	
		CHO	TFA	2%	1.08 (1.00, 1.17)	
		CHO	n-6 PUFA	2%	0.92 (0.89, 0.95)	
	HPFS, USA	CHO	n-3 PUFA	0.3%	0.96 (0.93, 1.00)	
		CHO	FAT	5%	0.97 (0.95, 0.99)	
		CHO	SFA	5%	1.07 (1.01, 1.14)	
CHO		PUFA	5%	0.71 (0.65, 0.79)		
CHO		MUFA	5%	0.95 (0.89, 1.02)		
CHO		TFA	2%	1.34 (1.20, 1.50)		
Wu, 2020 (32)	CHNS, China	CHO	n-6 PUFA	2%	0.88 (0.84, 0.92)	
		CHO	n-3 PUFA	0.3%	0.97 (0.94, 1.01)	
		A-oil	P-oil	8 g/2000 kcal	0.96 (0.92, 1.00)	
Zeng, 2022 (33)	NHANES, USA	CHO	FAT	5%	1.00 (0.97, 1.02)	Age, sex, energy, BMI, smoking, alcohol, education, family income to poverty ratio, physical activity, diabetes, race/ethnicity, marital status
		CHO	PF	5%	0.97 (0.93, 1.00)	
		CHO	AF	5%	0.99 (0.96, 1.03)	
		CHO	SFA	5%	1.04 (0.98, 1.11)	
		CHO	MUFA	5%	0.99 (0.92, 1.06)	
		CHO	PUFA	5%	0.92 (0.87, 0.96)	
		CHO	PRO	5%	0.97 (0.94, 1.00)	
		CHO	PP	5%	0.93 (0.90, 0.97)	

		CHO	AP	5%	0.97 (0.94, 1.01)	
Zhao, 2023 (34)	NIH-AARP, USA	Low-quality CHO	High-quality CHO	3%	0.992 (0.989, 0.994)	Age, sex, energy, BMI, smoking, alcohol, education, physical activity, race/ethnicity, marital status
		Low-quality CHO	UFA	3%	0.988 (0.984, 0.992)	
		Low-quality CHO	SFA	3%	1.036 (1.029, 1.043)	
		Low-quality CHO	AP	3%	0.989 (0.984, 0.994)	
		Low-quality CHO	PP	3%	0.901 (0.889, 0.913)	
		SFA	Low-quality CHO	3%	0.967 (0.964, 0.970)	
		SFA	High-quality CHO	3%	0.965 (0.962, 0.968)	
		SFA	AP	3%	0.965 (0.960, 0.970)	
		SFA	PP	3%	0.897 (0.886, 0.909)	
Zhou, 2022 (35)	CHNS, China	CHO	PRO	10.1%	1.32 (1.10, 1.59)	Age, sex, energy, BMI, smoking, alcohol, SBP, education levels, urban or rural residents, regions, occupations, physical activity, insoluble fiber intake, sodium intake, potassium intake
				11.1%	1.00 (reference)	
				12.1%	1.19 (0.98, 1.44)	
				13.3%	1.19 (0.97, 1.47)	
				14.7%	1.37 (1.07, 1.77)	
Zhuang, 2019a (36)	NIH-AARP	SFA	TFA	2%	1.03 (1.01, 1.05)	Age, sex, energy, BMI, smoking, alcohol, education, marital status, household income, physical activity, aspirin use, history of hypertension, history of hypercholesterolemia, perceived health condition, history of heart disease, stroke, diabetes, cancer at baseline, hormones use for women, multi-vitamin use, race
		SFA	MUFA	5%	0.84 (0.80, 0.87)	
		SFA	Animal MUFA	5%	0.92 (0.87, 0.98)	
		SFA	Plant MUFA	5%	0.85 (0.82, 0.89)	
		SFA	PUFA	5%	0.82 (0.81, 0.84)	
		SFA	n-3 PUFA	0.3%	0.99 (0.96, 1.01)	
		SFA	n-6 PUFA	2%	0.92 (0.91, 0.93)	
		CHO	SFA	1-SD	1.09 (1.08, 1.10)	
		CHO	TFA	1-SD	1.01 (1.00, 1.02)	
		CHO	MUFA	1-SD	1.00 (0.99, 1.02)	
		CHO	Animal MUFA	1-SD	1.05 (1.04, 1.07)	

		CHO	Plant MUFA	1-SD	0.98 (0.97, 0.99)		
		CHO	PUFA	1-SD	0.98 (0.97, 0.98)		
		CHO	n-3 PUFA	1-SD	1.00 (0.99, 1.01)		
		CHO	n-6 PUFA	1-SD	0.97 (0.96, 0.98)		
Zhuang, 2019b (37) (men) ^c	CHNS, China	CHO	SFA	2.6%	1.00 (reference)	Age, energy, BMI, smoking, alcohol, education, income, physical activity, baseline hypertension, baseline diabetes, marital status, residence, location	
				5.1%	0.91 (0.70, 1.17)		
				7.3%	0.93 (0.68, 1.28)		
				10.9%	0.95 (0.62, 1.47)		
		PUFA	SFA	1%	1.03 (0.94, 1.13)		
		MUFA	SFA	1%	1.30 (1.14, 1.48)		
Zhuang, 2019b (37) (women) ^c		CHO	SFA	2.5%	1.00 (reference)		Age, energy, BMI, smoking, alcohol, education, income, physical activity, baseline hypertension, baseline diabetes, marital status, residence, location
				4.9%	1.14 (0.86, 1.52)		
				7.1%	1.20 (0.84, 1.70)		
				10.8%	1.65 (1.03, 2.62)		
		PUFA	SFA	1%	0.95 (0.86, 1.04)		
		MUFA	SFA	1%	1.07 (0.91, 1.27)		

AF animal fat; animal MUFA monounsaturated fatty acids of animal origin; A-oil animal oil; AP animal protein; BMI body mass index; CHAMP Concord Health Ageing in Men Project; CHNS Chinese Health and Nutrition Survey; CHO carbohydrates; CI confidence interval; d day; EPIC European Prospective Investigation into Cancer and Nutrition; FFQ food frequency questionnaire; g/d grams/day; HEALS Health Effects of Arsenic Longitudinal Study; HPFS Health Professionals Follow-Up Study; HR hazard ratio; HRT hormone replacement therapy; InCHIANTI Invecchiare in Chianti aging in the Chianti area; IWHS Iowa Women's Health Study; JACC Japan Collaborative Cohort; JPHC Japan Public Health Center-based Prospective Cohort; kcal kilocalories; KIHD Kuopio Ischaemic Heart Disease Risk Factor Study; KoGES Korean Genome and Epidemiology Study; M men; MMSE Mini-Mental State Examination; MUFA monounsaturated fatty acids; n-3 PUFA n-3 polyunsaturated fatty acids; n-6 PUFA n-6 polyunsaturated fatty acids; NCS Norwegian Counties Study; NHANES National Health and Nutrition Examination Survey; NHANES III National Health and Nutrition Examination Survey III; NHS Nurses Health Study; NIH-AARP National Institutes of Health - American Association of Retired Persons Diet and Health Study; NR not reported; PHFO partially hydrogenated fish oil; PHVO partially hydrogenated vegetable oil; plant MUFA monounsaturated fatty acids of plant origin; P-oil oil from plant origin; PP plant protein; PREDIMED PREvención con Dieta MEDiterránea; PRO protein; PUFA polyunsaturated fatty acid; PURE Prospective Urban Rural Epidemiology; rTFA ruminant trans- fatty acids; SD standard deviation; SFA saturated fatty acid; SUN Seguimiento Universidad de Navarra; T2D type 2 diabetes; TFA trans- fatty acids; UFA unsaturated fatty acids; UKB United Kingdom Biobank; ULSAM Uppsala Longitudinal Study of Adult Men; W women; WHI Women's Health Initiative; WHR waist-to-hip ratio;

^a Mono-/Disaccharides, refined CHO, sugar, liquid sugars, low-quality CHO were used to form the node "low-quality CHO / Mono-/ Disaccharides" for the carbohydrate-origin subnetwork; other CHO, complex CHO, starch, high-quality CHO were used to form the node "high-quality CHO / Polysaccharides" for the carbohydrate-origin subnetwork

^b The adjustments for remaining macronutrients according to a substitution model were reported for every analysis (eg, for a substitution of CHO for PRO: fat was adjusted; for a substitution of MUFA for CHO: PRO, SFA, PUFA (and TFA) were adjusted, for a substitution of AP for CHO: PP and fat were adjusted, etc)

^c The estimates for men and women were pooled

^d The estimates are risk ratios; Only the confidence interval for the highest quintile was specified in the study; the confidence intervals for the 2nd – 4th quintile were transferred on this basis.

^e The estimates TFA from PHFO, TFA from PHVO, rTFA (men) and rTFA (women) were pooled

^f The estimates for different age categories were pooled

Supplemental table 4: Reasons for exclusion of specific comparisons from the network meta-analysis

Author, year	Cohort, country	↓ Nutrient ^a	↑ Replacement ^a	Unit ^b	Hazard ratio (95% CI)	Reason for exclusion
Chen, 2020 (5)	Rotterdam, Netherlands	FAT	AP	5%	1.16 (1.02, 1.33)	No matching network, the protein-origin subnetwork was analyzed using fatty acids as comparison and not total fat
		FAT	PP	5%	1.04 (0.85, 1.27)	No matching network, the protein-origin subnetwork was analyzed using fatty acids as comparison and not total fat
Guasch Ferre, 2015 (11)	PREDIMED, Spain	CHO	TFA	5%	45 (0.16, 12995.85)	Very high inconsistency of the effect estimate
Hernandez-Alonso, 2016 (13)	PREDIMED, Spain	FAT	AP	5%	1.42 (1.05, 1.91)	No matching network, the protein-origin subnetwork was analyzed using fatty acids as comparison and not total fat
		FAT	PP	5%	1.72 (0.74, 3.99)	No matching network, the protein-origin subnetwork was analyzed using fatty acids as comparison and not total fat
Laguna, 2021 (19)	PREDIMED, Spain	Liquid sugars	Total solid sugar	5%	0.77 (0.57, 1.04)	No matching network, no suitable node for the carbohydrate-origin subnetwork
Li, 2022 (21)	NHANES, USA	Low-quality CHO	UFA	5%	0.78 (0.65, 0.95)	No matching network, the carbohydrate-origin subnetwork was analyzed using PUFA and MUFA as opposed to UFA
		SFA	Low-quality CHO	5%	0.83 (0.60, 1.15)	Comparison was reported twice, overlap ^c

Zhao, 2023 (34)	NIH-AARP, USA	Low-quality CHO	High quality CHO	5%	0.99 (0.98, 0.99)	Very high inconsistency of the effect estimate
		Low-quality CHO	UFA	5%	0.98 (0.97, 0.99)	No matching network, the carbohydrate-origin subnetwork was analyzed using PUFA and MUFA as opposed to UFA
		Low-quality CHO	SFA	5%	1.06 (1.05, 1.07)	Comparison was reported twice in this study, overlap ^c
Zhuang 2019b (37)	CHNS, China	MUFA	SFA	5%	2.56 (1.53, 4.26)	Overlap ^c with study by Mao et al. (22)

AP animal protein; CHNS Chinese Health and Nutrition Survey; CHO carbohydrates; CI confidence interval; HR hazard ratio; MUFA monounsaturated fatty acids; NHANES National Health and Nutrition Examination Survey; NIH-AARP National Institutes of Health - American Association of Retired Persons Diet and Health Study; PP plant protein; PREDIMED PREvención con Dieta MEDiterránea; PUFA polyunsaturated fatty acid; SFA saturated fatty acid; TFA trans- fatty acids; UFA unsaturated fatty acids;

^a Mono-/Disaccharides, refined CHO, sugar, liquid sugars, low-quality CHO were used to form the node “low-quality CHO / Mono-/ Disaccharides” for the carbohydrate-origin subnetwork; other CHO, complex CHO, starch, high-quality CHO were used to form the node “high-quality CHO / Polysaccharides” for the carbohydrate-origin subnetwork

^b This evaluation was conducted after harmonizing all substitutions to a 5% energy level, according to Greenland and Longnecker method (38) (if estimates were presented per quantiles/unit of intake/exchange), or extrapolation (eg, from 1% to 5%)

^c If there was an overlap, we chose the most conservative estimate

Supplemental table 5: League table for the overall macronutrient network (5% isocaloric energy substitution) for the outcome all-cause mortality

FAT	0.97 [0.95, 1.00]	0.99 [0.96, 1.02]
0.97 [0.96, 1.00]	CHO	1.01 [0.99, 1.03]
0.98 [0.96, 1.01]	1.01 [0.99, 1.03]	PRO

CHO carbohydrates; FAT fat; HR hazard ratio; PRO protein

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ FAT (increase) vs. ↓ CHO (decrease) are displayed in the first row second column (HR: 0.97, 95% CI: 0.95, 0.99) and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.03.

Supplemental table 6: GRADE assessment of all-cause mortality for the overall macronutrient network (5% isocaloric energy substitution);

Number of participants (n= 1 572 571) and number of mortality events (n= 239 450)

		Direct evidence			Indirect evidence		Network Meta-Analysis	
Comparison	N studies	Proportion direct evidence	HR (95% CI)	Certainty of evidence	HR (95% CI)	Certainty of evidence	HR (95% CI)	Certainty of evidence
↑ FAT								
↓ CHO	14	93	0.97 [0.95, 1.00]	⊕⊕⊕○ ¹	0.98 [0.91, 1.06]	⊕⊕○○	0.97 [0.96, 1.00]	⊕⊕⊕○
↓ PRO	9	68	0.99 [0.96, 1.02]	⊕⊕○○ ^{1,2}	0.97 [0.93, 1.01]	⊕⊕○○	0.98 [0.96, 1.01]	⊕⊕○○
↑ CHO								
↓ PRO	19	94	1.01 [0.99, 1.03]	⊕⊕○○ ^{1,2}	1.04 [0.96, 1.12]	⊕⊕○○	1.01 [0.99, 1.03]	⊕⊕○○

⊕⊕⊕⊕ High; ⊕⊕⊕○ Moderate; ⊕⊕○○ Low; ⊕○○○ Very low; ↑ increase; ↓ decrease

95% CI 95% confidence interval; CHO carbohydrates; FAT fat, GRADE Grading of Recommendations Assessment, Development and Evaluations; HR hazard ratio; PRO protein; RoB risk of bias;

¹ downgraded by 1 level for RoB: less than 2/3 of the studies (and their contributing weight) were rated with a low RoB, and less than 2/3 of the studies were rated with a high RoB, OR more than 2/3 of the studies (and their contributing weight) were rated with a high RoB, but the effect estimate in the subgroup analysis, excluding studies with a high RoB, was robust.

² downgraded by 1 level for inconsistency: The point estimates differ substantially between primary studies, and the corresponding 95% CI overlap only minimally or not at all. We found no clinical or methodological explanation for this inconsistency

Supplemental table 7: League table for the fatty acids expanded network (5% isocaloric energy substitution) for the outcome all-cause mortality

PUFA	0.92 [0.86, 0.99]	0.86 [0.80, 0.92]	0.64 [0.56, 0.73]	0.90 [0.84, 0.96]	0.99 [0.86, 1.14]
0.94 [0.88, 1.01]	MUFA	0.91 [0.86, 0.97]	0.74 [0.65, 0.84]	0.94 [0.88, 1.01]	0.95 [0.82, 1.09]
0.86 [0.81, 0.91]	0.91 [0.86, 0.97]	SFA	0.85 [0.75, 0.97]	1.06 [1.00, 1.13]	1.01 [0.91, 1.13]
0.75 [0.67, 0.84]	0.80 [0.72, 0.89]	0.87 [0.78, 0.97]	TFA	1.18 [1.05, 1.32]	1.04 [0.60, 1.82]
0.90 [0.84, 0.95]	0.95 [0.90, 1.01]	1.04 [0.99, 1.11]	1.20 [1.08, 1.33]	CHO	0.99 [0.86, 1.13]
0.91 [0.82, 1.01]	0.96 [0.87, 1.07]	1.06 [0.96, 1.16]	1.21 [1.05, 1.39]	1.01 [0.92, 1.12]	PRO

CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids; The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PUFA (increase) vs. ↓ MUFA (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis. For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.09.

Supplemental table 8: League table for the MUFA-origin network (5% isocaloric energy substitution) for the outcome all-cause mortality

Plant MUFA	0.81 [0.76, 0.85]	0.85 [0.80, 0.90]	0.78 [0.66, 0.92]	0.90 [0.85, 0.95]
0.81 [0.76, 0.85]	Animal MUFA	1.05 [0.98, 1.12]	1.01 [0.85, 1.20]	1.12 [1.05, 1.19]
0.85 [0.80, 0.90]	1.05 [0.99, 1.12]	SFA	0.92 [0.77, 1.11]	1.06 [1.00, 1.13]
0.79 [0.67, 0.94]	0.99 [0.84, 1.16]	0.94 [0.79, 1.11]	TFA	1.12 [0.94, 1.32]
0.90 [0.85, 0.95]	1.12 [1.05, 1.18]	1.06 [1.00, 1.13]	1.13 [0.96, 1.33]	CHO

Animal MUFA monounsaturated fatty acids of animal origin; CHO carbohydrates; HR hazard ratio; Plant MUFA monounsaturated fatty acids of plant origin; SFA saturated fatty acids; TFA trans-fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ plant MUFA (increase) vs. ↓ animal MUFA (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.04.

Supplemental table 9: League table for the PUFA-origin network (5% isocaloric energy substitution) for the outcome all-cause mortality

n-3 PUFA	0.92 [0.74, 1.13]	0.81 [0.57, 1.15]	0.70 [0.58, 0.86]	0.83 [0.43, 1.58]	0.82 [0.66, 1.01]	0.83 [0.59, 1.17]
0.84 [0.70, 1.01]	n-6 PUFA	0.96 [0.76, 1.21]	0.86 [0.77, 0.97]	0.98 [0.54, 1.78]	0.85 [0.77, 0.94]	0.99 [0.81, 1.22]
0.75 [0.58, 0.97]	0.90 [0.73, 1.10]	MUFA	0.98 [0.78, 1.24]	1.02 [0.56, 1.86]	0.96 [0.76, 1.21]	1.03 [0.82, 1.30]
0.69 [0.57, 0.83]	0.82 [0.74, 0.92]	0.91 [0.74, 1.12]	SFA	1.04 [0.58, 1.88]	1.06 [0.92, 1.22]	1.05 [0.85, 1.29]
0.77 [0.42, 1.41]	0.92 [0.51, 1.64]	1.02 [0.56, 1.86]	1.12 [0.62, 2.00]	TFA	0.94 [0.52, 1.69]	1.01 [0.56, 1.82]
0.72 [0.59, 0.86]	0.85 [0.77, 0.94]	0.95 [0.77, 1.17]	1.04 [0.92, 1.17]	0.93 [0.52, 1.66]	CHO	1.08 [0.87, 1.32]
0.78 [0.61, 0.98]	0.93 [0.77, 1.11]	1.03 [0.82, 1.30]	1.13 [0.94, 1.35]	1.01 [0.56, 1.82]	1.09 [0.91, 1.30]	PRO

CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; n-3 PUFA n-3 polyunsaturated fatty acids; n-6 PUFA n-6 polyunsaturated fatty acids; PRO protein; SFA saturated fatty acids; TFA trans-fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ n-3 PUFA (increase) vs. ↓ n-6 PUFA (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HR's and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.10.

Supplemental table 10: League table for the fat-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

PF	0.98 [0.96, 1.00]	0.95 [0.93, 0.98]	1.03 [0.99, 1.07]
0.98 [0.96, 1.00]	AF	0.97 [0.95, 0.99]	1.04 [1.00, 1.08]
0.95 [0.93, 0.98]	0.97 [0.95, 1.00]	CHO	1.09 [1.05, 1.13]
1.03 [0.99, 1.07]	1.05 [1.01, 1.09]	1.08 [1.04, 1.12]	PRO

AF animal fat; CHO carbohydrates; HR hazard ratio; PF plant fat; PRO protein;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PF (increase) vs. ↓ AF (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HR and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.01.

Supplemental table 11: GRADE assessment of all-cause mortality for the fat-origin subnetwork (5% isocaloric energy substitution); Number of participants (n= 258 291) and number of mortality events (n= 17 471)

		Direct evidence			Indirect evidence		Network Meta-Analysis	
Comparison	N studies	Proportion direct evidence	HR (95% CI)	Certainty of evidence	HR (95% CI)	Certainty of evidence	HR (95% CI)	Certainty of evidence
↑ PF								
↓ AF	3	100	0.98 [0.96, 1.00]	⊕⊕○○ ¹	NA	NA	0.98 [0.96, 1.00]	⊕⊕○○
↓ CHO	2	96	0.95 [0.93, 0.98]	⊕⊕○○ ¹	0.88 [0.78, 0.99]	⊕⊕○○	0.95 [0.93, 0.98]	⊕⊕○○
↓ PRO	1	89	1.03 [0.99, 1.07]	⊕⊕○○ ¹	1.02 [0.91, 1.14]	⊕⊕○○	1.03 [0.99, 1.07]	⊕○○○ ²
↑ AF								
↓ CHO	2	96	0.97 [0.95, 0.99]	⊕⊕○○ ¹	1.05 [0.92, 1.19]	⊕⊕○○	0.97 [0.95, 1.00]	⊕⊕○○
↓ PRO	1	92	1.04 [1.00, 1.08]	⊕⊕○○ ¹	1.14 [1.00, 1.30]	⊕⊕○○	1.05 [1.01, 1.09]	⊕⊕○○

⊕⊕⊕⊕ High; ⊕⊕⊕○ Moderate; ⊕⊕○○ Low; ⊕○○○ Very low; ↑ increase; ↓ decrease

95% CI 95% confidence interval; AF animal fat; CHO carbohydrates; GRADE Grading of Recommendations Assessment, Development and Evaluations; HR hazard ratio; NA not applicable (the proportion of evidence was 100% for the direct estimate); PF plant fat; PRO protein; RoB risk of bias;

¹ downgraded by 2 levels for RoB: More than 2/3 of the studies (and their contributing weight) were rated with a high RoB. No subgroup analysis for RoB could be conducted to test to robustness of the effect estimates.

² downgraded by 1 level for imprecision: The 95% CI includes a RR/HR of 1 and the 95% CI is not narrow (maximal width of 0.05).

Supplemental table 12: League table for the protein-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

PP	0.87 [0.83, 0.91]	0.98 [0.88, 1.10]	1.02 [0.91, 1.15]	0.90 [0.84, 0.97]	0.93 [0.53, 1.64]	0.88 [0.85, 0.92]
0.87 [0.84, 0.91]	AP	1.01 [0.92, 1.10]	1.04 [0.95, 1.14]	0.99 [0.93, 1.05]	0.95 [0.55, 1.66]	1.00 [0.97, 1.03]
0.86 [0.80, 0.94]	0.99 [0.92, 1.07]	PUFA	1.05 [0.95, 1.17]	1.04 [0.95, 1.14]	0.93 [0.53, 1.63]	1.02 [0.94, 1.11]
0.92 [0.84, 1.00]	1.05 [0.96, 1.14]	1.06 [0.96, 1.17]	MUFA	0.98 [0.89, 1.08]	0.99 [0.56, 1.73]	0.95 [0.87, 1.04]
0.86 [0.82, 0.91]	0.99 [0.94, 1.04]	1.00 [0.92, 1.09]	0.95 [0.86, 1.03]	SFA	1.00 [0.57, 1.74]	0.97 [0.89, 1.05]
0.87 [0.50, 1.51]	0.99 [0.57, 1.73]	1.01 [0.58, 1.76]	0.95 [0.54, 1.66]	1.01 [0.58, 1.75]	TFA	0.97 [0.56, 1.69]
0.88 [0.84, 0.91]	1.00 [0.97, 1.03]	1.01 [0.94, 1.10]	0.96 [0.88, 1.04]	1.01 [0.96, 1.07]	1.01 [0.58, 1.75]	CHO

AP animal protein; CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; PP plant protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids; The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PP (increase) vs. ↓ AP (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.05.

Supplemental table 13: League table for the carbohydrate-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

High-quality CHO	0.98 [0.93, 1.03]	0.99 [0.91, 1.07]	1.04 [0.96, 1.13]	0.98 [0.93, 1.04]	0.93 [0.54, 1.60]	0.99 [0.94, 1.04]
0.97 [0.92, 1.02]	Low-quality CHO	1.01 [0.93, 1.09]	1.07 [0.99, 1.17]	1.00 [0.94, 1.06]	0.97 [0.56, 1.66]	1.02 [0.97, 1.08]
0.97 [0.90, 1.05]	1.01 [0.93, 1.08]	PUFA	1.03 [0.94, 1.14]	1.03 [0.94, 1.12]	0.86 [0.50, 1.48]	0.99 [0.91, 1.08]
1.02 [0.95, 1.11]	1.06 [0.98, 1.14]	1.05 [0.96, 1.15]	MUFA	0.98 [0.89, 1.07]	0.92 [0.53, 1.58]	0.97 [0.89, 1.06]
0.96 [0.91, 1.02]	1.00 [0.94, 1.05]	0.99 [0.91, 1.07]	0.94 [0.87, 1.02]	SFA	0.92 [0.53, 1.58]	1.02 [0.96, 1.09]
0.91 [0.53, 1.55]	0.93 [0.55, 1.60]	0.93 [0.54, 1.60]	0.89 [0.52, 1.52]	0.94 [0.55, 1.61]	TFA	1.11 [0.65, 1.92]
0.99 [0.94, 1.04]	1.02 [0.97, 1.08]	1.02 [0.94, 1.10]	0.97 [0.89, 1.05]	1.03 [0.97, 1.09]	1.09 [0.64, 1.88]	PRO

CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ high-quality CHO (increase) vs. ↓ low-quality CHO (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.05.

Supplemental table 14: GRADE assessment of all-cause mortality for the carbohydrate-origin subnetwork (5% isocaloric energy substitution);

Number of participants (n= 633 358) and number of mortality events (n= 185 350)

		Direct evidence			Indirect evidence		Network Meta-Analysis	
Comparison	N studies	Proportion direct evidence	HR (95% CI)	Certainty of evidence	HR (95% CI)	Certainty of evidence	HR (95% CI)	Certainty of evidence
↑ High-quality CHO								
↓ Low-quality CHO	5	94	0.98 [0.93, 1.03]	⊕⊕○○ ²	0.85 [0.69, 1.03]	⊕⊕○○	0.97 [0.92, 1.02]	⊕○○○ ⁴
↓ PUFA	3	89	0.99 [0.91, 1.07]	⊕○○○ ^{2,3}	0.86 [0.69, 1.08]	⊕○○○	0.97 [0.90, 1.05]	⊕○○○ ⁴
↓ MUFA	3	88	1.04 [0.96, 1.13]	⊕⊕○○ ²	0.89 [0.72, 1.12]	⊕⊕○○	1.02 [0.95, 1.11]	⊕○○○ ⁴
↓ SFA	5	93	0.98 [0.93, 1.04]	⊕⊕○○ ^{1,3}	0.77 [0.63, 0.95]	⊕⊕○○	0.96 [0.91, 1.02]	⊕○○○ ⁴
↓ TFA	2	99	0.93 [0.54, 1.60]	⊕⊕○○ ²	0.03 [0.00, 13.97]	⊕⊕○○	0.91 [0.53, 1.55]	⊕○○○ ⁴
↓ PRO	4	98	0.99 [0.94, 1.04]	⊕○○○ ^{2,3}	0.96 [0.71, 1.30]	⊕⊕○○	0.99 [0.94, 1.04]	⊕○○○ ⁴
↑ Low-quality CHO								
↓ PUFA	3	90	1.01 [0.93, 1.09]	⊕○○○ ^{2,3}	1.00 [0.78, 1.27]	⊕○○○	1.01 [0.93, 1.08]	⊕○○○ ⁴
↓ MUFA	3	90	1.07 [0.99, 1.17]	⊕⊕○○ ²	0.92 [0.72, 1.17]	⊕⊕○○	1.06 [0.98, 1.14]	⊕○○○ ⁴
↓ SFA	5	97	1.00 [0.94, 1.06]	⊕⊕○○ ^{1,3}	0.93 [0.68, 1.28]	⊕⊕○○	1.00 [0.94, 1.05]	⊕○○○ ⁴
↓ TFA	2	99	0.97 [0.56, 1.66]	⊕⊕○○ ²	0.01 [0.00, 5.61]	⊕⊕○○	0.93 [0.55, 1.60]	⊕○○○ ⁴
↓ PRO	4	89	1.02 [0.97, 1.08]	⊕⊕○○ ^{1,3}	1.04 [0.88, 1.22]	⊕○○○	1.02 [0.97, 1.08]	⊕○○○ ⁴

⊕⊕⊕⊕ High; ⊕⊕⊕○ Moderate; ⊕⊕○○ Low; ⊕○○○ Very low; ↑ increase; ↓ decrease

95% CI 95% confidence interval; CHO carbohydrates; GRADE Grading of Recommendations Assessment, Development and Evaluations; HR hazard ratio; MUFA monounsaturated fatty acids; PRO protein, PUFA polyunsaturated fatty acids; RoB risk of bias; SFA saturated fatty acids; TFA trans-fatty acids

¹ downgraded by 1 level for RoB: less than 2/3 of the studies (and their contributing weight) were rated with a low RoB, and less than 2/3 of the studies were rated with a high RoB, OR more than 2/3 of the studies (and their contributing weight) were rated with a high RoB, but the effect estimate in the subgroup analysis, excluding studies with a high RoB, was robust.

² downgraded by 2 levels for RoB: More than 2/3 of the studies (and their contributing weight) were rated with a high RoB. No subgroup analysis for RoB could be conducted to test to robustness of the effect estimates.

³ downgraded by 1 level for inconsistency: The point estimates differ substantially between primary studies, and the corresponding 95% CI overlap only minimally or not at all. We found no clinical or methodological explanation for this inconsistency.

⁴ downgraded by 1 level for imprecision: The 95% CI includes a RR/HR of 1 and the 95% CI is not narrow (maximal width of 0.05).

Supplemental table 15: SIDE splitting approach comparing direct and indirect evidence for the overall macronutrient network (5% isocaloric energy substitution) for the outcome all-cause mortality

	Direct	Indirect	Ratio of HRs	p-value
↑ FAT vs. ↓ CHO	0.97 [0.95, 1.00]	0.98 [0.91, 1.06]	0.99 [0.92, 1.08]	0.89
↑ FAT vs. ↓ PRO	0.99 [0.96, 1.02]	0.97 [0.93, 1.01]	1.02 [0.97, 1.07]	0.49
↑ CHO vs. ↓ PRO	1.01 [0.99, 1.03]	1.04 [0.96, 1.12]	0.97 [0.89, 1.06]	0.49

CHO carbohydrates; FAT fat; HR hazard ratio; PRO protein; ↑ increase; ↓ decrease

Estimates are hazard ratios with corresponding 95% confidence interval

Supplemental table 16: SIDE splitting approach comparing direct and indirect evidence for the fatty acids expanded network (5% isocaloric energy substitution) for the outcome all-cause mortality

	Direct	Indirect	Ratio of HRs	p-value
↑ PUFA vs. ↓ MUFA	0.92 [0.86, 0.99]	1.11 [0.92, 1.35]	0.83 [0.67, 1.01]	0.06
↑ PUFA vs. ↓ SFA	0.86 [0.80, 0.92]	0.84 [0.69,1.03]	1.02 [0.83, 1.27]	0.83
↑ PUFA vs. ↓ TFA	0.64 [0.56, 0.73]	1.07 [0.88, 1.30]	0.60 [0.47, 0.75]	<0.001
↑ PUFA vs. ↓ CHO	0.90 [0.84, 0.96]	0.88 [0.74, 1.05]	1.02 [0.85, 1.24]	0.81
↑ PUFA vs. ↓ PRO	0.99 [0.86, 1.14]	0.82 [0.70, 0.95]	1.22 [0.99, 1.50]	0.06
↑ MUFA vs. ↓ SFA	0.91 [0.86, 0.97]	0.90 [0.75; 1.08]	1.01 [0.84, 1.23]	0.88
↑ MUFA vs. ↓ TFA	0.74 [0.65, 0.84]	0.95 [0.78, 1.16]	0.78 [0.62, 0.99]	0.04
↑ MUFA vs. ↓ CHO	0.94 [0.88, 1.01]	1.01 [0.86, 1.19]	0.93 [0.78, 1.11]	0.42
↑ MUFA vs. ↓ PRO	0.95 [0.82, 1.09]	0.98 [0.85; 1.14]	0.96 [0.78, 1.18]	0.69
↑ SFA vs. ↓ TFA	0.85 [0.75, 0.97]	0.92 [0.76, 1.12]	0.92 [0.73, 1.17]	0.51
↑ SFA vs. ↓ CHO	1.06 [1.00, 1.13]	0.95 [0.82; 1.11]	1.11 [0.94, 1.31]	0.22
↑ SFA vs. ↓ PRO	1.01 [0.91, 1.13]	1.23 [1.01, 1.51]	0.82 [0.65, 1.03]	0.09
↑ TFA vs. ↓ CHO	1.18 [1.05, 1.32]	1.30 [0.98, 1.72]	0.91 [0.67, 1.23]	0.54
↑ TFA vs. ↓ PRO	1.04 [0.60, 1.82]	1.22 [1.06; 1.41]	0.85 [0.48, 1.52]	0.59

CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids; ↑ increase; ↓ decrease
 Estimates are hazard ratios with corresponding 95% confidence interval

Supplemental table 17: SIDE splitting approach comparing direct and indirect evidence for the MUFA-origin network (5% isocaloric energy substitution) for the outcome all-cause mortality

	Direct	Indirect	Ratio of HRs	p-value
↑ Plant MUFA vs. ↓ Animal MUFA	0.81 [0.76, 0.85]	NA	NA	NA
↑ Plant MUFA vs. ↓ SFA	0.85 [0.80, 0.90]	0.88 [0.64, 1.22]	0.96 [0.69, 1.33]	0.80
↑ Plant MUFA vs. ↓ TFA	0.78 [0.66, 0.92]	1.25 [0.57, 2.74]	0.62 [0.28, 1.39]	0.25
↑ Plant MUFA vs. ↓ CHO	0.90 [0.85, 0.95]	1.11 [0.53, 2.34]	0.81 [0.38, 1.70]	0.57
↑ Animal MUFA vs. ↓ SFA	1.05 [0.98, 1.12]	1.20 [0.86, 1.68]	0.87 [0.62, 1.23]	0.44
↑ Animal MUFA vs. ↓ TFA	1.01 [0.85, 1.20]	0.75 [0.42, 1.34]	1.35 [0.74, 2.47]	0.33
↑ Animal MUFA vs. ↓ CHO	1.12 [1.05, 1.19]	1.07 [0.55, 2.12]	1.04 [0.53, 2.05]	0.91

animal MUFA monounsaturated fatty acids of animal origin; CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; NA not applicable (the proportion of evidence was 100% for the direct estimate); plant MUFA monounsaturated fatty acids of plant origin; SFA saturated fatty acids; TFA trans-fatty acids; ↑ increase; ↓ decrease
Estimates are hazard ratios with corresponding 95% confidence interval

Supplemental table 18: SIDE splitting approach comparing direct and indirect evidence for the PUFA-origin network (5% isocaloric energy substitution) for the outcome all-cause mortality

	Direct	Indirect	Ratio of HRs	p-value
↑ n-3 PUFA vs. ↓ n-6 PUFA	0.92 [0.74, 1.13]	0.60 [0.40, 0.90]	1.53 [0.97, 2.43]	0.07
↑ n-3 PUFA vs. ↓ MUFA	0.81 [0.57, 1.15]	0.70 [0.49, 1.01]	1.15 [0.69, 1.92]	0.58
↑ n-3 PUFA vs. ↓ SFA	0.70 [0.58, 0.86]	0.59 [0.35, 0.99]	1.20 [0.69, 2.11]	0.52
↑ n-3 PUFA vs. ↓ TFA	0.83 [0.43, 1.58]	0.51 [0.10, 2.51]	1.62 [0.29, 9.11]	0.58
↑ n-3 PUFA vs. ↓ CHO	0.82 [0.66, 1.01]	0.38 [0.24, 0.59]	2.17 [1.31, 3.58]	0.002
↑ n-3 PUFA vs. ↓ PRO	0.83 [0.59, 1.17]	0.73 [0.53, 1.01]	1.14 [0.71, 1.82]	0.58
↑ n-6 PUFA vs. ↓ MUFA	0.96 [0.76, 1.21]	0.70 [0.45, 1.08]	1.38 [0.84, 2.26]	0.20
↑ n-6 PUFA vs. ↓ SFA	0.86 [0.77, 0.97]	0.55 [0.39, 0.78]	1.56 [1.09, 2.23]	0.02
↑ n-6 PUFA vs. ↓ TFA	0.98 [0.54, 1.78]	0.12 [0.005, 2.95]	8.38 [0.32, 222.36]	0.20
↑ n-6 PUFA vs. ↓ CHO	0.85 [0.77, 0.94]	0.89 [0.55, 1.42]	0.96 [0.59, 1.55]	0.86
↑ n-6 PUFA vs. ↓ PRO	0.99 [0.81, 1.22]	0.76 [0.54, 1.08]	1.30 [0.87, 1.95]	0.20

CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; n-3 PUFA n-3 polyunsaturated fatty acids; n-6 PUFA n-6 polyunsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids; ↑ increase; ↓ decrease

Estimates are hazard ratios with corresponding 95% confidence interval

Supplemental table 19: SIDE splitting approach comparing direct and indirect evidence for the fat-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

	Direct	Indirect	Ratio of HRs	p-value
↑ PF vs. ↓ AF	0.98 [0.96, 1.00]	NA	NA	NA
↑ PF vs. ↓ CHO	0.95 [0.93, 0.98]	0.88 [0.78, 0.99]	1.08 [0.96, 1.22]	0.19
↑ PF vs. ↓ PRO	1.03 [0.99, 1.07]	1.02 [0.91, 1.14]	1.01 [0.89, 1.14]	0.85
↑ AF vs. ↓ CHO	0.97 [0.95, 0.99]	1.05 [0.92, 1.19]	0.92 [0.81, 1.05]	0.23
↑ AF vs. ↓ PRO	1.04 [1.00, 1.08]	1.14 [1.00, 1.30]	0.91 [0.80, 1.05]	0.19

AF animal fat; CHO carbohydrates; HR hazard ratio; NA not applicable (the proportion of evidence was 100% for the direct estimate); PF plant fat; PRO protein; ↑ increase; ↓ decrease
 Estimates are hazard ratios with corresponding 95% confidence interval

Supplemental table 20: SIDE splitting approach comparing direct and indirect evidence for the protein-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

	Direct	Indirect	Ratio of HRs	p-value
↑ PP vs. ↓ AP	0.87 [0.83, 0.91]	0.88 [0.81, 0.97]	0.99 [0.89, 1.09]	0.82
↑ PP vs. ↓ PUFA	0.98 [0.88, 1.10]	0.76 [0.68, 0.85]	1.30 [1.10, 1.53]	0.002
↑ PP vs. ↓ MUFA	1.02 [0.91, 1.15]	0.80 [0.71, 0.91]	1.27 [1.07, 1.51]	0.01
↑ PP vs. ↓ SFA	0.90 [0.84, 0.97]	0.81 [0.75, 0.89]	1.11 [0.99, 1.24]	0.08
↑ PP vs. ↓ TFA	0.93 [0.53, 1.64]	0.11 [0.01, 2.31]	8.34 [0.38, 181.11]	0.18
↑ PP vs. ↓ CHO	0.88 [0.85, 0.92]	0.82 [0.73, 0.93]	1.07 [0.94, 1.23]	0.29
↑ AP vs. ↓ PUFA	1.01 [0.92, 1.10]	0.92 [0.79, 1.08]	1.09 [0.91, 1.31]	0.34
↑ AP vs. ↓ MUFA	1.04 [0.95, 1.14]	1.06 [0.88, 1.28]	0.98 [0.80, 1.21]	0.86
↑ AP vs. ↓ SFA	0.99 [0.93, 1.05]	0.99 [0.90, 1.09]	1.00 [0.89, 1.12]	0.94
↑ AP vs. ↓ TFA	0.95 [0.55, 1.66]	87.09 [0.31, 24507.53]	0.01 [0.00, 3.16]	0.12
↑ AP vs. ↓ CHO	1.00 [0.97, 1.03]	1.01 [0.88, 1.17]	0.99 [0.85, 1.15]	0.88

95% CI 95% confidence interval; AP animal protein; CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; n-3 PUFA n-3 polyunsaturated fatty acids; n-6 PUFA n-6 polyunsaturated fatty acids; PP plant protein; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids; ↑ increase; ↓ decrease
 Estimates are hazard ratios with corresponding 95% confidence interval

Supplemental table 21: SIDE splitting approach comparing direct and indirect evidence for the carbohydrate-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

	Direct	Indirect	Ratio of HRs	p-value
↑ High-quality CHO vs. ↓ low-quality CHO	0.98 [0.93, 1.03]	0.85 [0.69, 1.03]	1.16 [0.94, 1.42]	0.17
↑ High-quality CHO vs. ↓ PUFA	0.99 [0.91, 1.07]	0.86 [0.69, 1.08]	1.14 [0.91, 1.44]	0.26
↑ High-quality CHO vs. ↓ MUFA	1.04 [0.96, 1.13]	0.89 [0.72, 1.12]	1.17 [0.92, 1.48]	0.20
↑ High-quality CHO vs. ↓ SFA	0.98 [0.93, 1.04]	0.77 [0.63, 0.95]	1.28 [1.03, 1.58]	0.03
↑ High-quality CHO vs. ↓ TFA	0.93 [0.54, 1.60]	0.03 [0.00, 13.97]	28.50 [0.07, 12491.81]	0.28
↑ High-quality CHO vs. ↓ PRO	0.99 [0.94, 1.04]	0.96 [0.71, 1.30]	1.03 [0.76, 1.41]	0.84
↑ Low-quality CHO vs. ↓ PUFA	1.01 [0.93, 1.09]	1.00 [0.78, 1.27]	1.01 [0.78, 1.30]	0.95
↑ Low-quality CHO vs. ↓ MUFA	1.07 [0.99, 1.17]	0.92 [0.72, 1.17]	1.17 [0.90, 1.52]	0.24
↑ Low-quality CHO vs. ↓ SFA	1.00 [0.94, 1.06]	0.93 [0.68, 1.28]	1.07 [0.77, 1.48]	0.68
↑ Low-quality CHO vs. ↓ TFA	0.97 [0.56, 1.66]	0.01 [0.00, 5.61]	97.65 [0.17, 56693.01]	0.16
↑ Low-quality CHO vs. ↓ PRO	1.02 [0.97, 1.08]	1.04 [0.88, 1.22]	0.98 [0.83, 1.17]	0.85

CHO carbohydrates; HR hazard ratio; MUFA monounsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids; ↑ increase; ↓ decrease
 Estimates are hazard ratios with corresponding 95% confidence interval

Supplemental table 22: Results of the design by treatment test (global test for statistical inconsistency in the network meta-analysis for the outcome all-cause mortality)

	p-value
Overall macronutrient network	p = 0.28
Fatty acids expanded network	p = 0.005
MUFA-origin network	p = 0.06
PUFA-origin network	p < 0.001
Fat-origin subnetwork	p = 0.20
Protein-origin subnetwork	p < 0.001
Carbohydrate-origin subnetwork	p < 0.001

Supplemental table 23: P-scores for the overall macronutrient network (5% isocaloric energy substitution) for the outcome all-cause mortality

	P-score
FAT	0.95
PRO	0.45
CHO	0.10

CHO carbohydrates; PRO protein

Supplemental table 24: P-scores for the fatty acids expanded network (5% isocaloric energy substitution) for the outcome all-cause mortality

	P-score
PUFA	0.99
MUFA	0.75
PRO	0.55
CHO	0.48
SFA	0.24
TFA	0.00

CHO carbohydrates; MUFA monounsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

Supplemental table 25: P-scores for the MUFA-origin network (5% isocaloric energy substitution) for the outcome all-cause mortality

	P-score
Plant MUFA	1.00
CHO	0.72
SFA	0.44
TFA	0.18
Animal MUFA	0.16

Animal MUFA monounsaturated fatty acids of animal origin; CHO carbohydrates; Plant MUFA monounsaturated fatty acids of plant origin; SFA saturated fatty acids; TFA trans-fatty acids;

Supplemental table 26: P-scores for the PUFA-origin network (5% isocaloric energy substitution) for the outcome all-cause mortality

	P-score
n-3 PUFA	0.96
n-6 PUFA	0.72
PRO	0.51
TFA	0.47
MUFA	0.42
CHO	0.27
SFA	0.15

CHO carbohydrates; MUFA monounsaturated fatty acids; n-3 PUFA n-3 polyunsaturated fatty acids; n-6 PUFA n-6 polyunsaturated fatty acids; PRO protein; SFA saturated fatty acids; TFA trans-fatty acids;

Supplemental table 27: P-scores for the fat-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

	P-score
PRO	0.97
PF	0.68
AF	0.34
CHO	0.00

AF animal fat; CHO carbohydrates; PF plant fat; PRO protein;

Supplemental table 28: P-scores for the protein-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

	P-score
PP	0.94
MUFA	0.68
TFA	0.46
CHO	0.43
AP	0.40
PUFA	0.31
SFA	0.29

AP animal protein; CHO carbohydrates; MUFA monounsaturated fatty acids; PP plant protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

Supplemental table 29: P-scores for the carbohydrate-origin subnetwork (5% isocaloric energy substitution) for the outcome all-cause mortality

	P-score
MUFA	0.81
High-quality CHO	0.68
PRO	0.58
PUFA	0.41
TFA	0.38
Low-quality CHO	0.33
SFA	0.30

CHO carbohydrates; MUFA monounsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

Supplemental table 30: Subgroup analysis for the overall macronutrient network, including American cohort studies (5% isocaloric energy substitution);

Number of participants (n= 771 011) and number of mortality events (n= 174 566)

FAT	0.98 [0.95, 1.01]	1.02 [0.97, 1.06]
0.98 [0.96, 1.01]	CHO	1.02 [0.99, 1.04]
1.00 [0.97, 1.03]	1.02 [1.00, 1.04]	PRO

CHO carbohydrates; CI confidence interval; FAT fat; HR hazard ratio; PRO protein

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ FAT (increase) vs. ↓ CHO (decrease) are displayed in the first row second column (HR: 0.97, 95% CI: 0.95, 0.99) and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.03.

Supplemental table 31: Subgroup analysis for the fatty acids expanded network, including American cohort studies (5% isocaloric energy substitution);

Number of participants (n= 593 658) and number of mortality events (n= 182 925)

PUFA	0.88 [0.79, 0.98]	0.78 [0.70, 0.86]	0.62 [0.53, 0.72]	0.83 [0.75, 0.92]	NA
0.89 [0.81, 0.98]	MUFA	0.89 [0.80, 0.98]	0.70 [0.60, 0.81]	0.95 [0.86, 1.06]	NA
0.79 [0.72, 0.87]	0.89 [0.81, 0.98]	SFA	0.82 [0.71, 0.95]	1.09 [0.98, 1.21]	1.13 [0.94, 1.37]
0.64 [0.56, 0.74]	0.72 [0.63, 0.83]	0.81 [0.70, 0.93]	TFA	1.37 [1.18, 1.59]	NA
0.85 [0.78, 0.94]	0.96 [0.87, 1.05]	1.08 [0.98, 1.18]	1.33 [1.16, 1.53]	CHO	NA
0.90 [0.73, 1.11]	1.01 [0.82, 1.25]	1.13 [0.94, 1.37]	1.40 [1.11, 1.77]	1.05 [0.85, 1.30]	PRO

CHO carbohydrates; CI confidence interval; HR hazard ratio; MUFA monounsaturated fatty acids; NA not applicable; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PUFA (increase) vs. ↓ MUFA (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.10.

Supplemental table 32: Subgroup analysis for the protein-origin subnetwork, including American cohort studies (5% isocaloric energy substitution);

Number of participants (n= 684 084) and number of mortality events (n= 191 082)

PP	0.84 [0.81, 0.88]	0.83 [0.78, 0.88]	0.86 [0.83, 0.90]
0.87 [0.84, 0.90]	AP	0.94 [0.89, 0.99]	0.99 [0.96, 1.02]
0.82 [0.79, 0.86]	0.95 [0.91, 0.99]	SFA	NA
0.86 [0.83, 0.89]	0.99 [0.97, 1.02]	1.05 [1.00, 1.10]	CHO

AP animal protein; CHO carbohydrates; CI confidence interval; HR hazard ratio; NA not applicable; PP plant protein; SFA saturated fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PP (increase) vs. ↓ AP (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.03.

Supplemental table 33: Subgroup analysis for the overall macronutrient network, including studies with a single dietary assessment (5% isocaloric energy substitution);

Number of participants (n= 1 174 221) and number of mortality events (n= 185 772)

FAT	0.99 [0.96, 1.01]	0.97 [0.94, 1.01]
0.98 [0.96, 1.01]	CHO	1.00 [0.97, 1.02]
0.98 [0.95, 1.01]	1.00 [0.97, 1.02]	PRO

CHO carbohydrates; CI confidence interval; FAT fat; HR hazard ratio; PRO protein

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ FAT (increase) vs. ↓ CHO (decrease) are displayed in the first row second column (HR: 0.97, 95% CI: 0.95, 0.99) and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.03.

Supplemental table 34: Subgroup analysis for the protein-origin subnetwork, including studies with a single dietary assessment (5% isocaloric energy substitution);

Number of participants (n= 675 408) and number of mortality events (n= 175 283)

PP	0.87 [0.82, 0.92]	0.96 [0.81, 1.14]	1.16 [0.96, 1.41]	0.89 [0.82, 0.97]	0.88 [0.83, 0.93]
0.86 [0.82, 0.91]	AP	0.99 [0.88, 1.12]	1.20 [1.03, 1.40]	1.01 [0.94, 1.09]	1.03 [0.98, 1.07]
0.81 [0.72, 0.90]	0.94 [0.84, 1.04]	PUFA	1.21 [1.04, 1.41]	1.17 [1.03, 1.34]	1.12 [1.01, 1.25]
0.98 [0.85, 1.12]	1.13 [0.99, 1.30]	1.21 [1.04, 1.41]	MUFA	0.97 [0.82, 1.14]	0.93 [0.80, 1.07]
0.86 [0.80, 0.91]	0.99 [0.94, 1.06]	1.06 [0.95, 1.19]	0.88 [0.76, 1.01]	SFA	0.96 [0.85, 1.08]
0.88 [0.83, 0.93]	1.02 [0.98, 1.06]	1.09 [0.98, 1.21]	0.90 [0.78, 1.03]	1.02 [0.96, 1.09]	CHO

AP animal protein; CHO carbohydrates; CI confidence interval; HR hazard ratio; MUFA monounsaturated fatty acids; PP plant protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PP (increase) vs. ↓ AP (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.05.

Supplemental table 35: Sensitivity analysis for the overall macronutrient network, excluding studies with a high risk of bias (5% isocaloric energy substitution);

Number of participants (n= 1 161 535) and number of mortality events (n= 209 817)

FAT	0.97 [0.94, 1.00]	0.96 [0.91, 1.02]
0.97 [0.94, 0.99]	CHO	1.00 [0.97, 1.02]
0.97 [0.94, 1.00]	1.00 [0.98, 1.03]	PRO

CHO carbohydrates; CI confidence interval; FAT fat; HR hazard ratio; PRO protein

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ FAT (increase) vs. ↓ CHO (decrease) are displayed in the first row second column (HR: 0.97, 95% CI: 0.95, 0.99) and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.03.

Supplemental table 36: Sensitivity analysis for the fatty acids expanded network, excluding studies with a high risk of bias (5% isocaloric energy substitution);

Number of participants (n= 623 244) and number of mortality events (n= 187 630)

PUFA	0.84 [0.76, 0.92]	0.76 [0.69, 0.83]	0.62 [0.55, 0.71]	0.83 [0.76, 0.91]	NA
0.87 [0.79, 0.95]	MUFA	0.88 [0.80, 0.95]	0.73 [0.64, 0.83]	0.93 [0.86, 1.01]	NA
0.76 [0.69, 0.83]	0.88 [0.81, 0.95]	SFA	0.85 [0.74, 0.97]	1.10 [1.02, 1.20]	1.07 [0.90, 1.28]
0.65 [0.57, 0.74]	0.75 [0.66, 0.85]	0.85 [0.75, 0.96]	TFA	1.30 [1.14, 1.48]	NA
0.83 [0.76, 0.91]	0.95 [0.88, 1.03]	1.09 [1.00, 1.18]	1.28 [1.13, 1.44]	CHO	NA
0.82 [0.67, 1.00]	0.94 [0.77, 1.14]	1.07 [0.90, 1.28]	1.26 [1.01, 1.56]	0.99 [0.81, 1.20]	PRO

CHO carbohydrates; CI confidence interval; HR hazard ratio; MUFA monounsaturated fatty acids; NA not applicable; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PUFA (increase) vs. ↓ MUFA (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.09.

Supplemental table 37: Sensitivity analysis for the protein-origin subnetwork, excluding studies with a high risk of bias (5% isocaloric energy substitution);

Number of participants (n= 782 644) and number of mortality events (n= 207 369)

PP	0.85 [0.81, 0.89]	0.83 [0.78, 0.89]	0.84 [0.81, 0.88]
0.85 [0.82, 0.89]	AP	0.94 [0.89, 1.00]	1.00 [0.98, 1.03]
0.82 [0.78, 0.86]	0.96 [0.91, 1.01]	SFA	NA
0.85 [0.82, 0.89]	1.00 [0.97, 1.03]	1.04 [0.99, 1.10]	CHO

AP animal protein; CHO carbohydrates; CI confidence interval; HR hazard ratio; NA not applicable; PP plant protein; SFA saturated fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PP (increase) vs. ↓ AP (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.03.

Supplemental table 38: Sensitivity analysis for the overall macronutrient network, excluding studies with high relative residual effects (5% isocaloric energy substitution);

Number of participants (n= 1 520 063) and number of mortality events (n= 213 593)

FAT	0.97 [0.95, 0.99]	0.99 [0.96, 1.02]
0.97 [0.95, 0.99]	CHO	1.01 [0.99, 1.03]
0.98 [0.96, 1.00]	1.01 [0.99, 1.03]	PRO

CHO carbohydrates; CI confidence interval; FAT fat; HR hazard ratio; PRO protein

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ FAT (increase) vs. ↓ CHO (decrease) are displayed in the first row second column (HR: 0.97, 95% CI: 0.95, 0.99) and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.03.

Supplemental table 39: Sensitivity analysis for the fatty acids expanded network, excluding studies with high relative residual effects (5% isocaloric energy substitution);

Number of participants (n= 1 027 288) and number of mortality events (n= 242 504)

PUFA	0.91 [0.84, 0.99]	0.87 [0.80, 0.94]	0.54 [0.45, 0.65]	0.89 [0.83, 0.97]	0.99 [0.85, 1.16]
0.94 [0.87, 1.01]	MUFA	0.92 [0.85, 0.99]	0.70 [0.58, 0.84]	0.94 [0.87, 1.01]	0.94 [0.81, 1.10]
0.86 [0.80, 0.93]	0.92 [0.86, 0.98]	SFA	0.79 [0.66, 0.95]	1.05 [0.98, 1.13]	1.01 [0.90, 1.14]
0.74 [0.64, 0.86]	0.79 [0.68, 0.91]	0.86 [0.74, 0.99]	TFA	1.15 [0.99, 1.33]	1.04 [0.59, 1.84]
0.89 [0.83, 0.96]	0.95 [0.88, 1.02]	1.03 [0.97, 1.10]	1.21 [1.05, 1.39]	CHO	0.99 [0.85, 1.14]
0.91 [0.81, 1.02]	0.97 [0.86, 1.08]	1.05 [0.95, 1.17]	1.23 [1.04, 1.46]	1.02 [0.91, 1.14]	PRO

CHO carbohydrates; CI confidence interval; HR hazard ratio; MUFA monounsaturated fatty acids; PRO protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids; The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PUFA (increase) vs. ↓ MUFA (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.10.

**Supplemental table 40: Sensitivity analysis for the protein origin network, excluding studies with high relative residual effects (5% isocaloric energy substitution);
Number of participants (n= 1 021 954) and number of mortality events (n= 224 522)**

PP	0.87 [0.83, 0.91]	0.98 [0.88, 1.10]	1.02 [0.91, 1.15]	0.90 [0.84, 0.97]	0.93 [0.53, 1.64]	0.88 [0.85, 0.92]
0.87 [0.84, 0.91]	AP	1.01 [0.92, 1.10]	1.04 [0.95, 1.14]	0.99 [0.93, 1.05]	0.95 [0.55, 1.66]	1.01 [0.97, 1.04]
0.86 [0.80, 0.94]	0.99 [0.92, 1.07]	PUFA	1.05 [0.95, 1.17]	1.04 [0.95, 1.14]	0.93 [0.53, 1.63]	1.02 [0.94, 1.11]
0.91 [0.84, 1.00]	1.05 [0.97, 1.14]	1.06 [0.96, 1.17]	MUFA	0.98 [0.89, 1.08]	0.99 [0.56, 1.73]	0.95 [0.87, 1.04]
0.86 [0.82, 0.91]	0.99 [0.94, 1.04]	1.00 [0.92, 1.09]	0.94 [0.86, 1.03]	SFA	1.00 [0.57, 1.74]	0.97 [0.89, 1.05]
0.87 [0.50, 1.51]	1.00 [0.57, 1.73]	1.01 [0.58, 1.76]	0.95 [0.54, 1.66]	1.01 [0.58, 1.75]	TFA	0.97 [0.56, 1.69]
0.88 [0.84, 0.91]	1.01 [0.98, 1.04]	1.02 [0.94, 1.10]	0.96 [0.88, 1.04]	1.02 [0.96, 1.07]	1.01 [0.58, 1.76]	CHO

AP animal protein; CHO carbohydrates; CI confidence interval; HR hazard ratio; MUFA monounsaturated fatty acids; PP plant protein; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

The HRs are established by the replacement of the lower nutrient with the one above, eg, the direct and network HR for ↑ PP (increase) vs. ↓ AP (decrease) are displayed in the first row second column and second row first column, respectively.

The upper triangle (marked blue) displays the HRs and 95% CI from direct comparison; the lower triangle (marked yellow) displays the HRs and 95% CI established from network meta-analysis.

For the upper triangle, HRs < 1 favor the row-defining treatment. For the lower triangle, HRs < 1 favor the column-defining treatment

The heterogeneity standard deviation (τ) was estimated at 0.05.

Supplemental appendix 1: Search terms

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 09, 2024

Search Strategy:

#	Searches	Hits
1	exp dietary carbohydrates/	102,664
2	((carbohydrate* or glucose or fructose or sucrose or starch or glycemic index) adj9 (intake* or diet* or consum* or nutrition* or food* or eat or eating or meal*)).ti,ab,kf.	89,308
3	1 or 2	171,988
4	exp dietary proteins/	107,970
5	exp plant proteins, dietary/	7,496
6	exp animal proteins, dietary/	66,041
7	(protein* adj9 (intake* or diet* or consum* or nutrition* or food* or eat or eating or meal*)).ti,ab,kf.	96,324
8	or/4-7	176,382
9	exp dietary fats/	99,164
10	exp dietary fats, unsaturated/	45,862
11	((((saturated or trans or monounsaturated or polyunsaturated or animal or plant) AND (fat or fats)) adj9 (intake* or diet* or consum* or nutrition* or food* or eat or eating or meal*)).ti,ab,kf.	27,324
12	((((linoleic acid or omega-6 or omega-3) adj9 (intake* or diet* or consum* or nutrition* or food* or eat or eating or meal*))).ti,ab,kf.	9,674
13	or/9-12	119,354
14	(macronutrient* adj9 (intake* or diet* or consum* or nutrition* or food* or eat or eating or meal*)).ti,ab,kf.	7,956
15	3 or 8 or 13 or 14	418,987
16	(substitut* or replac* or exchang*).mp.	1,405,623
17	(expense or increment*).mp.	167,232
18	(nutrient density or nutrient densities).mp.	1,171
19	proportional hazards models/	90,867
20	(cox adj3 (model* or regression)).mp.	173,953
21	or/16-20	1,774,505
22	15 and 21	33,925
23	cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/	1,652,366
24	(prospective or cohort* or observational or longitudinal or follow-up or cases or (case* and control*) or population-based).ti,ab,kf.	4,942,129
25	23 or 24	5,428,059
26	22 and 25	5,112

Database(s): **Embase (via Website)** 1946 to February 09, 2024

Search Strategy:

#	Searches	Hits
1	'carbohydrate intake'/exp	35,932
2	((carbohydrate* OR glucose OR fructose or sucrose OR starch OR 'glycemic index') NEAR/9 (intake* OR diet* or consum* OR nutrition* or food* OR eat OR eating OR meal*)):ti,ab,kw	119,275
3	#1 OR #2	137,317
4	'protein intake'/de	50,203
5	(protein* NEAR/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*)):ti,ab,kw	117,504
6	#4 OR #5	137,649
7	'fat intake'/exp	59,229
8	'edible oil'/exp	85,686
9	((saturated OR trans OR monounsaturated OR polyunsaturated OR animal or plant) NEAR/3 (fat OR fats) NEAR/9 (intake* OR diet* or consum* OR nutrition* OR food* OR eat OR eating OR meal*)):ti,ab,kw	14,969
10	(('linoleic acid' OR "omega 6" OR "omega 3") NEAR/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*)):ti,ab,kw	10,368
11	#7 OR #8 OR #9 OR #10	153,735
12	(macronutrient* NEAR/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*)):ti,ab,kw	10,513
13	#3 OR #6 OR #11 OR #12	382,605
14	substitut* OR replac* or exchang*	1,775,385
15	expense OR increment*	223,634
16	'nutrient density' OR 'nutrient densities'	1,367
17	'proportional hazards models'/de	105,437
18	cox NEAR/3 (model* OR regression)	291,061
19	#14 OR #15 OR #16 OR #17 OR #18	2,280,544
20	#13 AND #19	30,523
21	'cohort analysis'/de OR 'follow up'/de OR 'longitudinal study'/de OR 'prospective study'/de	3,644,104
22	prospective:ti,ab,kw OR cohort*:ti,ab,kw OR observational:ti,ab,kw OR longitudinal:ti,ab,kw OR 'follow up':ti,ab,kw OR cases:ti,ab,kw OR (case*:ti,ab,kw AND control*:ti,ab,kw) OR 'population-based':ti,ab,kw	7,025,813
23	#21 OR #22	8,045,638
24	#20 AND #23	6,296

Database(s): **Scopus (via Website)** 1946 to February 13, 2024

Search Strategy:

#	Searches	Hits
1	TITLE-ABS-KEY((carbohydrate* OR glucose OR fructose or sucrose OR starch OR "glycemic index") W/9 (intake* OR diet* or consum* OR nutrition* or food* OR eat OR eating OR meal*))	160,132
2	TITLE-ABS-KEY(protein* W/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*))	195,512
3	TITLE-ABS-KEY((saturated OR trans OR monounsaturated OR polyunsaturated OR animal or plant) W/3 (fat OR fats) W/9 (intake* OR diet* or consum* OR nutrition* OR food* OR eat OR eating OR meal*))	19,531
4	TITLE-ABS-KEY(("linoleic acid" OR "omega 6" OR "omega 3") NEAR/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*))	1,728
5	#1 OR #2 OR #3 OR #4	336,755
6	TITLE-ABS-KEY(substitut* OR replac* or exchang*)	3,963,135
7	TITLE-ABS-KEY(expense OR increment*)	565,157
8	TITLE-ABS-KEY("nutrient density" OR "nutrient densities")	1,859
9	TITLE-ABS-KEY(cox W/3 (model* OR regression))	190,267
10	#6 OR #7 OR #8 OR #9	4,674,072
11	TITLE-ABS-KEY(prospective OR cohort* OR observational OR longitudinal OR "follow up" OR cases OR (case* AND control*) OR population-based)	14,640,491
12	#5 AND #10 AND #11	5,517
	((TITLE-ABS-KEY((carbohydrate* OR glucose OR fructose OR sucrose OR starch OR "glycemic index") W/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*))) OR (TITLE-ABS-KEY((protein* W/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*)))) OR (TITLE-ABS-KEY(((saturated OR trans OR monounsaturated OR polyunsaturated OR animal or plant) W/3 (fat OR fats) W/9 (intake* OR diet* or consum* OR nutrition* OR food* OR eat OR eating OR meal*)))) OR (TITLE-ABS-KEY("linoleic acid" OR "omega 6" OR "omega 3") NEAR/9 (intake* OR diet* OR consum* OR nutrition* OR food* OR eat OR eating OR meal*))) AND ((TITLE-ABS-KEY(substitut* OR replac* or exchang*)) OR (TITLE-ABS-KEY(expense or increment*)) OR (TITLE-ABS-KEY("nutrient density" OR "nutrient densities")) OR (TITLE-ABS-KEY(cox W/3 (model* OR regression)))) AND (TITLE-ABS-KEY((prospective OR cohort* OR observational OR longitudinal OR "follow up" OR cases OR (case* AND control*) OR population-based)))	

Supplemental appendix 2: Detailed description and decision criteria for each domain in ROBINS-E assessment

Domain	Explanation	Judgements
<p>Risk of bias due to confounding</p>	<ul style="list-style-type: none"> • Is there potential for confounding of the effect of exposure in this study? • Did the authors use a multivariable-adjusted analysis method that controlled at least for age, sex, education/SES, smoking, alcohol consumption, physical activity? • Were confounding factors that were controlled for measured validly and reliably by the variables available in this study? • Did the authors avoid adjusting for post-exposure variables? <p><i>Notes:</i> Confounding is expected in all observational studies; thus, no study was assigned low risk of bias. Time-varying confounding was expected to be unlikely and is not expected to cause risk of bias in the present study.</p>	<p><u>Low risk of bias:</u> No bias is expected due to confounding, including time-varying confounding.</p> <p><u>Some concerns:</u> Confounding is expected for age, sex, smoking, alcohol consumption, education/SES, physical activity, and the authors performed a multivariable-adjusted analysis to control for these confounding factors. The variables adjusted for are valid and reliable measures of the confounding factors.</p> <p><i>or</i> SES is the only important covariate not included as confounding factor in the multivariable-adjusted analysis, but SES is not expected to vary substantially within the cohort (eg, NHS, HPFS).</p> <p><i>or</i> The authors statistically investigated whether the confounding factors have an effect on the risk estimate and excluded the confounder from the multivariable model if there was no effect on the overall effect estimate.</p> <p><u>High risk of bias:^a</u> At least one known important confounding factor was not measured or appropriately controlled for.</p> <p><i>or</i> The authors adjusted for post-exposure variables that are affected by exposure (eg, sodium intake and risk of stroke [adjustment for blood pressure during follow-up = intermediate biological variable on the causal pathway] → over adjustment).</p> <p><u>Very high risk of bias:^a</u> No adjustment was made for any covariate.</p> <p><i>or</i> The authors controlled for post-exposure variables, and the use of negative controls, or other considerations, suggest serious uncontrolled confounding.</p>

Risk of bias arising from measurement of exposure assessment

- Does the measured exposure well-characterize the exposure metric specified to be of interest in this study?
- Was the exposure likely to be measured with error, or misclassified?

Notes: Differential misclassification is not expected to occur in prospective cohort studies, since diet is reported before the occurrence of the outcome (39).
Some type of non-differential misclassification cannot be excluded (any dietary assessment method involves measurement error), thus no study was assigned low risk of bias.

Low risk of bias:

The exposure status is well characterised by the measurement and no measurement error is expected in its assessment.
and
The exposure was measured at multiple times, and is stable or changes only slightly over time.

Some concerns:

The exposure status is well characterised by the measurement, and was measured using an established or validated tool (eg, a validated FFQ/DHQ, **multiple** 24h recalls).
and (1) *or* (2)

- (1) The exposure was measured at multiple times, and it is stable or changes only slightly over time.
- (2) The exposure was measured by a single measurement assessing longer periods of time (ie, validated FFQ/DHQ), and is therefore assumed to be stable over time.

High risk of bias:

The exposure status is not well characterized by the measurement (eg, assumed from an indirect measurement or important sources of dietary intake are not considered).
or
The exposure was measured using a not validated tool.
or
The exposure was measured with a single measurement, which is unlikely to characterize the exposure over a longer period of time (eg, single 24h recall) and therefore cannot be assumed to be representative.
or
The exposure cannot be assumed to be stable over time.

Very high risk of bias:

Differential measurement error is expected (measurement error depends on the outcome).

<p>Risk of bias in selection of participants into the study</p>	<ul style="list-style-type: none"> • Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied? • Do start of follow-up and start of exposure coincide for most participants? • Were methods used that are likely to correct for the presence of selection biases? <p>Notes: In observational studies, it is unlikely that post-exposure variables influenced selection of participants into the study. Exclusion of participants may be mostly based on missing data, which will be considered in the domain referring to missings (see below).</p>	<p><u>Low risk of bias:</u> All participants who would have been eligible for the target study were included in the study. <i>and</i> The start of exposure and follow-up coincide.</p> <p><u>Some concerns:</u> The selection into the study may have been related to exposure and outcome but, the authors used appropriate methods to correct for the selection bias. <i>or</i> The start of exposure and follow-up do not coincide, but the association of exposure is constant over time.</p> <p><u>High risk of bias:</u> The selection into the study was related to exposure and outcome and this could not be corrected for in the analyses. <i>or</i> The start of exposure and follow-up do not coincide and the effect of exposure is not constant over time and this could not be corrected for in the analyses.</p> <p><u>Very high risk of bias:</u> The selection into the study was related to exposure and outcome and a sensitivity analysis is available that demonstrates substantial impact. <i>or</i> The start of exposure and follow-up do not coincide and the effect of exposure is not constant over time and a sensitivity analysis is available that demonstrates substantial impact.</p>
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<p>Risk of bias due to post-exposure interventions</p>	<ul style="list-style-type: none"> • Were there post-exposure interventions that were influenced by prior exposure during the follow-up period? <p><i>Notes:</i> In prospective observational studies, post-exposure interventions are unlikely. We don't expect any issues in this domain for our analysis.</p>	<p><u>Low risk of bias:</u> There were (probably) no interventions administered to alleviate the effect of exposures.</p> <p><u>Some concerns:</u> Post-exposure interventions were identified and the analysis corrected for the effect of these interventions.</p> <p><u>High risk of bias:</u> Post-exposure interventions were identified and the analysis did not correct for the effect of these interventions</p>
<p>Bias due to missing data</p>	<ul style="list-style-type: none"> • Were there missing outcome data? • Were participants excluded due to missing data on exposure status? • Were participants excluded due to missing data on other variables needed for analysis? • Did the authors perform a complete case analysis? • Was an appropriate method used to correct for bias due to missing data (eg, appropriate imputation)? <p><i>Notes:</i> Missing data on exposure variables and other variables are expected to be missing at random and not related to exposure or outcome that have been assessed during follow-up.</p>	<p><u>Low risk of bias:</u> There was little loss-to-follow-up (<20%) and data on exposure and other variables were reasonably complete (<10% missing data) and was unlikely to introduce bias.</p> <p><i>or</i> The analysis addressed missing data and is likely to have removed any risk of bias.</p> <p><u>Some concerns:</u> There is a proportion (>10%) of missing data in the original cohort or a high proportion (>20%) of loss-to-follow-up, and the analysis is unlikely to have removed the risk of bias arising from the missing data (eg, using logistic regression).</p> <p><i>or</i> There is a significant proportion (>20%) of missing data but the authors addressed this issue by appropriate methods (ie, imputation of data).</p> <p><u>High risk of bias:</u> There are high proportions (>50%) of missing data and the analysis is unlikely to have removed the risk of bias arising from the missing data.</p> <p><i>or</i> The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.</p> <p><u>Very high risk of bias:</u> There are very high proportions (>50%) of missing data; and missing data were addressed inappropriately in the analysis.</p>

<p>Risk of bias due to measurement of the outcome</p>	<ul style="list-style-type: none"> • Were the methods of outcome assessment comparable across exposure groups? • Could the outcome measure have been influenced by knowledge of the exposure status? • Were any systematic error in measurement of the outcome related to exposure status? <p><i>Notes:</i> In prospective observational studies, it is not expected that outcome assessors were aware of exposure status of the participants.</p>	<p><u>Low risk of bias:</u></p> <p>The methods of outcome assessment were comparable across all exposure groups. <i>and</i></p> <p>The outcome measure was unlikely to be influenced by knowledge of the exposure status of study participants. <i>and</i></p> <p>Any error in measuring the outcome is unrelated to exposure status (ie, objective measures or self-reported outcomes that are mostly (≥90%) confirmed by a second source, eg, medical records, record linkage and death certificates).</p> <p><u>Some concerns:</u></p> <p>The methods of the outcome assessment were comparable across exposure groups, and any error in measuring the outcome may be minimally related to exposure status. <i>or</i></p> <p>The measurement of the outcome is not reliable (ie, confirmed records are available for <90% of all participants and the authors did not perform an additional analysis separating confirmed and probable cases).</p> <p><u>High risk of bias:</u></p> <p>The methods of outcome assessment were not comparable across exposure groups, and errors in measuring the outcome were related to exposure status. <i>or</i></p> <p>The outcome measure was subjective (ie, self-report of CVD, type 2 diabetes, etc by study participants or next of kin, without confirmation by a second source), and errors in measuring the outcome were related to exposure status.</p>
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<p>Risk of bias due to selection of the reported result</p>	<ul style="list-style-type: none"> • Was the result reported in accordance with an available, pre-determined analysis plan? • Is the reported effect estimate likely to be selected from multiple exposure measurements? • Is the reported effect estimate likely to be selected from multiple analyses of exposure-outcome relationship? • Is the reported effect estimate likely to be selected from different subgroups? <p><i>Notes:</i> In observational studies, it is unusual to publish an a priori analysis plan or protocol. Therefore, if the authors present a clear description of the conducted analyses (ie, methods section), and it appears to be consistent with the reported results; and the reported results correspond to all intended outcomes, analyses and sub cohorts (eg, postmenopausal women), low risk of bias can be adequate.</p> <p>However, if there are any inconsistencies/or no information between intended analyses and reported results, eg.:</p> <ul style="list-style-type: none"> • a substitution analysis was conducted in line with the methods section, but reported results were incomplete (eg, authors state that a substitution analysis for fat vs. carbohydrates was conducted, but estimates are not reported); • results of substitution analyses reported, but methodological approach not described; • there are inconsistencies between the adjustments described in the methods section and the adjustments for the corresponding reported estimates in the results section; <p>There is reason for some concerns in this domain. Multiple outcome measurements for the definition of CVD, mortality, type 2 diabetes, etc are not expected.</p>	<p><u>Low risk of bias:</u> The results are reported according to an a-priori analysis plan or protocol. There is a clear description of all analysis, the analyses are consistent, and all reported results correspond to all intended outcomes, analyses and sub-cohorts.</p> <p><u>Some concerns:</u> The results are reported according to an a-priori analysis plan or protocol, and there is indication of selection of the reported analysis among multiple analyses; or there is indication of selection of the cohort or subgroups for analysis and reporting on basis of the results (eg, estimates not shown for all analyses).</p> <p><i>or</i> There is no a-priori analysis plan or protocol and there appear to be no issues with the exposure, multiple analyses (eg, effect estimates were similar when different multiple analyses were used), or the selection or definition of subgroups, but there are inconsistencies/or no information between intended and reported analyses.</p> <p><u>High risk of bias:</u> There is a high risk of selective reporting from multiple exposure measurements, outcomes measurements, or multiple analyses of data.</p> <p><i>or</i> The cohort or subgroup is selected from a larger study for analysis and appears to be reported based on the results. (up to 2)</p> <p><u>Very high risk of bias:</u> There is a high risk of selective reporting from multiple exposure measurements, or outcomes measurements, or multiple analyses of data or the cohort or subgroup is selected from a larger study for analysis and appears to be reported based on the results. (more than 2)</p>
<p>Overall judgement</p>	<p><u>Low risk of bias</u></p>	<p>The study is judged to be at low risk of bias for all domains.</p>
	<p><u>Some concerns</u></p>	<p>The study is judged to be at low risk of bias or some concerns for all domains.</p>
	<p><u>High risk of bias</u></p>	<p>The study is judged to be at high risk of bias in at least one domain, but no domains are at very high risk of bias.</p>

	Very high risk of bias	The study is judged to be at very high risk of bias in at least one domain.
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CVD cardiovascular disease; DHQ diet history questionnaire; FFQ food frequency questionnaire; HPFS Health Professional Follow up Study; NHS Nurses' Health Study; SES socioeconomic status

^aTriage: A (very) high risk of bias in the first domain leads to a triage. The further domains will not be considered for evaluation, as the overall judgement will already be at high risk of bias. (40)

Supplemental appendix 3: Handling of substitution analyses reported per kcal/d or g/d

If a study expressed the isocaloric replacement of dietary (macro)nutrients as kcal/d or g/d we calculated the 5% exchange accordingly. The substitution for g/d was transformed into kcal/d by multiplying with specific caloric values for each nutrient (for carbohydrates $f_c = 4kcal$, fat $f_f = 9kcal$, and protein $f_p = 4kcal$), which was then divided by the amount of total energy (mean, kcal/d) in order to establish the value as percentage. Afterwards the percent exchange was calculated to 5%.

For example for Das et al (6) we multiplied the mean of each quintile by the factor 4 (exchange of carbohydrates with protein), and divided each value by 2103 kcal/d, which was the total amount of energy consumed per day. We proceeded by estimating the linear estimate using Greenland and Longnecker method (38).

Quintile	Protein intake (g/d)	Protein intake (kcal/d)	Protein intake (% of total energy)
Quintile 1	72.0	288.2	13.7
Quintile 2	86.4	345.6	16.4
Quintile 3	100.4	401.6	19.1
Quintile 4	115.7	462.8	22.0
Quintile 5	132.7	530.7	25.2

g/d grams/day; kcal/d kilocalories/day

Quintiles of protein intake reported by Das et al. (6). Intakes were calculated as kcal/d and % of total energy intake by multiplying by 4 and dividing by 2103kcal/d, which was the mean of total amount of energy consumed per day.

Supplemental appendix 4: Handling of multiple publications on the same cohort:

If more than one publication reported different treatment comparisons from the same cohort and the comparison did not share any common nodes, we treated them as separate cohort studies. If more than one publication reported different treatment comparisons from the same cohort and the comparison did share a common node, we treated them as a single cohort study for the analyses, but we adjusted the respective weight accordingly. If a study reported a direct comparison, while within another the indirect^a comparison was available, we included the reported comparison. In order to do so, we did not use the calculation of the indirect^a comparison and inflated the variance of the arm by the factor $\frac{\text{number of comparisons}}{\text{number of arms}-1}$. This arises as consequence of the factor being $f = \frac{k}{2}$, where k is the number of arms, when a study reports all relevant comparisons. Since there are $n = \frac{k(k-1)}{2}$ comparisons in a fully connected study, this generalises to $f = \frac{n}{k-1}$. In a second approach both studies are merged to a multi-arm study, by applying the factor $f = \frac{\text{number of joined arms}}{\text{number of reported arms}}$. For example, if a 3-arm study is merged with a 7-arm study we adjust its variances by $\frac{7}{3}$. Since multi-arm studies are adjusted by the netmeta package by a factor $= \frac{k}{2}$, we override this by dividing $\frac{k}{2}$ and afterwards applying the correct factor $f = \frac{k'}{k}$, where k' is the number of the merged multi-arm study. The difference of these approaches is, the calculation of the indirect comparisons is done by the random effects model applied in the final NMA, while in our approach a fixed effect model is used in order to merge two cohort studies of the same cohort to a larger multi-arm study.

^a Note that the term "indirect" in this case, is not the same as the computation of indirect estimates for the NMA. Here, "indirect" refers to a comparison that was available **within** a study. For example, Das et al. (6) reported estimates for the substitution of PRO vs CHO and PRO vs FAT and based on this, the "not reported" effect estimate for the substitution of FAT vs CHO was estimated. The analysis is specified in supplemental appendix 5.

Supplemental appendix 5: Handling of missing or inconsistent risk estimates and variances:

Estimates:

Due to secondary nature of substitution analyses in nutritional epidemiological publications, not every estimate was always provided for all possible comparisons. However, “not reported” estimates are estimated based on the “reported” relative effects within a study. Ideally, a multi-arm study reports consistent effect estimates, where $k-1$ comparisons (k = number of arms) are needed to derive all other possible effect estimates for a given network. These comparisons form a “spanning tree”. In this case excess effects can be dismissed in order to build the design matrix. We proceeded by calculating arm-based study specific effects. For every study, nuisance parameter ie, taking an arbitrary arm as 0, were used. Note that these arm effects are later converted back to contrast-based effects for inclusion into the NMA and thus their values are not relevant to the analysis and are not reported or interpreted. Afterwards the arm-based study specific were merged if required and all relative effects were then included into netmeta for the final NMA.

Whenever more than $k-1$ effects were reported by a study we assessed the consistency by comparing the reported effects with those calculated by the spanning tree. In order to do so, the spanning tree with the maximum precision was selected and residuals between reported and calculated effect were compared. If the residual of the observed effect was higher than 30% and the associated Q value ($\sum residual_i^n weights_i^n$), with $weights_i^n$ being the inverse of the variances of residuals, resulted in a p-value < 0.90 we recorded the cohort study as study with “high residual effect”.

Variances:

Every arm specific effect requires a corresponding variance (ie, there are k arms and k variances).

If a study reports k or more variances for the comparisons and they are consistent, we select the variances corresponding to the $k-1$ arms identified by the spanning tree and add the additional relative variance, which forms a triangle with the spanning tree. After which arm-based variances are established by the design matrix.

In case of inconsistency, the corresponding arm-based variance will be negative and must be dismissed. We proceed as if we only had $k-1$ variances reported and impute the missing value as the maximum variance between the variances of the other two comparisons consisting the respective triangle loop.

In case a study did not report higher-tier contrasts (eg, fat vs carbohydrates, fat vs protein), but did specify lower-tier origin-specific contrasts (eg, SFA vs carbohydrates, MUFA vs carbohydrates, etc), we approximated higher-tier contrast by pooling lower tier contrasts. This way we combined networks 2-7 or 3-7 with network 1 or 2 (original nodes \rightarrow higher-tier node, ie, SFA, MUFA, PUFA, TFA \rightarrow fat). We merged arm-based study-specific effects and variances as a fixed effect meta-analysis and we then converted effects to contrast based study effects which were used in the NMA.

Supplemental appendix 6: Detailed description and decision criteria for each domain in the GRADE assessment

Estimate	Domain	Judgement / explanation
<p>In order to establish the certainty of evidence for each comparison every direct, indirect and network estimate for all comparisons in a network must be evaluated. The guidance is adapted according to Brignardello-Petersen et al. and Izcovich et al. (41, 42).</p> <p>Due to the Risk of Bias evaluation with the ROBINS-E tool the GRADEing starts with a “high” certainty of evidence. Each downgrade leads to a decrease in certainty per one level. After downgrading by three levels, the certainty of the evidence is “very low” and it cannot be graded any lower (43).</p> <p>Threshold choice: Minimally contextualized approach using the null effect (Hazard ratio = 1) as threshold (44) due to the importance of the outcome all-cause mortality on a population level.</p> <p>The assessment of the certainty of evidence was conducted at network level and incorporated always the main nutrients of the network (ie, network 1: CHO vs. PRO). No comparison was graded twice (eg, CHO vs. PRO was graded for Network 1 only).</p>		
<p>Direct estimate</p>	<p>Risk of bias</p>	<p><u>Don't downgrade:</u> More than 2/3 of the studies (and their contributing weight) are rated with low RoB. <i>and</i> No cohort study is rated with high RoB.</p> <p><u>Downgrade by 1 level:</u> Less than 2/3 of the studies are rated with low RoB. <i>and</i> Less than 2/3 of the studies are rated with (very) high RoB, or more than 2/3 of the studies (and their contributing weight) are rated with a high RoB, but the subgroup analysis, excluding studies with a (very) high risk of bias, is robust.</p> <p><u>Downgrade by 2 levels:</u> More than 2/3 of the studies (and their contributing weight) are rated with a high RoB. <i>and</i> The estimate of the subgroup analysis, excluding studies with a (very) high risk of bias, differs from the main analysis, or there is no subgroup analysis.</p> <p><u>Downgrade by 3 levels:</u> More than 1/3 of the studies (and their contributing weight) are rated with a very high RoB. <i>and</i> The estimate of the subgroup analysis, excluding studies with a (very) high risk of bias, differs from the main analysis, or there is no subgroup analysis.</p>

	Inconsistency	<p><u>Don't downgrade:</u> The point estimates indicate a similar direction of effect and the corresponding 95% CI overlap to a high degree. <i>or</i> The point estimates show some heterogeneity, but this can be explained by differences between the studies.</p> <p><u>Downgrade by 1 level</u> The point estimates differ distinctly between studies. <i>and</i> The corresponding 95% CI overlap only minimally or not at all. <i>and</i> The statistical test for heterogeneity shows a low p-value and the I² value is large.</p>
	Indirectness	<p><u>Don't downgrade:</u> The intervention/exposure of the included studies as well as the population studied represents the research question of interest and directly measures outcomes of interest.</p> <p><u>Downgrade by 1 level:</u> The population of included studies differs markedly (in biology and/or physiology) from the population of interest and this could have a substantial impact on the magnitude effect. <i>or</i> The outcome measures are only available as surrogate parameters instead of the outcome intended. <i>or</i> The duration, intensity or modality of the intervention/exposure differs to an extent that the magnitude of effect could be influenced.</p>
	Publication bias	<p><u>Don't downgrade:</u> The funnel plot shows no asymmetry.</p> <p><u>Downgrade by 1 level:</u> The funnel plot shows a substantial asymmetry.</p>
	Overall GRADEing of the direct estimate	The certainty of evidence for the direct estimate can be rated as "high", "moderate", "low" or "very low".
Indirect estimate ^a	Starting point	<p>The most dominant first order loop for the indirect estimate is formed by two direct estimates / has only one additional node. For example the indirect evidence of A vs C is established by A vs B and B vs C (2 arms, additional node = B).</p> <p>If there are more than 1 first order loops the one with the higher number of studies and the lesser inverse variance is chosen.</p>

		The lower rating of the two comparisons forming the most dominant first order loop is the starting point for the evaluation of the indirect estimate.
	Intransitivity	<p><u>Don't downgrade:</u> Differences in the direct comparisons that form the indirect estimate are assumed to be differences relating only to the exposures of interest per each arm. There are probably no effect modifiers which lead to reasonable questioning of the credibility of the indirect estimate.</p> <p><u>Downgrade by 1 level:</u> Effect modifiers vary substantially between the two arms that form the indirect estimate and there is a strong assumption that this has an impact on the credibility of the indirect estimate.</p>
	Overall GRADEing of the direct estimate	The certainty of evidence for the indirect estimate can be rated as "high", "moderate", "low" or "very low", depending on the starting point.
Network estimate	Starting point	The higher rating of the direct and indirect estimate is the starting point for the assessment of the network estimate.
	Incoherence	<p><u>Don't downgrade:</u> The direct and indirect estimates as well as their corresponding 95% CI are coherent. The p-value for the comparison of the indirect and direct evidence is not significant.</p> <p><u>Downgrade by 1 level:</u> The direct and indirect estimates differ beyond chance and this difference cannot be explained. The p-value for the comparison of the indirect and direct evidence is significant.</p>
	Imprecision	<p><u>Don't downgrade:</u> The 95% CI doesn't cross the threshold (RR/HR of 1) and the ratio of the upper to the lower bound of the 95% CI is < 3. <i>or</i> The 95% CI crosses the threshold (RR/HR of 1) however, the 95% CI is narrow and as a result strongly indicates a null effect.</p> <p><u>Downgrade by 1 level:</u> The 95% CI includes a RR/HR of 1 and the 95% CI is not narrow enough (maximal width of 0.05) to justify a null effect.</p> <p><u>Downgrade by 2 levels:</u> The 95% CI includes a RR/HR of 1 and the ratio of the upper to the lower bound of the 95% CI is >3. <i>or</i> There is a large effect (HR/RR <0.5 or >2), the 95% CI doesn't cross the threshold of RR/HR = 1, but the ratio of the upper to the lower bound of the 95% CI is >3.</p>

	OPTION TO UPGRADE	<u>Prerequisite for the option to upgrade:</u> There was no downgrading for inconsistency and there was no downgrading for more than 1 levels for RoB. The direct and indirect estimates are coherent and there was no downgrading for imprecision.
	Dose-response	<u>Option to upgrade by 1 level:</u> The prerequisites are met and the analyses show a consistent dose-response relationship across and within all studies (>50% of studies must report a consistent dose response effect within the study).
	Large effect	<u>Option to upgrade by 1 level:</u> The prerequisites are met and there is a large effect (HR/RR <0.5 or >2) with a narrow 95% CI. <u>Option to upgrade by 2 levels:</u> The prerequisites are met and there is a large effect (HR/RR <0.2 or >5) with a narrow 95% CI.
Overall rating:		The overall certainty of evidence for each comparison can be rated as “high”, “moderate”, “low” or “very low”.

95% CI 95% confidence interval; CHO carbohydrates; GRADE grading of recommendations, assessment, development, and evaluations; HR hazard ratio; PRO protein; RR risk ratio; RoB Risk of bias; ROBINS-E tool Risk Of Bias In Non-randomized Studies - of Exposures tool

^a If the certainty of evidence of the direct estimate is “high” and the direct evidence contributes as much as the indirect evidence there is no need to grade the indirect estimate.

Supplemental appendix 7: List of excluded studies

Reason for exclusion	References
No exposure relevant substitution analysis (n = 675)	(45-294)(295-536)(537-719)
Wrong study design (n = 10)	(720-729)
Reason for exclusion from the present review ^a	References
Wrong outcome (all, n = 189):	(730-918)
<ul style="list-style-type: none"> Cancer (n = 24) 	(740, 752, 758, 762, 766, 776, 777, 797, 799, 804, 811, 817, 829, 844, 847, 854, 855, 861, 873, 878, 889, 890, 892, 918)
<ul style="list-style-type: none"> Cardiovascular disease (n = 51) 	(749, 750, 755, 760, 763, 765, 772, 773, 775, 779, 781, 783, 784, 787-790, 796, 798, 801, 802, 807, 813, 827, 830-835, 839, 845, 846, 850, 857, 866, 869, 872, 876, 877, 882, 887, 888, 894, 897, 903, 904, 908, 909, 912, 913)
<ul style="list-style-type: none"> Type 2 diabetes (n = 34) 	(731, 741, 748, 759, 760, 769, 770, 803, 808-810, 815, 820-822, 836, 838, 841, 848, 849, 851-853, 865, 870, 884-886, 891, 895, 896, 900, 901, 911)
<ul style="list-style-type: none"> Secondary Prevention (n = 20) 	(743-745, 756, 761, 764, 778, 786, 792, 795, 823, 826, 837, 856, 859, 863, 864, 873, 879, 910)
<ul style="list-style-type: none"> Age related outcomes (n = 23) 	(737, 747, 754, 767, 771, 782, 785, 791, 793, 816, 824, 842, 858, 868, 880, 881, 892, 898, 899, 905-907, 917)
<ul style="list-style-type: none"> Adiposity (n = 16) 	(730, 734-736, 738, 746, 780, 800, 812, 814, 825, 828, 843, 867, 874, 914)
<ul style="list-style-type: none"> Other diseases (n = 26) 	(732, 733, 739, 742, 751, 753, 757, 768, 774, 794, 805, 806, 818, 819, 840, 843, 860, 862, 869, 871, 875, 883, 893, 902, 915, 916)

^a References were excluded from the present review if no information on all-cause mortality was available. Some publications reported multiple outcomes.

Supplemental appendix 8: Analytical procedure for UK Biobank study

We were not able to use the published effect estimates from the substitution model by Ho et al. (14), since only the replacement of different nutrients as curves conditional on the current macronutrient intake were presented. Due to access to the raw UK Biobank data (Approved project 75001), we replicated the analysis as linear substitution model expanded for all relevant comparisons. We included participants with at least one complete 24h recall and plausible energy intake (males: >800 kcal/d and < 4200 kcal/d and females: >600 kcal/d and < 3500 kcal/d). An energy partition model was used to evaluate the substitution of different nutrients. In this model the difference between the coefficients for energy intake from substituted nutrients were calculated. The analysis was conducted at 5% energy substitution. Adjustments were conducted in concordance with the original paper by Ho et al. (14) (ie, age, sex, total energy intake, BMI, height, smoking status, daily alcohol and fiber intake, deprivation index, ethnicity, total physical activity, systolic blood pressure, baseline diabetes, and mental health disorders). Data from 208 294 participants with an average follow up of 13.2 years were analyzed (deaths from all-cause mortality was n= 12 611).

Supplemental appendix 9: Deviations from protocol

The systematic review protocol (including all pre-specific inclusion criteria) was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42023450706).

Pre-specified	Conducted	Reason for deviation
The carbohydrate-origin network was planned to contain the nodes: Glucose, fructose, sucrose, starch, fat, protein	The carbohydrate-origin network was analysed as follows: High quality carbohydrates / Polysaccharides, low quality carbohydrates / Mono-/Disaccharides, SFA, MUFA, PUFA, TFA, protein	Due to the limited data availability we were not able to analyze the pre-specified network. However, given the importance of this network, instead we provided an alternative network by classifying carbohydrates as "high quality" (including: complex, starch) to form the node "high quality carbohydrates / polysaccharides" and by classifying carbohydrates as "low quality" (including: sugar, mono-/disaccharides) to form the node "low quality carbohydrates / mono-/disaccharides".

MUFA monounsaturated fatty acids; PUFA polyunsaturated fatty acids; SFA saturated fatty acids; TFA trans-fatty acids;

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