Appendix 2:

Supplementary tables

(posted as supplied by authors)

Contents

eTable 1. Summary of measurement techniques of industrial, total, and ruminant TFA in prospective cohort studies.

3-Star Prospective Cohorts

Study	**Total TFA**	**Ruminant TFA**	**Industrial TFA**	**Isomers**	**CLA included**	**Tissues**		**Cross-validation**	**Database**	**Rating**
						Blood	Adipose	Diet records		
Ascherio et al., 1996 [131-item FFQ]	Yes and validated against adipose	Not measured	Not measured	Not reported	Unclear	No	Yes Hunter et al., 1992	Yes	Harvard University Food Composition Database (updated over time using USDA) supplemented by Slover et al. 1985; and Enig et al 1983 (two publications that tested trans fat composition of foods)	★★★

Study	Total TFA	Ruminant TFA	Industrial TFA	Isomers	CLA included	Tissues		Cross-validation	Database	Rating
						Blood	Adipose	Diet records		
Oh et al., 2005 NHS [131-item FFQ]	Yes	No	No	No	Unclear	No	Yes London et al., 1991	Yes Willett et al, 1985 not specifically for trans fats (0.51 vs. adipose)	USDA handbook no. 8 supplemented by Slover et al. 1985; and Enig et al 1983 (two publications that tested trans fat composition of foods)	★★★
Salmeron et al., 2001	Yes	No	No	No	Unclear	No	Yes London et al., 1991	Yes Willett et al, 1985 not specifically for trans fats (0.51 vs. adipose)	USDA handbook no. 8 supplemented by Slover et al. 1985; and Enig et al 1983 (two publications that tested trans fat composition of foods)	★★★

Study	Total TFA	Ruminant TFA	Industrial TFA	Isomers	CLA included	Tissues		Cross-validation	Database	Rating
						Blood	Adipose	Diet records		
He et al., 2003 HPFS	Yes	No	No	No	Unclear	No	Yes Hunter et al., 1992	Yes	Harvard University Food Composition Database (updated over time using USDA) supplemented by Slover et al. 1985; and Enig et al 1983 (two publications that tested trans fat composition of foods)	★★★
Van Dam et al, 2002 HPFS	Yes and validated against adipose	Not measured	Not measured	Not reported	Unclear	No	Yes Hunter et al., 1992	Yes	Harvard University Food Composition Database (updated over time using USDA) supplemented by Slover et al. 1985; and Enig et al 1983 (two publications that tested trans fat composition of foods)	★★★

Study	Total TFA	Ruminant TFA	Industrial TFA	Isomers	CLA included	Tissues		Cross-validation	Database	Rating
						Blood	Adipose	Diet records		
Song, 2004 WHS	Yes	Not measured	Not measured	Not reported	Unclear	No	Yes Hunter et al., 1992	Yes	Harvard University Food Composition Database (updated over time using USDA) supplemented by Slover et al. 1985; and Enig et al 1983 (two publications that tested trans fat composition of foods)	★★★
Willett et al., 1993 NHS	Yes	Yes	Yes	No	Unsure	No	Yes London et al., 1991	Yes Willett et al, 1985 not specifically for trans fats	USDA handbook no. 8 supplemented by Slover et al. 1985; and Enig et al 1983 (two publications that tested trans fat composition of foods)	★★★
Wang et al., 2015 CHS	Yes	Yes	Yes	Yes	Unsure	Yes	No	Yes Kumanyika et al. 1997; Feskanich et al., 1993	Harvard University Food Composition Database (updated over time using USDA)	★★★

2-Star Prospective Cohorts

Study	**Total TFA**	**Ruminant TFA**	**Industrial TFA**	**Isomers**	**CLA included**	**Tissues**		**Cross-validation**	**Database**	**Rating**
						Blood	Adipose	Diet records		
Oomen et al., 2001 [cross-check diet history] Zutphen Elders	Yes	No	Yes	18:1 and others	No	No	No	Yes, Bloemberg et al. 1989 (but not specifically trans)	TRANSFAIR 1995; Dutch food tables; national data for edible fats analyzed by Wageningen U (1985, 1990, 1995) using GC or I-R spec.	★★
Jakobsen 2007 4 Danish cohorts	No	Yes	No	No	Unclear	No	No	Yes Hoidrup et al. 2002; not specifically for trans fats	R-TFA achieved by combining information on food intake with content of TFA in milk fat and the content of TFA in ruminant animal products; using Denmark Food Tables (1986, 1989)	★★
Virtanen et al., 2014 KIHD	Yes	Not measured	Not measured	Not reported	No	No	No	Yes (0.63 vs. 4-day food record in n=50)	Finnish values of composition of foods	★★

1-Star Prospective Cohorts

Study	Total TFA	Ruminant TFA	Industrial TFA	Isomers	CLA included	Tissues		Cross-validation	Database	Rating
						Blood	Adipose	Diet records		
Pietinen et al., 1997 [276-item FFQ] (ATBC)	Yes and validated against DR	Yes and validated against DR	Yes and validated against DR	Elaidic Validated against DR	Unclear	No	No	Yes Pietinen et al., 1988 (but not specifically trans) but r-value for trans given in 1997 paper	Not stated	★
Meyer et al., 2001 IWHS	Yes	No	No	No	Unclear	No	No	Yes Munger et al., 1992 (with 5x24h recalls) but not specifically for trans fats	Not stated	★
Robien et al., 2011 IWHS	Yes	No	No	No	Unclear	No	No	Yes Vs. 5 x 24-h dietary recall surveys; not specifically trans	Not stated	★
Howard et al., 2006 WHI	Yes	No	No	No	Unclear	No	No	Yes, Patterson et al., 1999 vs. 24h-recalls (x4) and food records (4 d) but not specifically for trans fats	U Minnesota Nutrition coding center	★

Study	Total TFA	Ruminant TFA	Industrial TFA	Isomers	CLA included	Tissues		Cross-validation	Database	Rating
						Blood	Adipose	Diet records		
Simila et al., 2012 ATBC	Yes	Not measured	Not measured	Not reported	Unclear	No	No	Yes Pietinen et al., 1988 (but not specifically trans) but r-value for trans given in 1997 paper	Not stated	★
Meyer et al., 2001 IWHS	Yes	No	No	No	Unclear	No	No	Yes Munger et al., 1992 (with 5x24h recalls) but not specifically for trans fats	Not stated	★

0-Star Prospective Cohorts

Study	Total TFA	Ruminant TFA	Industrial TFA	Isomers	CLA included	Tissues		Cross-validation	Database	Rating
						Blood	Adipose	Diet records		
Xu et al., 2006 [24h recall] Strong Heart Study	Yes	No	No	No	Unclear	No	No	No; only single 24-h recall	NCC Nutrient Database Version 36 (NDS-R 2005)	-
Knekt et al., 2013 FMHC	Yes	No	No	No	Unclear	No	No	Short and long-term reproducibility	Unclear	-

Guide to star Rating

★★★ Validated, Reproducible FFQ (cross-validated) + Measures in adipose tissue or blood + Updated nutrient database

★★ 2 of the above

★ 1 of the above

- None of the above

Assessment of *trans* fat measures

To assess the accuracy of trans fats measures in studies which did not directly measure concentrations in blood or adipose tissues, we assessed the potential for misclassification. The lowest risk of misclassification was for those studies which 1) used a food-frequency questionnaire validated against multiple-day prospective diet records or 24-hour recalls; and 2) directly measured adipose tissue trans-fatty acids in a subset of the population; and 3) analyzed dietary intake using an updated database of foods. A study which accomplished all 3 was rated *** (low risk of misclassification); 2 of 3 ** (moderate risk of misclassification); 1 of 3 * (at risk of misclassification); or 0 of 3 – (high risk of misclassification). For assessment of ruminant trans fats, the most common approach was to use the known nutrient composition from food tables for dairy and meat products to estimate ruminant trans fats, and possibly supplemented by direct measurement using gas chromatography.

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Ascherio et al. 1996 United States Health Professionals' Follow-up Study	40-75	100	43 757	734 Total MI 229 CHD Deaths	6	Mean Saturated Fat Intake *(validated FFQ)*	Q5 vs. Q1 (14.8 to 7.2% E)	Events were self reported and confirmed by medical record review. Deaths confirmed by next of kin, co-workers, postal authorities or the National Death Index.	Age, energy, BMI, smoking habits, alcohol consumption, physical activity, history of hypertension or high blood cholesterol, family history of MI <60-years, profession, dietary fibre	9	National Institutes of Health (USA)
Atkinson et al. 2011 United Kingdom Caerphilly Prospective Study (CaPS)	45-59	100	3 265	225 Strokes	22	Saturated Fat Intake (*validated* SQFFQ)	Q5 vs. Q1 (not reported)	Events were self reported, and supplemented by inspection of hospital and general practitioner notes, radiology records and post-mortem reports, and by further questioning of study participants of close relatives. Two independent experts confirmed the final diagnosis.	Age, total energy, smoking status, adult social class, marital status, alcohol intake, vitamin C intake, vegetable fibre intake, blood pressure, cholesterol, BMI, fasting glucose, diabetes, atrial fibrillation, childhood social class, existing ischemic heart disease	8	National Health Service Executive (UK)
Boniface et al. 2002 United Kingdom	40-75	46	2 676	155 CHD Deaths	16	Mean Saturated Fat Intake (*validated* FFQ)	Q5 vs. Q1 (Men: 8.2 to 7.4% E) (Women: 5.8 to 2.4% E)	Monitoring of death certificates by the Office for National Statistics	Age, alcohol consumption, smoking habits, frequency of exercise, BMI, blood pressure, social class, deprivation index	7	UK Higher Education Funding Council (UK)
de Oliveira et al. 2012 United States MESA Cohort	45-84	~ 50	5 209	316 Cases of CVD 231 CHD Events	10	Median Saturated Fat Intake (*validated* FFQ)	Q5 vs. Q1 (25.30 to 12.20-g/day)	Cardiovascular incidence data was obtained through cohort examinations, follow-up calls, medical record abstractions, or obituaries. Self-reported diagnoses and CVD-related records (death certificates, autopsy reports, and medical records) were reviewed by a medical endpoints committee and deaths for subjects with loss to follow-up was identified by contacting family members.	Energy intake, sex, age, race-ethnicity, field center, education level, active leisure, sedentary leisure, alcohol intake, smoking, BMI, dietary supplement use, cholesterol-lowering medication use, intake of fruits and vegetables, and energy-adjusted intakes of: dietary fibre, vitamin E, trans fat, PUFA	9	University of Texas, Research Institute of Texas, NIH (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Esrey et al. 1996 Canada Lipid Research Clinics	30-79	45 (age 30-59); 53 (age 60-79)	4546	92 CHD death	12	Total saturated fat (*24-hour recall*)	1% increase in SFA intake	Medical record review by independent nosologist	Age, sex, energy intake, serum lipids, SBP, smoking, BMI, glucose intolerance	6	Dairy Bureau of Canada, Health and Welfare Canada
Fehily et al. 1993 United Kingdom Caerphilly Prospective Ischemic Heart Disease Study	45-59	100	2512	148 major IHD events	5	Mean saturated fat intake (7d + validated SQFFQ)	Q5 vs. Q1 (>36.2 to ≤22.3 % E)	Chest pain questionnaire, electrocardiogram, notifications of death from the Office of Population Censuses and Surveys, hospital notes	Age, BMI, smoking habit, presence of IHD at baseline	7	Not Provided
Gillman et al. 1997 United States Framingham Heart Study	45-65	100	832	61 Ischemic Strokes	20	Total Saturated Fatty Acid Intake Intake of Saturated Fat (24h recall)	≈15% E	Reviewed by panel of 3 physician investigators	Age, energy, SBP, smoking, glucose intolerance, BMI, physical activity, LVH, alcohol, fruits and vegetables	7	National Heart, Lung, and Blood Institute (USA)
Goldbourt et al. 1993 Israel	40+	Not provided	11 876	3473 deaths (1098 CHD deaths)	23	Total saturated fat intake (validated short dietary questionnaire for 7-d diet recall)	Q5 vs. Q1 (49/161 to 61/192)	Evaluation of death certificates by research panel, autopsies	Age, presence of initial malignant disease,	7	Not provided
Harding et al. 2004 United Kingdom European Prospective Investigation of Cancer (EPIC) - Norfolk	40-74	Not provided	23 631	414 incident cases of diabetes	3-7	Total saturated fat intake (validated SQFFQ)	Q5 vs. Q1 (16.2 to 9.72 g/day)	Self-report of diabetes, physician-diagnosed diabetes, consumption of diabetes-specific medications, elevated HbA1c level, hospital admissions data, death certificate	Age, total energy intake, sex, family history of diabetes, smoking status, physical activity, protein, alcohol, BMI, waist:hip ratio	8	Cancer research campaign, MRC, Stroke Association, British Heart Foundation, Department of Health, Commission of the European Union's Europe against Cancer Programme, Department for Environment, Food and Rural Affairs (Europe)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
He et al. 2003 United States Health Professionals' Follow-up Study	40-75	100	43 732	725 total stroke; 455 ischemic stroke, 125 haemorrhagic stroke	14	Median intake of saturated fat (validate SQFFQ)	Q5 vs. Q1 (31 to 17 g/day)	Blind record review by MD; fatal stroke reported by next of kin corroborated against national death index	BMI, physical activity, history of hypertension, smoking status, aspirin use, alcohol, dietary potassium, dietary fiber, dietary vitamin E, fruits and vegetables, total energy intake, hypercholesterolemia at baseline, polyunsaturated, monounsaturated, and saturated fat	7	National Institutes of Health (USA)
Howard et al. 2006 United States Womens' Health Initiative Randomized Controlled Dietary Modification Trial	50-79	0	31 258	146 major CHD events	1	Total saturated fat intake (validated FFQ)	Intervention vs. Control (8.1 to 11.8 % E)	Medical update questionnaire, analysis of medical records of all overnight hospitalisations, analyzed by physicians	Age, baseline CHD, HRT, randomization, BMI, hypertension, dyslipidemia, smoking, diabetes, physical activity, energy expenditure, ethnicity, education, income, psychological stress	8	National Heart, Lung and Blood Institute (USA)
Hu et al. 1997 United States Nurses' Health Study	34-59	0	80 082	939 events (658 non-fatal MI, 281 deaths)	14	Total intake of saturated fats (validated SQFFQ)	Q5 vs. Q1 (18.8 to 10.7 % E)	Review of medical records by study physicians, interviews and letters for confirmation of hospitalization. Death confirmed by National Death Index, next of kin or postal system	Age, time period, BMI, smoking, menopausal status, parental history of MI before 65 years, multivitamin use, vitamin E supplementation, alcohol consumption, history of hypertension, aspirin use, vigorous exercise, percent energy from protein, total energy intake, dietary cholesterol	9	National Institute of Health (USA)
Hu et al. 1999 United States Nurses' Health Study	34-59	0	80 082	939 incidence cases of major CHD	14	Median saturated fat intake (validated FFQ)	Q5 vs. Q1 (17.2 to 9.5 % E)	Review of medical records by study physicians, interviews and letters for confirmation of hospitalization. Death confirmed by National Death Index, next of kin or postal system	Age, time period, BMI, smoking, menopausal status, parental history of MI before 60 years, vitamin E supplement use, alcohol consumption, history of hypertension, aspirin use, vigorous exercise, monounsaturated fats, polyunsaturated fats, trans fats, protein, dietary cholesterol, total energy	9	National Institute of Health (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Jakobsen et al. 2004 Denmark 1914 & 1936 cohorts, MONICA I, MONICA III	30-71	50	3 686	326 fatal or non-fatal CHD events	16	Percent energy intake from Saturated fats (*validated* 7-day weighted food record)	Men: 24.8 vs. 14.5 Women: 24.8 vs. 14.1	Identified by record linkage to the National Patient Registry (includes references for all hospitalizations), Cause of Death Registry	Energy intake, cohort identification, % energy derived from protein or other major types of fatty acids, familial history of MI, smoking, physical activity, educational attainment, alcohol consumption, dietary fibre, dietary cholesterol, systolic blood pressure, BMI,	8	Danish Heart Foundation, Danish Medical Research Council (Denmark)
Jakobsen et al. 2010 Denmark Diet, Cancer and Health Cohort Study	50-64	47	53 644	1943 incident MI	12	Mean saturated fat intake (validated SQFFQ)	Increased in HR for MI with each 5% increase in SFA	Identified by record linkage to the National Patient Registry (includes references for all hospitalizations), Cause of Death Registry	Glycemic carbohydrates, proteins, MUFA & PUFA (as % of total energy intake), total energy intake, alcohol consumption, BMI, education, smoking status, physical activity, history of hypertension	7	European Commission, Danish Council for Strategic Research (EU, Denmark)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Leosdottir et al. 2007 Sweden Malmo Diet and Cancer Study	≈59	39	28 098	908 acute coronary events; 648 ischemic strokes	8.4	Total saturated fatty acids *(7-day diary + FFQ)*	M: 20.9 vs 12.7% W: 21.3 vs 12.8%	Local and national registries	Age, smoking, alcohol, SES, marital status, physical activity, BMI, fiber, blood pressure	7	Swedish Scientific Council; Swedish Cancer Foundation ; Anna Jonssons Memorial Fund; Swedish Heart and Lung Foundation , Region of Skåne (Sweden) European Commissio n (Europe)
Leosdottir et al. 2005 Sweden Malmo Diet and Cancer Study	≈59	39	28 098	1250 deaths (339 from CVD)	6.6	Total saturated fatty acids (7-day diary + FFQ)	Q4 vs. Q1 (M: 44.6 to. 40.1 % E) (F: 45.3 to 41.2 % E)	Local and national registries	Age, alcohol, smoking, social class, marital status, physical activity, BMI, fibre intake, monounsaturated and polyunsaturated fats, total fat intake for ratio between unsaturated and saturated fats	7	Swedish Scientific Council; Swedish Cancer Foundation; Anna Jonssons Memorial Fund; Swedish Heart and Lung Foundation, Region of Skåne (Sweden) European Commission (Europe)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Lindstrom et al. 2006 Finland Diabetes Prevention Study	55	33	522	Incident cases of diabetes (75 in intervention, 110 in control)	7	Reductions in saturated fats to <10% energy	Intervention: 13% E Control: 15% E, proportion of saturated fat	Diagnosis with diabetes based on a second oral glucose tolerance test	Adjustment for baseline level, levels at last visit, treatment group, study centre, sex, age, and baseline 2-h post-challenge plasma glucose concentration	5	Academy of Finland, Joho Vainio Foundation, Ministry of Education, Novo Nordisk Foundation, Yrjo Jahnsson Foundation, Finnish Diabetes Research Foundation, Kuopio and Oulu Hospitals (Finland)
Mann et al. 1997 United Kingdom	16-79	38	10 802	456 deaths (64 IHD, 392 all cause mortality)	13.3	Total saturated fat intake (SQFFQ)	Q3 vs. Q1 (M: 41 to 14.6 g/day) (F: 38.1 to 13.7 g/day	Review of death certificates	Age, sex, smoking habit, social class	6	Not stated
McGee et al. 1985 United States Honolulu Heart Program	45-60+	100	7 088	542 total deaths; 61 stroke deaths; 99 CHD deaths	10	Total saturated fat (*24-hour recall*)	≥50 g vs. <10 g, but also continuous	Physician panel review	Age, SBP, BMI, physical activity, cigarettes smoked	6	Not stated
Meyer et al. 2001 United States Iowa Women's Health Study	55-69	0	35 988	1890 incident cases of diabetes	11	Median intake of saturated fatty acids (validated FFQ)	Q5 vs. Q1 (86.6 to 55.7 g/day)	Survey asking if participant had been diagnosed with diabetes by a physician, for the first time	Age, total energy, waist-to-hip ratio, BMI, physical activity, smoking, alcohol consumption, education, marital status, residential area, hormone replacement, fat subtypes, dietary protein, dietary magnesium, cereal fibre, vitamin E, vegetable fat, dietary cholesterol	6	National Cancer Institute (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Oh et al. 2005 United States Nurses' Health Study	30-55	0	78 778	1766 incident cases of CHD (1241 non-fatal MI, 525 CHD deaths)	20	Total saturated fatty acids (*validated FFQ*)	Q5 vs. Q1 (17.6 to 10.1 median % energy)	Self-reported non-fatal MI, confirmed with review of medical records. Fatal CHD was confirmed by hospital records or autopsy or if CHD was listed as cause of death on the death certificate.	Age, BMI, smoking, alcohol intake, parental history of MI, history of hypertension, menopausal status, hormone use, aspirin use, multivitamin use, vitamin E supplement use, physical activity, energy, protein, cholesterol, intakes of monounsaturated, polyunsaturated, *trans*-fat, α-linoleic acid, marine n-3 fatty acids, cereal fibre, fruits and vegetables.	9	National Institutes of Health (US)
Pietinen et al. 1997 Finland Finish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	50-69	100	21 930	1399 major coronary events (first non-fatal MI), 635 coronary deaths	6	Median saturated fatty acid intake (*validated* FFQ)	Q5 vs Q1 (67.5 to 34.7-g/day)	National hospital discharge registered diagnosis and obtained hospital and pathology reports; deaths confirmed through national population register	Age, treatment group, smoking, BMI, blood pressure, energy, alcohol, fibre, education, physical activity	8	National Cancer Institute (USA), Academy of Finland
Posner et al. 1991 United States Framingham Study	45-65	100	813	213 CHD	16	Total saturated fatty acid intake (24h recall)	15.2 vs. 10% SFA (age 45-55), 14.8 vs. 10% SFA (age 56-65)	Reviewed by a panel of three investigators. Clinical examinations were used to diagnose MI	Total energy intake, heart rate, systolic blood pressure, serum total cholesterol level, glucose intolerance, number of cigarettes smoked per day, left ventricular hypertrophy, physical activity, Metropolitan relative weight	8	National Heart, Lung, and Blood Institute (USA)
Salmeron et al. 2001 United States Nurses' Health Study	34-59	0	84 204	2507 incident cases of T2DM	14	Median intake of saturated fatty acids (validated SQFFQ)	Q5 vs. Q1 (18.8 to 10.7 %E)	Follow-up questionnaire asking for incident cases of diabetes, supplementary questionnaire for new cases and confirmed by review of medical records. Deaths identified from state vital records, National Death Index, or were reported by next of kin, and postal system	Age, BMI, time period, smoking, parental history of diabetes, alcohol consumption, physical activity, percentage of energy from protein, total energy intake, dietary cholesterol	9	National Institutes of Health (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Sauvaget et al. 2004 Japan Adult Health Study (subcohort of the Life Span Study)	35-89	38	3731	90 stroke deaths (60 from cerebral infarction)	14	Mean saturated fatty acid intake (24h dietary recall)	Q3 vs Q1 (21 to 7 g/day)	Events were determined by analysis of nationwide family registration system of Japan and by obtaining copies of death certificates	Radiation dose, city of exposure, smoking and drinking status, BMI, history of hypertension and diabetes, fruit and vegetable intake, markers of nutritional status, lymphocyte count, blood cholesterol level, total energy intake, weight	5	Radiation Effects Research Foundation, Japanese Ministry of Heath, Labour and Welfare (Japan) US Departmen t of Energy (USA)
Simila et al. 2012 Finland Finish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	50-69	100	25 943	1098 incident diabetes cases	12	Median saturated fat intake (validated FFQ)	Q1 vs. Q5 (44.8 to 36.1 % E)	Incident cases of diabetes were identified from the drug reimbursement register	Age, energy, intervention group, BMI, smoking, physical activity, coffee consumption, alcohol, protein (replacement of fat) and vice versa, other macronutrient subgroups (TFA, MUFA, PUFA)	8	US Public Health Service contracts, National Cancer Institute (USA) Academy of Finland
Song et al. 2004 United States Women's Health Study	≥45	0	37 309	1558 incident cases of T2DM	8.8	Median saturated fat intake (validated SQFFQ)	Q5 vs. Q1 (25.8 to 13.8 g/day)	Annual follow-up to determine new diagnoses of T2DM, supplemental questionnaire, contact with primary care physician.	Age, BMI, total energy intake, smoking, exercise, alcohol use, family history of diabetes, fibre intake, glycemic load, magnesium, total fat	7	National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Tanasescu et al. 2004 United States Nurses' Health Study	50-75	0	5 672	619 cases of CVD (268 non-fatal MI, 183 fatal MI, 168 strokes)	~10	Median saturated fat intake (validated FFQ)	Q5 vs. Q1 (19.1 to 10.8 % E)	Self-reported MI confirmed by physician review of medical records. Deaths were reported by next of kin, work associates, postal authorities, or National Death Index	Age, smoking, postmenopausal hormone use, parental history of MI before 60y, alcohol intake, physical activity, BMI, total caloric intake, protein intake, fibre intake, multivitamin use, vitamin E supplement use, medication use	8	NIH (USA)
Tucker et al. 2005 United States Baltimore Longitudinal Study of Aging	34-80	100	501	71 deaths from CHD	18	Mean saturated fat intake, as percent of total dietary intake (7-d diet record)	Survivors: 12.3% CHD Deaths: 13.8% Non-CHD Deaths: 14.0%	Consensus of three physicians using death certificates, hospital records, and/or autopsy data.	Age at first visit, total energy intake, BMI, smoking, alcohol use, dietary supplements, physical activity	8	US Department of Agriculture Agricultural Research Service, NIH National Institute on Aging Intramural Program (USA)
van Dam et al. 2002 United States Health Professionals' Follow-up Study	40-75	100	42 504	1321 incident cases of T2DM	12	Median saturated fat intake (validated FFQ)	Q5 vs. Q1 (14 to 7.6 % E)	Supplementary questionnaire provided to any new diagnoses of diabetes, validated by blinded physician	Age, total energy intake, time period, physical activity, smoking, alcohol consumption, hypercholesterolemia, hypertension, family history of type 2 diabetes, cereal fibre, magnesium, BMI	8	National Institute of Health (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Wu et al. 2011 United Sates Cardiovascular Health tudy	≥65	37	2 890	631 CHD events, 61 sudden cardiac arrest events	7	Mean saturated fatty acid intake (particularly palmitic) (validated SQFFQ)	~ 25.3 (23.5-27.5)	Determined by a centralized morbidity and mortality committee	Total energy, age, sex, race, education, income, smoking status, prevalent diabetes, hypertension, stroke, transient ischemic attack, BMI, physical activity, alcohol use, total fat intake, phospholipid concentrations of long-chain n-3 fatty acids and trans FAs, systolic BP, fasting HDL cholesterol, LDL cholesterol, triglycerides, C-reactive protein, fibrinogen, incident angina, phospholipid concentration of 14:0	9	National Heart, Lung and Blood Institute, NIH Office of Dietary Supplements National Institute of Neurological Disorders and Stoke (USA)
Xu et al. 2006 United States Strong Heart Study	45-74	36	2 938	436 incident CHD (298 non-fatal CHD, 138 fatal CHD)	7	Total saturated fatty acid intake (24-hour recall)	47-59 y: 12.2 vs. 1.7% E 60-79 y: 11.7 vs. 11.1% E	CHD events during the follow-up period were ascertained from annual mortality and morbidity surveillance or at the third examination. Fatal CHD events were confirmed by medical records.	Sex, age, study, center, diabetes, BMI, HDL-C, LDL-C, triacylglycerol, smoking, alcohol, hypertension, dietary protein, total energy	7	National Heart, Lung and Blood Institute (US)
Yaemsiri et al. 2012 United States Womens' Health Initiative	50-79	0	87 025	1,049 ischemic stroke, 101 atherosclerotic stroke, 269 lacunar stroke, 244 cardioembolic stroke	7.6	Median intake of saturated fatty acids (validated FFQ)	Q5 vs. Q1 (26.1 to 12.9 g/day)	Self report; adjudicated by local physicians and centrally by trained neurologists	Age, race, education, income, smoking, HRT use, physical activity, alcohol, history of CHD, history of A. Fib, history of diabetes, aspirin use, use of antihypertensives, use of cholesterol-lowering medication, BMI, SBP, total energy, vitamin E, fruits and vegetables intake, fiber	8	National Heart, Lung, and Blood Institute (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Yaemsiri et al. 2012 United States Womens' Health Initiative	50-79	0	87 025	1,049 ischemic stroke, 101 atherosclerotic stroke, 269 lacunar stroke, 244 cardioembolic stroke	7.6	Median intake of saturated fatty acids (validated FFQ)	Q5 vs. Q1 (26.1 to 12.9 g/day)	Self report; adjudicated by local physicians and centrally by trained neurologists	Age, race, education, income, smoking, HRT use, physical activity, alcohol, history of CHD, history of A. Fib, history of diabetes, aspirin use, use of antihypertensives, use of cholesterol-lowering medication, BMI, SBP, total energy, vitamin E, fruits and vegetables intake, fiber	8	National Heart, Lung, and Blood Institute (USA)
Yamagishi et al. 2013 Japan Japan Public Health Center-based (JPHC) Prospective Study	45-74	46	81,931	3192 incident strokes (610 MI, 116 sudden cardiac deaths)	11.1	Median saturated fatty acid intake (validated FFQ)	Q5 vs. Q1 (24.9 to 9.6 g/day)	Physicians in hospitals, or study investigators reviewed the medical records of participants that required hospitalisation	Total energy intake, age, sex, cohort, baseline BMI, smoking, alcohol intake, sports in leisure time, walking and standing time, perceived mental stress, employment status, energy-adjusted intakes of carbohydrate, cholesterol, vegetables, fruit, calcium	7	Ministry of Health, Labour, and Welfare of Japan, Ministry of Education, Culture, Sports, Science, and Technology Japan
Yamagishi et al. 2013; U.S.A.; Atherosclerosis Risk in Communities (ARIC) Study	45-64	48	3,870	168 ischemic strokes	20	Total saturated fat, isomers (CE and PPL)	Q4 vs. Q1	Calls to participants, review of hospital discharge lists, death certificates; physician-adjucated using National Survey of Stroke criteria	Age, sex, smoking, alcohol [also considered BMI, education, sports index, HRT use, energy intake, fish oil use	7	National Heart, Lung, and Blood Institute (USA), National Institutes of Health (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Wang et al. 2003 United States Atherosclerosis Risk in Communities (ARIC) Study	45-64	47	2 909	252 incident cases of diabetes	9	Plasma fatty acid concentration (for palmitic and stearic acid)	Incident diabetes: 12% E No diabetes: 11.6% E	Incident diabetes was identified during follow-up visits, or diagnosed by physician after baseline	Age, sex, baseline BMI, waist-to-hip ratio, alcohol intake, smoking, physical activity, education, parental history of diabetes	7	National Heart, Lung, and Blood Institute
Wiberg et al. 2006 Sweden Uppsala Longitudinal Study of Adult Men	≥50	100	2313	421 stroke or transient ischemic attack	32	Measured with fatty acid principle component (FPAC) for mean SFAs	Myrstic Acid: 1.2 (ICH) vs. 1.1 (no count) Palmitic Acid: 11.8 (ICH) vs. 11.7 (no count) % E	Swedish hospital discharge record and cause-of death registries	hypertension, diabetes, metabolic syndrome, serum cholesterol, atrial fibrillation, cardiovascular disease, smoking, physical activity, treatment with cardiovascular drugs at baseline, treatment with antihypertensive or antidiabetic medications or lipid-lowering drugs,	5	Medical Faculty at Uppsala University, the Uppsala Geriatric Fund, Swedish Heart Lung Foundation
Wu et al. 2011 United Sates Cardiovascular Health Study	≥65	37	2 890	631 CHD events, 61 sudden cardiac arrest events	7	Mean saturated fatty acid intake (stearic acid) (validated SQFFQ)	~ 13.4 (1.1)	Determined by a centralized morbidity and mortality committee	Total energy, age, sex, race, education, income, smoking status, prevalent diabetes, hypertension, stroke, transient ischemic attack, BMI, physical activity, alcohol use, total fat intake, phospholipid concentrations of long-chain n-3 fatty acids and trans FAs, systolic BP, fasting HDL cholesterol, LDL cholesterol, triglycerides, C-reactive protein, fibrinogen, incident angina, phospholipid concentration of 14:0	9	National Heart, Lung and Blood Institute, NIH Office of Dietary Supplements National Institute of Neurological Disorders and Stoke (USA)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Misirli et al. 2012 Greece European Prospective Investigation into Cancer and Nutrition (EPIC Study), Greek-EPIC Cohort	25-67	41	23 601	395 incident cases, 196 deaths from cerebrovascular diseases	10.6	Mean saturated fatty acid consumption (validated FFQ)	29.5 g/day with 12 g/day increments	Endpoint confirmed through medical records, nonfatal first events or through death certificates (for fatal events)	Sex, age, smoking status, BMI, education, physical activity level, energy intake, hypertension, diabetes mellitus, Mediterranean diet score	8	Stavros Niarchos Foundation , Hellentic Health Foundation (Greece)
Schoenaker et al. 2012 EURODIAB Prospective Complications Study (Multiple – Across Europe)	15-60	51	2 108	148 fatal and non-fatal CVD incident cases, 46-all cause death	7.4	Median saturated fat intake (validated 3d dietary record)	Q3 vs. Q1 (45.4 to 28.6 g/day)	Events determined using questionnaires, hospital records, death certificates, or other healthcare documents	Age, sex, energy, diabetes duration, HbA1c, smoking status, physical activity, alcohol, total dietary fibre, MUFA, PUFA, antihypertensive use, daily insulin dose and frequency	7	Welcome Trust, European Community and Diabetes UK, Gesellschaf t der Freunde und Forderer of Heinrich-Heine-University (Germany)
Schulze et al. 2008 Germany European Prospective Investigation into Cancer and Nutrition (EPIC Study), EPIC-Potsdam	35-65	39	25 067	844 incident cases of T2DM (physician-diagnosed)	7	Total saturated fat consumed (validated SQFFQ)	Q5 vs. Q1 of quintiles of carbohydrate intake (% energy) (M: 35.4 to 45.8 % E) (F: 32.6 to 42.9 %E)	Self-reports of diabetes diagnosis, diabetes-relevant medication or dietary treatment due to diabetes. Questionnaires were sent to diagnosing physician , only physician-diagnosed cases were included	Age, education, occupational activity, sport activity, cycling, smoking, alcohol intake, total energy intake, fibre intake, magnesium intake, PUFA:SFA ratio and MUFA:SFA ratio	8	Federal European Union, German Cancer Aid, Ministry of Science (Germany)

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Trichopoulou et al. 2006 Greece European Prospective Investigation into Cancer and Nutrition (EPIC Study), Greek-EPIC Cohort	NR	42	1013	80 deaths (46 CVD deaths, 19 from cancer, 15 from other causes)	4.5	(validated, interview-administered FFQ)	M: 28 g/day W: 23 g/day	Not mentioned	Gender, age, educational level, smoking, waist-to-height, hip circumference, physical activity, metabolic activity task score, total energy intake, treatment with insulin, treatment for hypertension at enrolment, treatment for hypercholesterolaemia at enrolment, flour, flakes, starches, pasta, rice, other grain, bread, crisp bread, rusks, breakfast cereals, biscuit, dough, pastry	8	Europe Against Cancer Program (EU), Greek Ministries of Health and Education
Seino et al. 1997 Japan Shibata Study	≥40	42	2283	460 deaths (141 from stroke)	15.5	Mean saturated fatty acid intake (validated SQFFQ)	Q4 vs. Q1 (15.4 to 7.2 g/day)	Annual follow-up examination and registration system where general practitioners, public health nurses, and ambulance personnel would notify the study of possible stroke patients. Death certificates, social insurance records and medical records of the clinics and hospitals were also reviewed periodically	Age, sex, diastolic blood pressure, atrial fibrillation; total fat adjusted intake of a specific type of lipid, total energy adjusted intake of total fat and total energy	7	Not reported
Kromhout et al. 2000 Finland, Italy, Greece, former Yugoslavia, Japan, USA, Netherlands Seven Countries Study	40-59	100	12 763	5973 deaths	25	Saturated fat intake (weighted record)	Multiple comparisons possible	Vital status established by Blackburn and/or Menotti	Age. Smoking, alcohol intake,	7	Netherlands Nutrition Foundation

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Alhazmi et al., 2013; Australia Longitudinal Study on Women's Health	45-50	0	9 101	311 incident cases	6	Saturated fat intake (Dietary Questionnaire for Epidemiological Studies; DQES)	Q5 vs. Q1	Self-reported t2dm; validated by linkage to Medicare (MBS) and Pharmaceutical Benefits Service (PBS)- 70% confirmed	Area of residence, education, current smoking, physical activity, self-rated health, menopausal status, BMI, alcohol, total energy, fibre, other fats	6	Australian Government Department of Health and Ageing
Chien et al., 2013; Japan (Chin-Shan)	≈60	47	3,602	568 deaths; 275 CVD events	≈10	Total saturated-fatty acids (Plasma)	56.3% vs. 45% of total fat	Official death certificates verified by house-to-house visits	Age, gender, BMI, smoking, drinking, marital status, education level, job and sports activity, hypertension, diabetes, LDL-C and HDL-C	7	National Science Council; National Taiwan University (Taiwan)
Wakai et al., 2014; Japan (JACC)	≈56	39	58,672	11,656 deaths; 1,665 CV deaths	19.3	Total saturated fat (validated SQFFQ)	7.3 vs. 3.0% E	Population registries (mandatory reporting); causes of death from death certificates	Age, area, education, smoking, alcohol, BMI, sleep duration, walking, F&V, total energy	8	Ministry of education, science, sports, culture of Japan; Japanese Ministry of Education, Culture, Sports, Science, and Technology, National Cancer Center Research Development Fund
Shekelle et al., 1981; U.S.A. (Western Electric Study)	40-55	100	1,900	215 CHD deaths	19	Total saturated fat (Burke diet history)	1-unit increase	Death certificats for all decedants reviewed and adjudicated according to ICD-8	Age, SBP, smoking, serum cholesterol, alcohol, BMI, ancestry	6	American and Chicago Heart Associations; private donors; National Cancer Institute
Kushi et al., 1985; U.S.A.-Ireland (Ireland-Boston Heart Study)	40-60	100	1,001	110 CHD deaths	23	Total saturated fat (Burke diet history)	Top 3rd vs. Bottom 3rd	Death certificates for all decedants reviewed and adjudicated according to ICD-9	Age, cohort, SBP, serum cholesterol, LVH, smoking, alcohol	6	NIH, Irish Heart Foundation, Harvard School of Public Health

eTable 2. Characteristics of included prospective cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)	Sex (% Men)	Number of Participants	Number of Events	Follow-up (years)	Exposures Assessed	Exposure Contrast	Outcome validation	Adjustment for confounders	NOS Score	Funding
Virtanen et al., 2014; Finland (Kuopio Ischemic Heart Disease Risk Factor Study)	42-60	100	1,981	183 fatal and 382 non-fatal CHD events	21.4	Total saturated fat (4-day prospective diet record)	Q4 vs. Q1 (22.8% vs. 13.4%)	Link to national death registry; adjudicated according to ICD-9	Age, examination year, energy intake, BMI, diabetes, hypertension, family history of CHD, pack-years of smoking, education, leisure-time physical activity, alcohol, fiber, % energy from protein, other fatty acids	9	University of Eastern Finland
Mahendran et al., 2014; Finland (METSIM Cohort)	45-73	100	735	30 incident type 2 diabetes cases	5	Erythrocyte fatty acids (total saturated and isomers)	1-unit increase	Some cases (23/30) diagnosed by OGTT at 5-y mark (remaining 7 unclear)	Age, BMI, smoking, physical activity, Matsuda insulin-sensitivity-index,	6	Academy of Finland, Institute of Biomedicine Physiology, Institute University of Eastern Finland, Kuopio University Hospital, Finnish Diabetes Research Foundation
De Goede et al., 2014; Netherlands (Zutphen Elderly Study)	65-85	100	686	132 incident CHD events	15	Total and food sources of saturated fat (*Cross-check diet history method*)	T3 vs. T1 (21.7 vs. 14.2%)	Municipal population registries and hospital or GP records	Age, smoking, BMI, physical activity, socioeconomic status, alcohol, total energy, carbohydrates, protein, MUFA, trans fats, dietary fibre	8	National Cancer Institute (U.S.), Academy of Finland

eTable 3. Characteristics of included nested case-control, and case-cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)[1]	Sex (% Men)[2]	Number of Cases/Controls	Case definition	Control definition	Follow-up (y)	Exposures Assessed	Exposure Contrast	Case assessment	Adjustment for confounders	NOS Score	Funding
Clarke et al. 2009 (Whitehall; nested case-control)	79 (5)	100	116/239 [1:2]	CHD deaths in individuals with no history of CVD at baseline	Participants in Whitehall with no history of CVD or statin use	30	Phosholipid fatty acids (16:0, 18:0, total SFA)	46.1% vs. 41.5% (4.6%) total SFA	Identified from Office for National Statistics	Age, employment grade, SBP, BMI, smoking, diabetes, apo A, HDL-C, apo-B, LDL-C, CRP, fibrinogen, albumin	6	British Heart Foundation(UK), Medical Research Council (UK), Fisheries Scholarship Grant, National Fisheries Institute (USA)
Hodge et al. 2007 (Melbourne Collaborative Cohort Study; prospective case-cohort)	58/55	51/43	346/3391 [1:10]	Self-reported type 2 diabetes	Randomly sampled from the cohort	4	Dietary saturated fat (total, 15:0, 16:0, 18:0), phospholipid fatty acids (total, 15:0, 16:0, 18:0)	Q5 vs. Q1 (not stated)	confirmed by family physician	Age, sex, country of birth, family history of DM, physical activity, alcohol, BMI, WHR	8	VicHealth, Cancer Council VIctoria, National Health and Medical Research Council (Australia)
Kröger et al. 2011 (EPIC-Potsdam; prospective case-cohort)	55/50	58/39	673/2114 [1:3]	Self-reported t2dm during follow-up	Random sample; representative of cohort at baseline	7	Erythrocyte fatty acids (14:0 to 18:0; 20:0 to 24:0, total SFA); also dietary fatty acids (14:0 to 20:0, 22:0; total SFA) by FFQ	Erythrocyte membrane FA (Q5 v Q1) [% total] 14:0 – 0.57 v. 0.23% 15:0- 0.32 v. 0.13% 16:0- 25.6 v. 19.8% 17:0-0.41 v. 0.26% 18:0- 15.1 v. 12.2% 20:0 0.52 v. 0.30% 21:0-0.07 v. 0.02% 22:0-2.15 v. 1.16% 23:0-0.39 v. 0.19% 24:0- 5.6 v. 3.1% Dairy: 0.71 v. 0.41% Total: 48.6 v. 41.2%	Self report; confirmed by interview with diagnosing physician	Age, sex, BMI, waist, cycling, sports activity, education, coffee intake, smoking, alcohol intake, occupational activity, fiber	8	Federal Ministry of Science, German Cancer Aid, German Research Foundation (Germany); European Community

[1] If a single number presented, represents mean age of all participants; if "x/y" then this is mean age of cases/controls

[2] If a single number presented, represents percentage of all participants who were men; if "x/y" then this percentage of cases/controls who were men

eTable 3. Characteristics of included nested case-control, and case-cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)[3]	Sex (% Men)[4]	Number of Cases/Controls	Case definition	Control definition	Follow-up (y)	Exposures Assessed	Exposure Contrast	Case assessment	Adjustment for confounders	NOS Score	Funding
Simon et al. 1995 (MRFIT; nested case-control; USA)	35-57	100	94/94 [1:1]	Men with fatal or non-fatal MI or sudden cardiac death	"Usual care" group subjects matched on age, randomization date, center	6.9	Cholesterol ester FA and phospholipids (14:0, 16:0, 18:0)	Per 1 standard deviation increase in % CE or PPL	Clinic, hospital records, next-of-kin interviews, death certificats, autopsy reports	Plasma cholesterol levels, DBP, tobacco use	7	National Heart, Lung, and Blood Institute (USA)
Sun et al. 2007 (Nurses' Health Study; USA; nested case-control)	30-55	0	166/327 [1:2]	Ischemic Heart Disease	From cohort, matched on age, smoking, fasting status, date of blood draw	6	Plasma and erythrocyte fatty acids (14:0, 15:0, 16:0, 17:0, 18:0); diet (14:0; 16:0)	T3 vs. T1 (%) [plasma] 15:0-> 0.21 vs. 0.11% 17:0-> 0.36 vs. 0.25% T3 vs. T1 (%) [erythrocyte] 15:0-> 0.14 vs. 0.07% 17:0-> 0.40 vs. 0.29%	Self reported; confirmed by medical record review by blinded study physicians	Age. date of blood draw, smoking, fasting status, BMI, post-menopausal status, physical activity, alcohol, aspirin, family history of MI, hypertension, hypercholesterolemia, history of diabetes, total *trans* fatty acids	9	National Institutes of Health (USA)
Matthan et al., 2014 (WHI-OS); nested case-control	67.8	0	1224/1224 [1:1]	CHD (hospitalized myocardial infarction [MI], definite silent MI, and coronary death defined as death consistent with CHD as the underlying cause	Selected from cohort without CVD, matched on age, date of enrollment, race/ethnicity, hysterectomy status at baseline	4.5	Total saturated fat, 12:0, 14:0, 15:0, 16:0, 18:0, 20:0, 22:0, 24:0 *(plasma PPL)*	Per SD	review of medical records and death certificate	Age, enrollment date, race/ethnicity, hysterectomy status, BMI, SBP, smoking, education, medication use, HRT use, carbohydrate, protein, and alcohol	8	

[3] If a single number presented, represents mean age of all participants; if "x/y" then this is mean age of cases/controls

[4] If a single number presented, represents percentage of all participants who were men; if "x/y" then this percentage of cases/controls who were men

eTable 3. Characteristics of included nested case-control, and case-cohort studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age (years)[5]	Sex (% Men)[6]	Number of Cases/Controls	Case definition	Control definition	Follow-up (y)	Exposures Assessed	Exposure Contrast	Case assessment	Adjustment for confounders	NOS Score	Funding
Salonen et al. 1985 (Finnish Heart Study; nested case-control)	55/54	76	92/92 [1:1]	CHD deaths	From cohort; matched on age, smoking, sex, cholsterol BP	5	Serum FA (total PUFA, total SFA)	Serum polyunsaturated/saturated FA ratio >0.28 vs. ≤0.28	National death certificate register; cause of death was that assigned by Central Statistical Office	Age. smoking, sex, cholesterol, BP, strong alcoholic beverages, absenteeism, diabetes, history of MI/angina in parent or sibling, cardiovascular medication, study area	6	Not stated
Pierucci et al. 2012 (nested case-control; ONCONUT, Italy)	67	62	97/194 [1:2]	Self-reported cases of MI	Randomly sected from cohort; matched on diabetes, gender, age	5	Dietary SFA (*validated FFQ*)	Q3 vs. Q1	Confirmed by discharge hospital records and ECG	Energy, age, gender, BMI, smoking, hypertension	7	Not stated
Forouhi et al.; Europe; EPIC InterAct (*case-cohort*)	52±9		12,132/15,919 [1:1]	self-reported incident diabetes data	Randomly selected noncases	16	Total SFA, 14:0, 15:0, 16:0, 17:0, 18:0, 20:0, 22:0, 23:0, 24:0 (*plasma PPL*)	Per 1-SD difference	linkage to primary care registers, secondary care registers, medication use (drug registers), hospital admissions, and mortality data	Age, centre, sex, physical activity, smoking, education, total energy, alcohol, BMI, meat, fruits and vegetables, soft drinks, total dairy products, HbA1c	8	European Union

[5] If a single number presented, represents mean age of all participants; if "x/y" then this is mean age of cases/controls

[6] If a single number presented, represents percentage of all participants who were men; if "x/y" then this percentage of cases/controls who were men

eTable 4. Characteristics of included retrospective case-control studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age	Sex (% Men)	No. Cases/Controls	Case definition	Control definition	Exposures assessed	Exposure contrast	Case Assessment	Adjustment for confounders	NOS score	Funding
Hodge et al. 1996 (Wanigelas, Koki)	~40	52	145/140	Those in the study diagnosed with NIDDM during follow-up	Matched for age, sex, with normal glucose	Dietary saturated fat; measured by FFQ administered by dietitian	10 g increase in total saturated fat	Diagnosed by a physician or observation of a 2h plasma glucose >10 mmol/L	Age, sex, BMI, WHR, physical activity	6	National Health and Medical Research Council (Australia)
Park et al. 2009 (Korea)	56 (14)	71	50/50	Consecutively recruited acute non-fatal MI admitted to Hanyang University Kuri Hospital	Matched on age and sex, with no history of CHD, cancer, hyperlipidemia, or diabetes	Erythrocyte SFA: 14:0, 16:0, 18:0	T3 vs. T1 (%) 14:0->0.37 v. ≤0.26% 16:0->22.6 vs <21.6% 18:0->18.1 vs <16.3%	Hospital chart review	Matching: age, sex Covariates: Age, sex, history of DM, family history of CHD, smoking, hypertension, glucose, total-C, HDL-C	3	Korean Research Foundation
Monteiro et al. 2007	>44	57	290/697	Consecutively admitted cases of ischemic stroke admitted to St. John's Hospital	Random digit dialling from parish registries in the hospital's catchement area	Dietary SFA (FFQ)	Men 12:0 0.5 vs. 0.2 g 14:0 2.2 vs. 1.2 g 16:0 15.7 vs. 11.4 g 18:0 6.7 vs. 4.6 g Women 12:0 0.5 vs. 0.2 g 14:0 2.0 vs. 1.2 g 16:0 13.0 vs. 9.9 g 18:0 5.7 vs. 4.1 g	Defined by clinical evaluation including imaging	Age, education, energy, physical activity, smoking, alcohol, hypertension, dyslipidemia, diabetes, family history of CVD	8	Project EPICardis, Science and Technology Foundation (Portugal)
Sun et al. 2011 (Nanjing, China)	63/61	69/64	108/129	Cases of CAD (fatal and non-fatal) admitted to Nanjing, CHINA hospitals based on symptoms and ECG	Matched controls (within 5y), sex, obesity, DM	Serum free FA (16:0, 18:1)	Serum palmitic acid:oleic acid ratio	CAD assessed independently by 2 angiographers; defined as ≥70% narrowing of lumen diameter of left anterior descending, left circumflex, R coronary artery; or ≥50% narrowing of left main	LDL-C:HDL-C, apo-B:HDL-C	5	National Natural Science Foundation, 973 Program, The "111" project, Natural Science Foundation of Jangsu Province (China)

eTable 4. Characteristics of included retrospective case-control studies of saturated fatty acids and health outcomes. (FA=fatty acids; DM=diabetes mellitus; CVD=cardiovascular disease; BMI=body mass index; MI=myocardial infarction; CHD=coronary heart disease; BP=blood pressure; ECG=electrocardiogram)

Source (Country)	Age	Sex (% Men)	No. Cases/Controls	Case definition	Control definition	Exposures assessed	Exposure contrast	Case Assessment	Adjustment for confounders	NOS score	Funding
Aslibekyan et al. 2012 (Costa Rica)	58	73	1815/1815	Cases of first non-fatal MI residing in Central Valley of Costa Rica	Matched on residence, age, sex	Adipose tissue FA (15:0 and 17:0)	Q5 vs. Q1 15:0 (0.30 vs. 0.13%) 17:0 (0.27 vs. 0.14%)	Assessed by 2 independent cardiologists in participating hospitals	Total energy, age/sex/residence, income, physical activity, WHR, alcohol, adipose tissue ALA, history of hypertension, dylsipidemia, or DM, adipose tissue CLA, dietary calcium	8	National Institutes of Health (USA)
Biong et al. 2006 (Norway)	62	72	100/98	Cases of first MI recruited from coronary care units of Ulleval Hospital (Oslo) and Østfold Central Hospital (Fredrikstat and Sarpsborg)	Frequency matched for age in 5-y intervals from catchement area of cases + friends and relatives of cases	Adipose tissue FA (14:0, 15:0 and 17:0)	Q4 v. Q1 14:0->4.20 vs. <3.1% 15:0->0.47 vs. <0.36% 17:0->0.30 vs. <0.24%	Unclear	Age, sex, WHR, smoking, family history of CHD, education	8	Not stated
Lopes et al. 1998 (Portugal)	58±11	100	214/214	Male patients ≥40 y.o. consecutively admitted to northern Portugal hospital with 1st MI, and 4-day survival	Population-based; men ≥40 y.o.; random digit dialing from catchement area of the hospital; no history of MI	Total saturated fat *(validated FFQ)*	Q4 vs. Q1 (cutoffs not stated)	Attending cardiologist	Matching: age, sex Covariates: Age, education, family history of MI, smoking, physical activity, total energy, BMI	7	Not stated
Suh et al. 2001	~55	100	108/142	Admitted to university teaching hospital	From departments of opthamology and orthopedic surgery with no history of CVD	Dietary total SFA (*validated FFQ)*	Per 1% of energy intake	ECG confirmed (≥50% stenosis)	BMI, smoking, energy intake, total fat	6	Basic Research Medical Fund (Korea)

eTable 5. Risk of bias of included reports from prospective cohort studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
Adult Health Study (Japan)	Sauvaget	1	2	2	5	Cohort exposed to Hiroshima atomic bomb may manifest CVD in unique ways; single-day food diary not validated; CVD prevalence at baseline unclear; attrition rate unclear
ATBC Study (Finland)	Pietinen 1997	4	1	3	8	Did not collect data on/or control for family history
ATBC Study (Finland)	Simila 2012	4	1	3	8	Did not collect data on/or control for family history
Atheroclerosis Risk in Communities (ARIC) study (USA)	Wang	4	1	2	7	Did not control for total energy intake; unclear if events formally adjudicated
Atheroclerosis Risk in Communities (ARIC) study (USA)	Yamagishi 2013 Cerebrovasc Dis	4	1	2	7	Did not control for family history; attrition rate unclear
Australian Longitudinal Study on Women's Health (Australia)	Alhazmi 2013	4	1	1	6	Did not control for family history; self-report of diabetes only with a 70% confirmation in a subset; attrition rate unclear
Baltimore Longitudinal Study of Aging (USA)	Tucker	4	1	3	8	Did not control for socioeconomic status or family history
Caerphilly Prospective Study (UK)	Atkinson	4	2	2	8	Attrition rate unclear
Caerphilly Prospective Study (UK)	Fehily	4	0	3	7	CVD prevalence at baseline ≈25%; Did not control for socioeconomic status, family history, or total energy intake
Cardiovascular Health Study (USA)	Ma, 2015	4	2	3	9	
Cardiovascular Health Study (USA)	Mozaffarian, 2010	4	2	3	9	
Cardiovascular Health study (USA)	Wang, 2015 [diabetes]	4	2	3	9	
Diet, Cancer and Health (Denmark)	Jakobsen 2010	4	0	3	7	Did not control for socioeconomic status or family history
EPIC-Greece (Greece)	Misirli	4	1	3	8	Did not control for family history

eTable 5. Risk of bias of included reports from prospective cohort studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
EPIC-Greece (Greece)	Trichopoulou	4	1	3	8	Did not control for family history
EPIC-Norfolk (UK)	Harding	4	1	3	8	Did not control for socioeconomic status
EPIC-Potsdam (Germany)	Schulze	4	1	3	8	Did not control for family history
EURODIAB Prospective Complications Study (16 European countries)	Shoenaker	4	0	3	7	Did not control for socioeconomic status or family history
Finnish Diabetes Prevention Study (Finland)	Lindstrom 2006	2	0	3	5	Participants with impaired glucose tolerance at baseline; did not control for socioeconomic status, smoking, total energy intake, or family history
Framingham Heart Study (USA)	Gillman	4	0	3	7	Did not control for socioeconomic status or family history
Framingham Heart Study (USA)	Posner	4	1	3	8	Did not control for family history
Health and Lifestyle Survey (UK)	Boniface	4	1	2	7	Did not control for total energy intake; deaths not formally adjudicated
Health Professionals' Follow-up Study (USA)	Ascherio 1996	4	2	3	9	
Health Professionals' Follow-up Study (USA)	He	4	1	2	7	Did not control for family history; attrition rate unclear
Health Professionals' Follow-up Study (USA)	van Dam	4	1	3	8	Did not control for family history
Honolulu Heart Program (USA)	McGee 1985	3	0	3	6	24-hour recall not validated; did not control for socioeconomic status or family history
Insulin Resistance Atherosclerosis Study (USA)	Santaren	4	1	3	8	Did not control for family history
Iowa Women's Health Study (USA)	Meyer	4	1	1	6	Did not control for family history; self-reported diabetes diagnoses with poor validity (36% overreporting)

eTable 5. Risk of bias of included reports from prospective cohort studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
Ireland–Boston Diet–Heart Study (USA, Ireland)	Kushi	3	0	3	6	Diet history not validated; Did not control for socioeconomic status or family history
Israeli Ischemic Heart Disease Study (Israel)	Goldbourt	4	0	3	7	Did not control for socioeconomic status or family history
Japan Collaborative Cohort (Japan)	Wakai	4	2	2	8	Response rate = 83%
Japan Public Health Center-based prospective Study (Japan)	Yamagishi 2013 Eur H J	4	1	2	7	No family history adjustment; no information on attrition rate
Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study (Finland)	Laaksonen	4	2	3	9	
Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study (Finland)	Virtanen	4	2	3	9	
Lipid Research Clinics (Canada)	Esrey	4	0	2	6	Did not control for socioeconomic status or family history; attrition rate unclear
Malmö Diet and Cancer Study (Sweden)	Leosdottir 2005; 2007	4	1	2	7	Did not control for family history; unclear if events formally adjudicated
METSIM cohort (Finland)	Mahendran 2014	4	0	2	6	Subset of METSIM cohort (n=1346 of10,197) representative of full cohort; did not control for family history or total energy intake; 23 of 30 incident cases of t2dm diagnosed at 5-y followup visit; 7 cases unclear ascertainment procedure
MONICA+ Cohorts (Denmark)	Jakobsen 2004; 2007	4	2	2	8	Events ascertained through record linkage only prior to 1977
Multi-Ethnic Study of Atherosclerosis (USA)	De Oliveira Otto; Mozafarrian 2013	4	2	3	9	
National Taiwan University Hospital Study (Taiwan)	Chien	4	1	2	7	Did not control for family history; response rate = 85%

eTable 5. Risk of bias of included reports from prospective cohort studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
Norwegian Countries Study (Norway)	Laake	4	1	1	6	Did not control for family history; events not formally adjudicated
Nurses' Health Study (USA)	Willett 1993	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Nurses' Health Study (USA)	Hu 1997	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Nurses' Health Study (USA)	Hu 1999	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Nurses' Health Study (USA)	Salmeron 2001	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Nurses' Health Study (USA)	Oh 2005	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Nurses' Health study (USA)	Tanasescu 2004	4	2	2	8	Attrition rate unclear
Nurses' Health study and Health Professionals' Follow-up studies (pooled; USA)	Yakoob 2014 (diabetes) and 2014 (stroke)	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Seven Countries Study (7 countries)	Kromhout	4	0	3	7	Did not control for age, socioeconomic status, total energy intake, or family history
Reasons for Geographical and Racial Differences is Stroke (USA)	Kiage 2013 [total mortality outcome]	4	2	2	8	Attrition rate unclear
Reasons for Geographical and Racial Differences is Stroke (USA)	Kiage 2014 [stroke outcome]	4	1	2	7	Did not control for family history; attrition rate unclear
Shibata City Cohort (Japan)	Seino	4	0	3	7	Did not control for socioeconomic status, smoking, or family history
Strong Heart Study (USA)	Xu 2006	3	1	3	7	Diet assessed with single 24-h recall; did not control for family history
Uppsala Longitudinal Study of Adult Men (Sweden)	Wiberg	3	0	2	5	No reliability measures for fatty acids; did not control for socioeconomic status, family history, or total energy intake; unclear if events formally adjudicated

eTable 5. Risk of bias of included reports from prospective cohort studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
Vegetarian Society Study (UK)	Mann	3	1	2	6	CVD prevalence at baseline unclear; Vegetarians may differ from omnivores in other health behaviours; attrition rate unclear
Western Electric Study (U.S.A.)	Shekelle	3	0	3	6	Diet history not validated; did not control for family history, socioeconomic status, or total energy intake
Western Norway B-Vitamin Intervention trial (Norway)	Puaschitz	4	0	0	4	All participants with coronary artery disease; did not control for socioeconomic status, total energy intake; death registry only; follow-up <5 years
Women's Health Initiative (USA)	Howard	4	1	3	8	Did not control for family history
Women's Health Initiative Observational Study (USA)	Yaemsiri 2012	4	1	3	8	Did not control for family history
Women's Health Study (USA)	Song	4	1	2	7	Did not control for socioeconomic status; attrition rate unclear
Zutphen Elderly Study (Netherlands)	Oomen	4	0	3	7	Did not control for family history or socioeconomic status
Zutphen Elderly Study (Netherlands)	De Goede	4	1	3	8	Did not control for family history

Multiple publications from a single cohort (e.g. Nurses' Health Study, Health Professionals Follow-up Study, Malmö Diet and Cancer Study) were each rated independently because they measured different exposures or outcomes in each publication.

eTable 6. Risk of bias of included prospective nested case-control/case-cohort and retrospective case-control studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
Prospective nested case-control						
Whitehall Study (UK)	Clarke	4	0	2	6	Did not control for or match on family history or total energy intake; unclear if events formally adjudicated
Cardiovascular Health Study (USA)	Lemaitre, 2006	4	1	3	8	Did not control for family history
European Prospective Investigation into Cancer (EPIC)-Norfolk (UK)	Khaw et al.	4	1	2	7	Did not control for total energy intake; attrition rate unclear
European Prospective Investigation into Cancer (EPIC)-Norfolk (UK)	Patel et al.	4	0	3	7	Did not control for total energy intake or socioeconomic status
Hunter Community Study (Australia)	Alhazmi	4	0	1	5	Did not control for or match on family history or total energy intake; self-report of type 2 diabetes only; 23% loss-to-follow up
ONCONUT Study (Italy)	Pierucci	4	0	3	7	Did not control for or match on socioeconomic status, smoking, or family history
Nurses' Health Study (USA)	Q Sun 2007 – AJCN	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Nurses' Health study (USA)	Q Sun 2007 – Circulation	4	2	3	9	Sampling from homogenous profession effectively controls for socioeconomic status
Women's Health Initiative-Observational Study (USA)	Matthan 2014	4	1	3	8	Did not control for total energy intake
Multiple Risk Factor Intervention Trial (USA)	Simon	4	0	3	7	Did not control for or match on family history or total energy intake

eTable 6. Risk of bias of included prospective nested case-control/case-cohort and retrospective case-control studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
Prospective case-cohort						
European Prospective Investigation into Cancer (EPIC)-InterAct (Europe)	Forouhi	4	1	3	8	Did not control for or match on family history
European Prospective Investigation into Cancer (EPIC)-Potsdam (Germany)	Kröger	4	1	3	8	Did not control for family history
Melbourne Collaborative Cohort (Australia)	Hodge	4	2	2	8	Attrition rate unclear
Retrospective case-control						
Costa Rica	Asilbekyan	4	1	3	8	Did not control for or match on family history
Costa Rica	Baylin	4	1	3	8	Did not control for or match on family history
Norway	Biong	4	1	3	8	Did not control for or match on total energy intake
Costa Rica	Colon-Ramos	4	1	3	8	Did not control for match on family history
Iran	Ghahremanpour	3	0	2	5	Unclear if cases were consecutively sampled; did not control for or match on age, total energy intake, socioeconomic status, or family history
Portugal	Lopes 1998	4	1	2	7	Did not control for match on family history; differential participation rates (85% of approached cases vs. 70% of approached controls)
Portugal	Lopes 2007	4	1	3	8	Overall low participation rate for adipose tissue biopsies, but similar in both cases and controls (16%); controls with biopsies were older, and more educated than cases
North Portugal	Monteiro	4	1	3	8	Did not control for or match on socioeconomic status
South Korea	Park	1	0	2	3	Catchement area of hospital serving cases and control sampling frame unclear; did not control for or match on socioeconomic status or total energy intake
Eastern Finland	Salonen	4	0	2	6	Did not control for or match on socioeconomic status or total energy intake
South Korea	Suh	4	0	2	6	Did not control for or match on socioeconomic status or family history
China	L Sun 2011	3	0	2	5	Source of cases unclear; did not control for or match on socioeconomic status, smoking, or total energy intake; participation rates in cases vs. controls unclear;
Paupa New Guinea	Hodge	4	0	2	6	Did not control for or match on smoking or family history; unclear if events formally adjudicated

eTable 6. Risk of bias of included prospective nested case-control/case-cohort and retrospective case-control studies as assessed with the Newcastle-Ottawa Scale

Study	References	Selection (4)	Comparability (2)	Outcome (3)	Total (9)	Comments
Retrospective case-control						
Rotterdam	van de Vijver	3	0	3	6	Sources of controls unclear; did not control for or match on socioeconomic status or family history
EURAMIC	Aro	3	0	2	5	Some controls were hospital controls or friends of cases; did not control for on match on socioeconomic status or family history, or total energy
United States	Block	2	2	2	6	Source of cases unclear, but used hospital controls
Norway	Pedersen	2	2	3	7	Catchement area of cases unclear; friend controls
Jordan	Mashal	2	0	2	4	Unclear catchement area of cases; control selection not described; did not control for or match on total energy intake or smoking
Adelaide	Clifton	4	1	2	7	Did not match on or control for family history or smoking

Multiple publications from a single cohort (e.g. Nurses' Health Study, Health Professionals Follow-up Study, Malmö Diet and Cancer Study) were each rated independently because they measured different exposures or outcomes in each publication.

eTable 7. Subgroup Analyses: Saturated fat and CHD Mortality (cohort studies)

Continent	Studies	Events	Total	RR	I^2	P_{Het}	P_{EM}
Europe	5	1,017	37,370	1.09 (0.81, 1.48)	79	0.001	0.586
Asia	2	1,098	8,961	0.86 (0.55, 1.35)	75	0.044	
America	8	855	53,528	1.35 (1.04, 1.76)	59	0.017	
Baseline Year							
<1976	7	1,586	18,007	1.13 (0.91, 1.39)	63	0.014	0.749
>=1976	8	1,384	39,948	1.22 (0.91, 1.63)	77	<0.001	
Follow-up							
<15 y	7	1,139	83,549	1.39 (0.87, 2.25)	81	<0.001	0.465
≥15 y	8	1,831	18,118	1.10 (0.95, 1.26)	52	0.041	
Typical age							
<60 y	10	1,259	68,275	1.28 (1.04, 1.59)	72	<0.001	0.183
>=60	5	1,711	33,437	0.93 (0.72, 1.21)	55	0.07	
Sex							
Men	9	2,639	79,715	1.03 (0.88, 1.21)	60	0.010	0.496
Women	1	56	1,451	1.40 (1.09, 1.79)	-	-	
Mixed	5	275	17,907	1.15 (0.97, 1.36)	75	0.003	
Events							
<100	8	500	21,084	1.39 (1.03, 1.88)	73	0.001	0.177
≥100	7	2,470	80,628	1.01 (0.82, 1.23)	66	0.007	
Smoking Prevalence *(not reported in 4 reports)*							
<25%	5	489	60,255	1.64 (1.17, 2.31)	39	0.162	0.150
>=25%	6	1,058	28,497	1.05 (0.78, 1.41)	76	0.001	
Typical Diet Saturated Fat							
<14%	7	1,581	67,678	1.36 (0.92, 2.01)	75	0.001	0.172
>=14%	8	1,389	34,034	1.10 (0.91, 1.33)	69	0.002	
Energy adjusted							
No	7	1,672	26,419	1.12 (0.95, 1.33)	66	0.007	0.844
Yes	8	1,348	75,293	1.24 (0.84, 1.83)	76	<0.001	
Exposure assessment							
24-h recall	4	230	7,124	1.41 (0.71, 2.80)	77	0.005	0.825
FFQ	7	2,161	89,205	1.08 (0.86, 1.36)	78	<0.001	
7-d diet record	1	71	501	1.72 (0.90, 3.30)	-	-	
28-d interview	1	215	1,900	1.11 (0.91, 1.36)	-	-	
Diet history, >1 but <7 d	2	293	2,982	1.17 (0.81, 1.70)	26	0.245	
Updated diet							
Yes	2	300	44,258	1.72 (1.14, 2.59)	0	1.000	0.242
No	13	2,670	57,484	1.10 (0.93, 1.31)	71	<0.001	
Study Risk of Bias (N-O S Score)							
<7	4	422	17,609	1.47 (1.07, 2.02)	64	0.039	0.173
>=7	11	2,548	84,103	1.05 (0.86, 1.28)	69	<0.001	
Adjusted for TC or LDL-C							
Yes	9	1,882	63,841	1.17 (0.93, 1.47)	68	0.002	0.972
No	6	1,088	37,871	1.15 (0.86, 1.54)	76	0.001	
Adjusted for BP							
Yes	7	2,164	37,549	0.97 (0.74, 1.28)	71	0.002	0.147
No	8	806	64,163	1.32 (1.07, 1.63)	65	0.005	

Studies= number of studies; **Events**= number of events; **total**= total number of participants; **RR**= most-adjusted relative risk estimate; I^2= proportion of heterogeneity within that subgroup due to between-studies (vs. between subgroup) heterogeneity; P_{het}= Cochran's Q test for presence of heterogeneity (significant at P<0.10); P_{EM}= test for between-subgroups difference in effect size ("effect modification")

eTable 8. Subgroup Analyses: Saturated fat and CVD Mortality (cohort studies)

Continent	Studies	Events	Total	RR	I^2	P_{Het}	P_{EM}
Europe	2	339	28,098	0.78 (0.47, 1.29)	27	0.240	0.429
Asia	3	3,453	62,403	1.00 (0.87, 1.15)	20	0.287	
Baseline Year							
<1990	3	3,453	62,403	1.00 (0.87, 1.15)	20	0.287	0.429
>=1990	2	339	28,098	0.78 (0.47, 1.29)	27	0.240	
Follow-up							
<15 y	2	339	28,098	0.78 (0.47, 1.29)	27	0.240	0.429
≥15 y	3	3,453	62,403	1.00 (0.87, 1.15)	20	0.287	
Typical age							
<60 y	2	339	28,098	0.78 (0.47, 1.29)	27	0.240	0.429
≥60 y	3	3,453	62,403	1.00 (0.87, 1.15)	20	0.287	
Sex							
Men	2	1,665	21,450	1.04 (0.89, 1.21)	0	0.670	0.763
Women	2	1,825	46,620	0.83 (0.49, 1.41)	55	0.096	
Mixed	1	60	3,731	0.58 (0.28, 1.20)	-	-	
Events							
<250	3	399	31,829	0.74 (0.52, 1.06)	0	0.375	0.098
≥250	2	3,393	58,672	1.02 (0.89, 1.24)	0	0.618	
Smoking Prevalence							
<25%	0	0	0	-	-	-	-
>=25%	5	3,792	90,501	0.97 (0.84, 1.12)	19	0.290	
Typical Diet Saturated Fat							
<14%	3	3,453	62,403	1.00 (0.87, 1.15)	20	0.287	0.429
>=14%	2	339	28,098	0.78 (0.47, 1.29)	27		
Energy adjusted							
No	3	399	31,829	0.74 (0.52, 1.06)	0	0.375	0.098
Yes	2	3,393	58,672	1.02 (0.89, 1.24)	0	0.618	
Exposure assessment							
24-h recall	1	60	3,731	0.58 (0.28, 1.20)	-	-	0.864
FFQ	2	3,393	58,672	1.02 (0.91, 1.14)	0	0.618	
7-d diet record	2	339	28,098	0.78 (0.47, 1.29)	27	0.240	
Updated diet							
Yes	0	0	0	-	-	-	-
No	5	3,792	90,501	0.97 (0.84, 1.12)	19	0.290	
Study Risk of Bias (N-O S Score)							
<7	1	60	3,731	0.58 (0.28, 1.20)	-	-	0.146
>=7	4	3,732	86,770	1.00 (0.90, 1.12)	0	0.417	
Adjusted for TC or LDL-C							
Yes	1	60	3,731	0.58 (0.28, 1.20)	-	-	0.146
No	4	3,732	86,770	1.00 (0.90, 1.12)	0	0.417	
Adjusted for BP							
Yes	0	0	0	-	-	-	-
No	5	3,792	90,501	0.97 (0.84, 1.12)	19	0.290	

Studies= number of studies; **Events**= number of events; **total**= total number of participants; **RR**= most-adjusted relative risk estimate; I^2= proportion of heterogeneity within that subgroup due to between-studies (vs. between subgroup) heterogeneity; P_{het}= Cochran's Q test for presence of heterogeneity (significant at P<0.10); P_{EM}= test for between-subgroups difference in effect size ("effect modification")

eTable 9. Subgroup Analyses: Saturated fat and total CHD (cohort studies)

Continent	Studies	Events	Total	RR	I^2	P_{Het}	P_{EM}
Asia	1	610	81,931	1.39 (0.93, 2.08)	-	-	0.379
America	8	3,751	131,227	1.05 (0.93, 1.18)	36	0.143	
Europe	8	2,022	54,258	1.07 (0.88, 1.31)	57	0.024	
Baseline Year							
<1983	9	2,761	55,454	1.08 (0.92, 1.26)	53	0.029	0.779
>=1983	8	3,622	211,962	1.04 (0.91, 1.20)	46	0.074	
Follow-up							
<15 y	11	4,159	219,177	1.03 (0.93, 1.16)	45	0.051	0.504
≥15 y	6	2,224	48,239	1.14 (0.89, 1.45)	56	0.043	
Typical age (*unable to split for 1 study*)							
<60 y	10	4,770	238,807	1.14 (1.00, 1.31)	47	0.048	0.017
≥60 y	6	1,177	25,671	0.92 (0.82, 1.03)	0	0.488	
Sex							
Men	10	2,354	75,919	0.97 (0.87, 1.09)	22	0.240	0.320
Women	4	2,075	78,530	1.26 (0.97, 1.62)	64	0.040	
Mixed	3	1,954	112,967	1.09 (0.89, 1.33)	22	0.276	
Events							
<150	10	971	40,209	1.13 (0.97, 1.32)	53	0.025	0.076
≥150	7	5,412	227,207	0.96 (0.87, 1.06)	0	0.486	
Smoking Prevalence*(not reported in 8 studies)*							
<25%	3	1,490	158,562	1.17 (0.97, 1.41)	35	0.217	0.149
>=25%	6	4,761	108,168	0.99 (0.87, 1.13)	37	0.164	
Typical Diet Saturated Fat							
<14%	7	4,148	212,345	1.06 (0.93, 1.21)	33	0.176	0.988
>=14%	10	2,235	55,071	1.07 (0.92, 1.25)	56	0.017	
Energy adjusted							
No	2	929	28,610	0.98 (0.77, 1.24)	0	0.354	0.721
Yes	15	5,454	238,806	1.06 (0.95, 1.19)	52	0.011	
Exposure assessment							
24-h recall	5	1,105	10,839	1.02 (0.86, 1.20)	38	0.166	0.476
FFQ	5	3,891	223,485	1.05 (0.88, 1.25)	63	0.028	
7-d diet record	6	1,387	33,092	1.14 (0.91, 1.44)	52	0.053	
Updated diet							
Yes	3	2,646	120,388	1.08 (0.90, 1.29)	44	0.169	0.817
No	14	3,737	147,028	1.06 (0.93, 1.19)	48	0.022	
Study Risk of Bias (N-O S Score)							
<7	0	0	0	- -	-	-	-
>=7	17	6,383	256,416	1.06 (0.96, 1.18)	47	0.019	
Adjusted for TC or LDL-C							
Yes	5	1,529	80,382	1.11 (0.97, 1.26)	37	0.176	0.361
No	12	4,854	187,034	1.03 (0.90, 1.19)	47	0.037	
Adjusted for BP							
Yes	12	1,511	159,074	1.03 (0.92, 1.16)	48	0.030	0.303
No	5	4,872	108,342	1.14 (0.96, 1.36)	24	0.259	

Studies= number of studies; **Events**= number of events; **total**= total number of participants; **RR**= most-adjusted relative risk estimate; $\mathbf{I^2}$= proportion of heterogeneity within that subgroup due to between-studies (vs. between subgroup) heterogeneity; $\mathbf{P_{het}}$= Cochran's Q test for presence of heterogeneity (significant at P<0.10); $\mathbf{P_{EM}}$= test for between-subgroups difference in effect size ("effect modification")

eTable 10. Subgroup Analyses: Saturated fat and ischemic stroke (cohort studies)

Continent	Studies	Events	Total	RR	I^2	P_{Het}	P_{EM}
Asia	5	2,438	98,005	0.82 (0.69, 0.98)	0	0.509	0.138
America	7	2,569	187,280	1.09 (0.88, 1.34)	72	0.001	
Europe	3	1,219	53,805	1.11 (0.95, 1.30)	0	0.612	
Baseline Year							
<1978	7	1,336	22,575	0.90 (0.72, 1.12)	56	0.033	0.183
>=1978	8	4,890	316,515	1.10 (0.92, 1.33)	62	0.010	
Follow-up							
<15 y	7	4,978	313,896	1.06 (0.95, 1.19)	3	0.405	0.419
≥15 y	8	1,080	21,324	0.94 (0.73, 1.21)	75	<0.0001	
Typical age (*unable to split for 3 studies*)							
<60 y	9	3,817	133,506	0.96 (0.80, 1.17)	74	<0.0001	0.529
≥60 y	3	395	23,601	1.12 (0.91, 1.39)	0	0.699	
Sex							
Men	8	1,892	108,550	0.94 (0.78, 1.12)	50	0.053	0.771
Women	1	1,049	87,025	1.16 (0.90, 1.50)	-	-	
Mixed	6	3,285	143,515	1.08 (0.82, 1.40)	72	0.003	
Events							
<300	8	1,084	24,409	0.93 (0.66, 1.31)	74	<0.0001	0.477
≥300	7	5,142	314,681	1.04 (0.99, 1.10)	0	0.425	
Smoking Prevalence *(not reported in 3 studies)*							
<25%	3	2,562	171,954	1.21 (0.73, 2.01)	86	0.001	0.347
>=25%	9	3,225	151,569	1.01 (0.89, 1.15)	45	0.068	
Typical Diet Saturated Fat							
<12%	5	3,578	261,123	0.96 (0.76, 1.21)	38	0.171	0.617
>=12%	9	2,648	77,967	1.04 (0.83, 1.29)	70	0.001	
(not reported in 1 study)							
Energy adjusted							
No	4	1,072	41,888	0.94 (0.67, 1.33)	59	0.063	0.643
Yes	11	5,194	297,202	1.04 (0.90, 1.19)	62	0.004	
Exposure assessment							
24-h recall	4	649	11,651	0.78 (0.55, 1.11)	46	0.133	0.060
FFQ	8	4,453	293,158	0.99 (0.87, 1.14)	22	0.253	
7-d diet record	1	648	28,098	1.22 (0.91, 1.64)	-	-	
Biomarker (phospholipid FA)	2	476	6,183	1.33 (0.79, 2.25)	91	0.001	
Updated diet							
Yes	6	4,322	283,129	1.03 (0.89, 1.18)	19	0.295	0.838
No	10	1,904	55,961	1.00 (0.82, 1.22)	69	0.001	
Study Risk of Bias (N-O S Score)							
<7	3	2,307	87,976	0.92 (0.73, 1.15)	63	0.066	0.358
>=7	12	3,919	251,114	1.06 (0.89, 1.26)	60	0.004	
Adjusted for TC or LDL-C							
Yes	6	2,352	187,655	1.04 (0.95, 1.13)	8	0.367	0.860
No	9	3,874	151,435	0.99 (0.79, 1.25)	72	<0.0001	
Adjusted for BP							
Yes	13	4,119	253,288	1.00 (0.89, 1.12)	38	0.078	0.378
No	2	2,107	83,695	1.21 (0.58, 2.53)	93	<0.0001	

Studies= number of studies; **Events**= number of events; **total**= total number of participants; **RR**= most-adjusted relative risk estimate; I^2= proportion of heterogeneity within that subgroup due to between-studies (vs. between subgroup) heterogeneity; P_{het}= Cochran's Q test for presence of heterogeneity (significant at P<0.10); P_{EM}= test for between-subgroups difference in effect size ("effect modification")

eTable 11. Characteristics of included prospective cohort studies of trans fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. of Participants	No. of Events	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Willett et al., 1993; United States (Nurses' Health Study I)	34-59	0	69,181	356 CHD	8	Total trans fatty acid; vegetable *trans*; animal *trans (validated FFQ)*	Q5 vs. Q1 (5.7 vs. 2.4 g/d)	self report; confirmed by medical record review; national death index	Age, smoking, BMI, hypertension, alcohol intake, menopausal status, PMH use, energy intake, dietary lipids, family history of MI <60, multivitamin use	9	National Institutes of Health (U.S.)
Ascherio et al., 1996; United States (Health Professionals' Follow-up Study)	40-75	100	43,757	734 total MI; 229 CHD deaths	6	Total *trans* fatty acids *(validated FFQ)*	Q5 vs. Q1 (4.3 to 1.5 g/d)	Self report; confirmed by medical record review, deaths confirmed by next of kin; national death index	Age, BMI, smoking, alcohol, physical activity, history of HTN/ high blood cholesterol, family history of MI<60; profession, dietary fiber, energy	9	National Institutes of Health (U.S.)
Oh et al., 2004; United States (Nurses' Health Study I)	34-59	0	78,778	1766 CHD; 1241 non-fatal MI and 525 CHD death	20	Total *trans* fatty acids *(validated FFQ)*	Q5 vs. Q1 (2.8 vs. 1.3% energy)	self report; confirmed by medical record review; national death index	Age, BMI, smoking, alcohol, parental history of MI, hypertension, menopausal status and hormone use, aspirin use, multivitamin use, vitamin E supplement use, physical activity, energy, protein, dietary cholesterol	9	National Institutes of Health (U.S.)
Oomen et al, 2001; Netherlands (Zutphen Elders' Study)	71 (5)	100	667	49 Fatal CHD 98 Non-fatal MI	6	Total *trans* fatty acids; ruminant *trans* fatty acids; manufactured C18:1 *trans*; other manufactured *trans (validated FFQ)*	Ruminant: T3 vs. T1 (6.4% vs. 2.4% energy)	self-report or hospital discharge data; confirmed by municipal registries	Age, total energy, BMI, smoking, alcohol, vitamin use, saturated fat, monounsaturated fat, polyunsaturated fat, dietary cholesterol, dietary fiber	7	Netherlands Prevention Foundation

eTable 11. Characteristics of included prospective cohort studies of trans fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. of Participants	No. of Events	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Pietinen et al., 1997; (α-tocopherol and β-carotene Study)	50-69	100	21,930	1,399 Major coronary events: first non-fatal MI; 635 coronary death	6	All *trans* isomers from 16-22C: C16:1 *trans*; C18:1 *trans*; C18:2 *trans*; C20:1 *trans (validated FFQ)*	Q4 vs. Q1: 3.9% vs. 0.9% energy Q4 vs. Q1: 4.0% vs. 0.9% energy; Per 2 g/d (≈1% energy)	National hospital discharge register diagnosis and obtained hospital and pathology reports; deaths through national population register	Age, treatment group, smoking, BMI, blood pressure, energy, alcohol, fiber, education, physical activity	8	National Cancer Institute (U.S.), Academy of Finland
Xu et al., 2006; United States (Strong Heart Study)	45-74	36	2,938	436 incident CHD; 298 non-fatal CHD + 138 fatal CHD	7.2	Total *trans* fatty acids *(24-hour recall)*	≈4.0 vs. 2.0% energy	Annual mortality and morbidity surveillance or at 3rd examination; confirmed by medical records	Sex, age, study center, diabetes, BMI, HDL-C, LDL-C, triacylglycerol, smoking, alcohol, hypertension, dietary protein, total energy	7	National Heart, Lung and Blood Institute (U.S.)
Howard et al., 2006; United States (Womens' Health Initiative RCT)	50-79	0	31,258	146 major CHD event	1	Total *trans* fatty acids *(validated FFQ)*	≈2.5% energy in control arm vs. <1.1% energy in intervention arm	Hospital records; death certificates	Age, baseline CHD, HRT , randomization, BMI, hypertension, dyslipidemia, smoking, diabetes, physical activity, energy expenditure, ethnicity, education, income, psychological stress	8	National Heart, Lung and Blood Institute (U.S.)
Jakobsen et al., 2007; Denmark (1914, 1936 cohorts; MONICA I & III)	30-71	50	3,686	374 total CHD	18	Ruminant *trans* fatty acids *(7-day weighed food record)*	Per 0.5 g/d	record linkage to Causes of Death registry; review of medical files	Energy, cohort, SBP, family history of MI, education, smoking, alcohol, % protein, % mono, % poly, dietary fiber, dietary cholesterol, industrially-produced TFA, % SFA, BMI, physical activity	8	Danish Heart Foundation; Danish Medical Research Council

eTable 11. Characteristics of included prospective cohort studies of trans fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. of Participants	No. of Events	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Laake et al., 2012; Norway (Norwegian Countries Study)	≈40	50	71,464	11,190 total mortality; 3870 CVD death; 2383 CHD death; 732 cerebrovascular death; 243 sudden death of unknown cause	26	Partially hydrogenated vegetable oil *trans*, partially hydrogenated fish oil *trans*, ruminant *trans (FFQ)*	5 categories (not quintiles; as % energy) PHVO: ≥1.65 vs. <0.15 PHFiO ≥2.35 vs. <0.85 rTFA (%): ≥0.85 vs. <0.4	Not stated	Age, sex, energy intake, SBP, BMI, smoking, education, SFA, unsaturated cis-FA, protein, cholesterol, and each type of TFA for the others	6	Throne–Holst Foundation for Nutrition Research (Marabou company)
Yaemsiri et al., 2012; United States (Womens' Health Initiative)	64 (7)	0	87,025	1,049 ischemic stroke, 101 atherosclerotic stroke, 269 lacunar stroke, 244 cardioembolic stroke	7.6	Total trans fatty acids *(validated FFQ)*	Q4 vs. Q1 6.1 vs. 2.2 g/d	Self report; adjudicated by local physicians and centrally by trained neurologists	Age, race, education, income, smoking, HRT use, physical activity, alcohol, history of CHD, history of A. Fib, history of diabetes, aspirin use, use of antihypertensives, use of cholesterol-lowering medication, BMI, SBP, total energy, vitamin E, fruits and vegetables intake, fiber	8	National Heart, Lung, and Blood Institute (U.S.)
He et al., 2003; United States (Health Professionals' Follow-up Study)	40-75	100	43,732	725 total stroke; 455 ischemic stroke, 125 haemorrhagic stroke	14	Total trans fatty acids *(validated FFQ)*	Q5 vs. Q1 4.42 vs. 1.67 g/d	Blind record review by MD; fatal stroke reported by next of kin corroborated against national death index	BMI, physical activity, history of hypertension, smoking status, aspirin use, alcohol, dietary potassium, dietary fiber, dietary vitamin E, fruits and vegetables, total energy intake, hypercholesterolemia at baseline, polyunsaturated, monounsaturated, and saturated fat	7	National Institutes of Health (U.S.)

eTable 11. Characteristics of included prospective cohort studies of trans fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. of Participants	No. of Events	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Knekt (personal communication 2013; *unpublished*); Finnish Mobile Health Clinics	40-69	50	3,980	519 fatal CHD	17	Total *trans* fatty acids (*Validated dietary interview*)	Q5 vs. Q1: 4.6 vs. 1.3 g/d (M); 3.4 vs. 0.9 g/d (W)	Cause of death registry using ICD-8	Age, lipids, blood pressure, BMI, MUFA, PUFA, SFA, smoking	n/a	n/a
Robien (as reported by Bendsen et al., 2011; unpublished); Iowa Womens' Health Study	55-69	0	32,766	1,875 fatal CHD	21	Total trans fatty acids (*validated FFQ*)	Q5 vs. Q1 (1.5%E contrast)	Cause of Death Registry using ICD-9	Age, BMI, education, alcohol, dietary cholesterol, total energy, fiber, n-3 fatty acids, MUFA, protein, PUFA, SFA, physical activity, smoking, use of post-menopausal hormones	n/a	n/a
Kiage et al., 2013 and 2014; United States (Reasons for Geographical and Racial Differences in Stroke cohort)	≈65	45	18,513	401 ischemic stroke events [2014] 1,572 all-cause deaths [2013]	7	Total trans fatty acids (*validated FFQ*)	Q5 vs. Q1 4.68 vs. 1.60 % energy	Next-of-kin report, national death index, and adjudicated	Sex, age, smoking, race, region, alcohol use, education, waist circumference, physical activity, diabetes, CHD, hypertension, stroke, heart failure, CKD, statin use, total energy, energy-adjusted SFA, MUFA, PUFA, protein, CHO	7 [2014] 8 [2013]	National Institutes of Neurological Disorders and Stroke, National Institutes of Health (U.S.)
van Dam et al., 2002; United States (Health Professionals' Follow-up Study)	40-75	100	42,504	1,321 type 2 diabetes	12	Total trans fatty acids (*validated FFQ*)	Q5 vs. Q1 2.0 vs. 0.7% energy	Self-report, confirmed by medical records, blinded study physician	Age, total energy, time, physical activity, smoking, alcohol, hypertension, hypercholesterolemia, family history, cereal fiber, magnesium, BMI	8	National Institutes of Health (U.S.)
Meyer et al., 2001; United States (Iowa Womens' Health Study)	56-69	0	35,988	1,890 type 2 diabetes	11	Total trans fatty acids (*validated FFQ*)	Q5 vs. Q1 5.2 vs. 2.2 g/d	Self-report (only validated in subsample)	Age, total energy, WHR, BMI, physical activity, smoking, alcohol, education, marital status, residence area, use of HRT, magnesium, cereal fiber, SFA, MUFA, w-3 FA, cholesterol	6	National Cancer Institute (U.S.)

eTable 11. Characteristics of included prospective cohort studies of trans fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. of Participants	No. of Events	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Salmeron et al., 2001; United States (Nurses' Health Study)	35-49	0	84,204	2,507 type 2 diabetes	14	Total trans fatty acids (*validated FFQ*)	Q5 vs. Q1 2.9 vs. 1.3% energy	Self-report, confirmed by medical records, blinded study physician	Age, BMI, time, smoking, family history of DM, alcohol, physical activity, protein (%), total energy, dietary cholesterol	9	National Institutes of Health (U.S.)
Song et al., 2004; United States (Women's Health Study)	>45	0	37,309	1,558 type 2 diabetes	8.8	Total trans fatty acids (*validated FFQ*)	Q5 vs. Q1 3.7 vs. 1.1 g/d	Self-report, MD confirmed in subsample	Age, BMI, total energy, smoking, exercise, alcohol, family history of DM, fiber, glycemic load, magnesium, total fat	7	National Institutes of Health (U.S.)
Simila et al., 2012; Finland (α-tocopherol and β-carotene Study)	50-69	100	25,943	1,098 type 2 diabetes	12	Total trans fatty acids (validated FFQ)	Replacement of 1% energy with carbohydrate	Registry of reimbursement for diabetes medications	Age, intervention, BMI, smoking, physical activity, coffee, total energy, protein, fat, SFA, MUFA, PUFA	8	U.S. Public Health Services (U.S.)
Mozaffarian et al., 2010; U.S. (Cardiovascular Health Study)	≈75	45	3,736	304 incident type 2 diabetes	14	Trans-palmitoleate (*plasma phospholipid*)	0.25% vs. 0.13% total FA	Assessed at annual study clinic visits by study physician	Age, sex, race, education, enrollment site, smoking, waist, CHD, physical activity, alcohol use, % energy from carbohydrate, % energy from protein, red meat, whole-fat dairy, low-fat dairy, total energy	9	National Heart, Lung and Blood Institute, NIH Office of Dietary Supplements, National Institute of Neurological Diseases and Stroke (U.S.)
Mozaffarian et al., 2013; U.S. (MESA)	62	47	2,281	205 type 2 diabetes	≈5	Trans-palmitoleate (*plasma phospholipid*)	0.10% vs. 0.03 total FA	Study physicians determined presence of DM each 2y study visit based on fasting glucose (≥126 mg/dl)	Age, sex, race, education, field center, smoking, alcohol use, physical activity, BMI, waist circumference	9	National Heart, Lung, and Blood Institute, NIH NIDDK, Harvard Bunge Fellowship Fund (U.S.)

eTable 11. Characteristics of included prospective cohort studies of trans fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. of Participants	No. of Events	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Chien et al., 2013; Japan (Chin-Shan)	≈60	47	3,602	568 deaths; 275 CVD events	≈10	Total trans-fatty acids (*Plasma*)	10.4% vs. 7.3% of total fat	Official death certificates verified by house-to-house visits	Age, gender, BMI, smoking, drinking, marital status, education level, job and sports activity, hypertension, diabetes, LDL-C and HDL-C	7	National Science Council; National Taiwan University (Taiwan)
Virtanen et al., 2014; Finland (Kuopio Ischemic Heart Disease Risk Factor Study)	42-60	100	1,981	183 fatal and 382 non-fatal CHD events	21.4	Total trans fatty acids *(4-day prospective diet record)*	Q4 vs. Q1 (1.5 vs. 0.7% of energy)	Link to national death registry; adjudicated according to ICD-9	Age, examination year, energy intake, BMI, diabetes, hypertension, family history of CHD, pack-years of smoking, education, leisure-time physical activity, alcohol, fiber, % energy from protein, other fatty acids	9	University of Eastern Finland
Wang et al., 2015; USA; Cardiovascular Health Study	74±5	74	4,207 (of which 2,919 had plasma PPL TFA)	407 incident type 2 diabetes	20	Total trans fatty acids (FFQ); t-16:1n9, t-18:1, c/t-18:2, t/c-18:2, t/t-18:2, t-16:1n7 *(plasma PPL)*	Q4 vs. Q1 Mean intake of total TFA = 3.7±1.3 g/d	Self-reported diagnosis by new use of insulin/ hypoglycemic meds during f/u; elevated non-fasting glucose; or elevated 2-h glucose challenge	Age, sex, rage, education, enrollment site, smoking, alcohol, physical activity, BMI, waist circumference, CVD, hypertension at baseline, coffee, red meat, fiber, glycemic load, PUFA, SFA, total energy, "healthy diet score"	9	National Heart, Lung, and Blood Institute (NHLBI); Office of Dietary Supplements; National Institutes of Neurological Disorders and Stroke; National Institute on Aging

eTable 11. Characteristics of included prospective cohort studies of trans fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. of Participants	No. of Events	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Santaren et al., 2014; USA; Insulin Resistance Atherosclerosis Study	40-60	55	659	103 incident type 2 diabetes	5	Trans 16:1n7 *(plasma PPL)*	T3 vs. T1 (0.4 vs. 0.2 mol% FA)	Diabetes diagnosed on end-of-study visit using American Diabetes Association criteria for fasting or 2h-post challenge glucose, oral hypoglycemic agent or insulin use	Age, sex, ethnicity, study center, physical activity, smoking, alcohol, eduction, total energy, fruit and vegetables, red meat, soft drinks, fiber	8	Dairy Farmers of Canada, National Heart, Lung, and Blood Institute
Yakoob et al., 2014; USA; Nurses' Health and Health Professionals Followup Studies	30-75	50	3,347	254 incident type 2 diabetes	14	Trans 16:1n7*(plasma PPL)*	Q4 vs. Q1 plasma FA biomarkers	Self-report; validated by supplementary questionnaires on symptoms, diagnostic tests, and medical therapy	Age, race, month of blood collection, smoking, physical activity, alcohol, family history of t2dm and MI, menopausal status, fish, processed and unprocessed meats, fruits, vegetables, whole grains, coffee, sugar-sweetened beverages, glycemic load, dietary calcium, PUFA, trans fatty acids, total energy, and CVD status	9	American Heart Association, Founders Affiliate

eTable 12. Characteristics of included prospective nested case-control and case-cohort of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/ Participants [Case:Control]	Case definition	Control definition	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Lemaitre et al., 2006; USA; Cardiovascular Health Study *(nested case-control)*	77±6	60	224/428 [1:1]	Fatal myocardial infarction or fatal events with chest pain within 72 hours of death; or had a history of chronic IHD. Myocardial infarction was defined on the basis of cardiac enzyme levels, chest pain, and serial ECG changes	Random CHS participants who did not experience a fatal IHD event and did not use fish oil supplements	2-10	Trans 18:1 (12 trans-18:1; 11 trans-18:1; 10 trans-18:1; and mix of 6 to 8 trans-18:1); Trans 18:2 (9 cis, 12 trans-18:2 and 9 trans, 12 cis 18:2); trans 16:1 (7-trans 16:1; 9-trans 16:1) (plasma phospholipid)	Interquintile range: Total trans: 1.39% Trans 16:1: 0.13% Trans 18:2: 0.13% Trans 18:1: >20th %ile vs. <20th %ile	Cardiologist reviewed all fatal IHD records, including hospital records; interviews with physicians, next-of-kin, and/or witnesses; death certificates; and autopsy reports to identify sudden cardiac deaths	Matching: gender, clinic site, entry cohort, age (±5y), time of blood draw (±90d), follow-up duration Covariates: diabetes mellitus, education, smoking, congestive heart failure, stroke history, DHA+EPA	8	National Heart, Lung and Blood Institute (USA); National Institute of Neurological Disorders (USA)
Sun et al., 2007; USA; Nurses' Health Study (*nested case-control*)	61±6	0	166/493 [1:2]	CHD deaths were identified from autopsy reports, hospital records, or death certificates, Nonfatal MI by WHO criteria	randomly selected with risk-set sampling (ie, controls were selected from the rest of the nondiseased participants at the time of diagnosis of the cases	6	Total *trans*, all C18:1 *trans*, all C18:2 *trans* (Erythrocyte)	Total *trans:* ~0.14%, all C18:1 *trans*:~1.2%, all C18:2 *trans:* 0.37%	Charts reviewed by MD blind to exposure status	Age, smoking, fasting status, time of blood draw, BMI, menopausal status, hormone use, physical activity, alcohol, parental history of MI <65, hypertension, hypercholesterolemia, diabetes, LC *n*-3 fatty acids and total *n*-6 fatty acids	7	National Institutes of Health (USA)

eTable 12. Characteristics of included prospective nested case-control and case-cohort of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/ Participants [Case:Control]	Case definition	Control definition	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Khaw et al., 2012; UK; EPIC-Norfolk *(nested case-control)*	62±8	52	2424/7354 [1:2]	hospital admission and/or died with CHD as cause of death	Cohort members alive and free of known cardiovascular disease during follow-up to 2009	13	Total trans, C16:1n9t, C18:1n9t *(plasma phospholipid)*	% total fatty acids Total trans: ~2.04% Trans 18:1: ~1.67% Trans 18:2: ~0.21% Trans 16:1: ~0.17%	Deaths: National Health Service Central register; CHD events via medical record inspection	Age, sex, BMI, smoking, alcohol intake, physical activity, plasma vitamin C, social class, education, diabetes, SBP, cholesterol	7	Medical Research Council UK; Cancer Research UK
Hodge et al., 2007; Australia; Melbourne Collaborative Cohort Study *(case-cohort)*	55±8	44	364/3737 [1:10]	Self-reported type 2 diabetes 4 y. after baseline	Random sample of the cohort	4	Total *trans (phospholipid and FFQ)*	Plasma *trans*: 1.03% (cases); 0.81% (controls) Plasma CLA: 0.30% (cases); 0.27% (controls)	Self-reported diabetes confirmed with person's family doctor (84% confirmed)	Age, sex, country of birth, family history of DM, physical activity, alcohol, BMI, waist to hip ratio	8	VicHealth; The Cancer Council (Victoria); National Health and Medical Research Council
Patel et al., 2010; UK; EPIC-Norfolk *(nested case-control)*	64	53	199/184 [1.1:1]	self-report of diabetes or a diabetes medication on any of the follow-up health and lifestyle questionnaires; or diabetes medication brought to the follow-up health check visit	Randomly selected noncases from the entire EPIC Norfolk cohort at baseline	13	Diet: total Trans *(validated FFQ)* Biomarker: total trans, 16:1n-9t, 18:1n-9t *(plasma PPL; and erythrocyte membrane PPL)*	Diet and PPL: T3 vs. T1	Record linkage: general practice diabetes registers, hospital outpatient diabetes registers, and hospital admissions information for diabetes.	Age, sex, family history of DM, smoking, physical activity, alcohol	8	Medical Research Council UK and Cancer Research UK, European Union; Stroke Association; British Heart Foundation; the Department of Health; Food Standards Agency; Ministry of Agriculture, Fisheries and Food; Wellcome Trust

eTable 12. Characteristics of included prospective nested case-control and case-cohort of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/ Participants [Case:Control]	Case definition	Control definition	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Kröger et al. 2011; Germany; EPIC-Potsdam *(case-cohort)*	53	58 cases; 39 controls	673/2,787 [1:3]	self-report of diabetes or a diabetes medication on any of the follow-up health and lifestyle questionnaires; or diabetes medication brought to the follow-up health check visit	Randomly selected noncases from the entire EPIC Potsdam cohort at baseline	7	Total TFA, C16:1n-7t, C18:1n-9t+C18:1n7t (erythrocyte membrane)	Q5 vs. Q1 (0.94 vs. 0.54% FA)	Incident cases verified by diagnosing physician	Age, sex, BMI, waist, cycling, sports activity, education, coffee intake, smoking, alcohol intake, occupational activity, fiber	8	Federal Ministry of Science, Germany; European Union; German Cancer Aid; European Community; German Research Foundation

eTable 13. Characteristics of included retrospective case-control studies of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/ Participants [Case:Control]	Case definition	Control definition	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Lemaitre et al., 2006; USA; Cardiovascular Health Study *(nested case-control)*	77±6	60	224/428 [1:1]	Fatal myocardial infarction or fatal events with chest pain within 72 hours of death; or had a history of chronic IHD. Myocardial infarction was defined on the basis of cardiac enzyme levels, chest pain, and serial ECG changes	Random CHS participants who did not experience a fatal IHD event and did not use fish oil supplements	2-10	Trans 18:1 (12 trans-18:1; 11 trans-18:1; 10 trans-18:1; and mix of 6 to 8 trans-18:1); Trans 18:2 (9 cis, 12 trans-18:2 and 9 trans, 12 cis 18:2); trans 16:1 (7-trans 16:1; 9-trans 16:1) (plasma phospholipid)	Interquintile range: Total trans: 1.39% Trans 16:1: 0.13% Trans 18:2: 0.13% Trans 18:1: >20th %ile vs. <20th %ile	Cardiologist reviewed all fatal IHD records, including hospital records; interviews with physicians, next-of-kin, and/or witnesses; death certificates; and autopsy reports to identify sudden cardiac deaths	Matching: gender, clinic site, entry cohort, age (±5y), time of blood draw (±90d), follow-up duration Covariates: diabetes mellitus, education, smoking, congestive heart failure, stroke history, DHA+EPA	8	National Heart, Lung and Blood Institute (USA); National Institute of Neurological Disorders (USA)
Sun et al., 2007; USA; Nurses' Health Study (*nested case-control*)	61±6	0	166/493 [1:2]	CHD deaths were identified from autopsy reports, hospital records, or death certificates, Nonfatal MI by WHO criteria	randomly selected with risk-set sampling (ie, controls were selected from the rest of the nondiseased participants at the time of diagnosis of the cases	6	Total *trans*, all C18:1 *trans*, all C18:2 *trans* (Erythrocyte)	Total *trans:* ~0.14%, all C18:1 *trans*:~1.2%, all C18:2 *trans:* 0.37%	Charts reviewed by MD blind to exposure status	Age, smoking, fasting status, time of blood draw, BMI, menopausal status, hormone use, physical activity, alcohol, parental history of MI <65, hypertension, hypercholesterolemia, diabetes, LC *n*-3 fatty acids and total *n*-6 fatty acids	7	National Institutes of Health (USA)

eTable 13. Characteristics of included retrospective case-control studies of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/ Participants [Case:Control]	Case definition	Control definition	Follow-up (y)	Exposures assessed	Exposure contrast	Outcome validation	Adjustment for confounders	NOS score	Funding
Khaw et al., 2012; UK; EPIC-Norfolk *(nested case-control)*	62±8	52	2424/7354 [1:2]	hospital admission and/or died with CHD as cause of death	Cohort members alive and free of known cardiovascular disease during follow-up to 2009	13	Total trans, C16:1n9t, C18:1n9t *(plasma phospholipid)*	% total fatty acids Total trans: ~2.04% Trans 18:1: ~1.67% Trans 18:2: ~0.21% Trans 16:1: ~0.17%	Deaths: National Health Service Central register; CHD events via medical record inspection	Age, sex, BMI, smoking, alcohol intake, physical activity, plasma vitamin C, social class, education, diabetes, SBP, cholesterol	7	Medical Research Council UK; Cancer Research UK
Hodge et al., 2007; Australia; Melbourne Collaborative Cohort Study *(case-cohort)*	55±8	44	364/3737 [1:10]	Self-reported type 2 diabetes 4 y. after baseline	Random sample of the cohort	4	Total *trans (phospholipid and FFQ)*	Plasma *trans*: 1.03% (cases); 0.81% (controls) Plasma CLA: 0.30% (cases); 0.27% (controls)	Self-reported diabetes confirmed with person's family doctor (84% confirmed)	Age, sex, country of birth, family history of DM, physical activity, alcohol, BMI, waist to hip ratio	8	VicHealth; The Cancer Council (Victoria); National Health and Medical Research Council
Patel et al., 2010; UK; EPIC-Norfolk *(nested case-control)*	64	53	199/184 [1.1:1]	self-report of diabetes or a diabetes medication on any of the follow-up health and lifestyle questionnaires; or diabetes medication brought to the follow-up health check visit	Randomly selected noncases from the entire EPIC Norfolk cohort at baseline	13	Diet: total Trans *(validated FFQ)* Biomarker: total trans, 16:1n-9t, 18:1n-9t *(plasma PPL; and erythrocyte membrane PPL)*	Diet and PPL: T3 vs. T1	Record linkage: general practice diabetes registers, hospital outpatient diabetes registers, and hospital admissions information for diabetes.	Age, sex, family history of DM, smoking, physical activity, alcohol	8	Medical Research Council UK and Cancer Research UK, European Union; Stroke Association; British Heart Foundation; the Department of Health; Food Standards Agency; Ministry of Agriculture, Fisheries and Food; Wellcome Trust

eTable 13. Characteristics of included retrospective case-control studies of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/Controls	Case definition	Control definition	Exposures assessed	Exposure contrast	Case Assessment	Adjustment for confounders	NOS score	Funding
Aro et al., 1994; EURAMIC; 8 European countries	≈54	100	671/717 [0.9:1]	Men with first MI	Men without a history of MI, recruited from catechement area and frequency-matched in 5-y age groups; or hospital controls; or referred by local GPs or friends of cases	Trans 18:1	Q4 vs. Q1 2.63 vs. 1.12%FA	confirmed by elecrocardiographic and enzyme changes	Matching: Age Covariates: centre, smoking, BMI	5	British Heart Foundation, Dutch Ministry of Health, Spanish FIS, German Federal Health Office, Norwegian Research Council, Russian Ministry of Science, Swiss NRF (grant 32-31312-91), and the Yrjo Jahnsson Foundation, Finland.
Baylin et al., 2003; Costa Rica	57	74	482/482 [1:1]	Men and women survivors of a first acute MI at any of the three recruiting hospitals in the catchment area	population controls randomly identified with data from the National Census and Statistics Bureau of Costa Rica	Trans 16:1, Trans 18:1, Trans 18:2, Total	Q5 vs. Q1 Total: 4.4 vs. 1.8 g/100g; 16:1: 0.115 vs. 0.044 18:1: 2.54 vs. 0.94 18:2: 2.04 vs. 0.75	Confirmed by two independent cardiologists	Matching: age, sex, area of residence Covariates: income, history of diabetes, history of hypertension, physical activity, smoking, years living in the house, alcohol, adipose tissue α-linolenic acid, dietary vitamin E, saturated fat, total energy, BMI, WHR, multivitamin use, folate, fiber	8	National Institutes of Health

eTable 13. Characteristics of included retrospective case-control studies of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/Controls	Case definition	Control definition	Exposures assessed	Exposure contrast	Case Assessment	Adjustment for confounders	NOS score	Funding
Colon-Ramos et al., 2006; Costa Rica	≈54	73	1797/1797 [1:1]	Men and women survivors of first MI at 3 recruiting hospitals	Randomly sampled from area of residence of case using data from National Census and Statistic Bureau	Total *trans*, 18:1 *trans*, 18:2 *trans (adipose tissue)*	Q5 vs. Q1 1994-1999: Total *trans*: 4.40 vs. 1.85 g/100 g 18:1 *trans*: 2.54 vs. 0.93 g/100 g 18:2 *trans*: 2.02 vs. 0.75 g/100 g 2000-2003 Total *trans*: 3.42 vs. 1.84 18:1 *trans*: 1.94 vs. 0.85 18:2 *trans*: 1.40 vs. 0.74	Confirmed by 2 independent cardiologists	Matching: Age, sex, area of residence Covariates: Income, history of diabetes, history of hypertension, physical activity, smoking status, alcohol intake, adipose tissue α-linolenic acid, vitamin E intake, saturated fat, total energy	8	NIDDK; National Institutes of Health (U.S.)
Ghahremanpour et al., 2008; Iran	53 (8)	69	105/68 [1.5:1]	Men and women <75 y.o. with no previous admission for CVD events, or treatment for diabetes or dyslipidemia; angiographically proven coronary artery stenosis from Rajaee Hospital (Tehran)	Healthy volunteers with no history of CVD and same exclusion criteria	Total *trans*; 18:1 *trans*, 18:2 *trans*, 16:1 *trans* (*Adipose tissue*)	IQR (g/100 g) total *trans*: 13.7; 18:1 *trans*: 11.3; 18:2 *trans*: 4.6; 16:1 *trans*: 1.5	Unclear	Matching: age, sex Covariates: Hypertension, smoking, triglyceride, adipose tissue PUFA	5	Not stated

eTable 13. Characteristics of included retrospective case-control studies of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/Controls	Case definition	Control definition	Exposures assessed	Exposure contrast	Case Assessment	Adjustment for confounders	NOS score	Funding
Park et al., 2009; South Korea	56 (14)	71	50/50 [1:1]	Consecutively recruited acute non-fatal MI admitted to Hanyang University Kuri Hospital	Matched to controls on age and sex, with no history of CHD, cancer, hyperlipidemia, or diabetes	total *trans*; *trans* 18:1n-9; *trans* 18:2n-6 *trans* (*Erythrocyte*)	T3 vs. T1 (total *trans*) >0.45% vs. ≤0.06% T3 vs. T1 (18:1n-9 *trans*) >0.35% vs. ≤0.22% T3 vs. T1 (18:2n-6 *trans*) >0.29% vs. ≤0.19%	Hospital chart review	Matching: age, sex Covariates: Age, sex, history of DM, family history of CHD, smoking, hypertension, glucose, total-C, HDL-C	3	Korean Research Foundation
Pedersen et al., 2000; Norway	62 (8)	72	100/98 [1:1]	First MI admitted to the coronary care unit of Ostfold Central Hospital (Fredrikstat/Sarpsborg) and Illeval Hospital (Oslo)	Recruited from hospital catchment areas; supplemented with friends of cases, state and municipal employees, recreational seniors (within 2 months of case)	total *trans (adipose)*	Q5 vs. Q1 >4.75% vs. <3.35%	Hospital chart review	Matching: sex, age, location Covariates: Age, sex, WHR, smoking family history, α-LNA, α-LA	7	Throne Holst's Foundation for Nutrition Research; Norwegian Association of Margarine Producers; DeNoFa Fabriker AS; Tine Norwegian Dairies (Norway)
Block et al., 2009; United States	61 (12)	66	768/768 [1:1]	Identified from registry of patients with confirmed diagnosis of ACS (acute MI or unstable angina)	Outpatients from same hospitals having routine blood draw for clinical testing	Total *trans*, *trans* oleic acid, *trans*,*trans* linoleic acid, *trans* palmitic acid (*erythrocyte*)	Per 1-SD increased in TFA	3 physicians reviewed charts; attained consensus on the final diagnosis	Matching: age, sex, race Covariates: Lipid levels, BMI, diabetes, hypertension, family history of CAD, personal history of MI or revascularization, alcohol, smoking, statin use, aspirin/ anticoagulant use, education, cell [EPA and DHA]	6	St. Luke's Hospital Foundation; NIH (U.S.)

eTable 13. Characteristics of included retrospective case-control studies of *trans* fatty acids and health outcomes.

Source (Country)	Age	Sex (% Men)	No. Cases/Controls	Case definition	Control definition	Exposures assessed	Exposure contrast	Case Assessment	Adjustment for confounders	NOS score	Funding
Lopes et al., 2007; Portugal	58±11	100	214/214 [1:1]	Male patients ≥40 y.o. consecutively admitted to northern Portugal hospital with 1st MI, and 4-day survival	Population-based; men ≥40 y.o.; random digit dialing from catchement area of the hospital; no history of MI	Total *trans,* 18:1 *trans;* 18:2 *trans (validated FFQ* and *adipose)*	Interquintile range: Total trans: 1.39% Trans 18:2: 0.13% Trans 18:1: >20th %ile vs. <20th %ile	Attending cardiologist	Matching: age, sex Covariates: Age, education, family history of MI, smoking, physical activity, total energy, BMI	8	Not stated
Mashal et al., 2012; Jordan	33-51	Cases: 74; Controls 31	100/91 [1:1]	CHD cases diagnosed within the past 1yr at the King Hussein Medical Center	Apparently healthy personnel from the same hospital and friends and relatives	Total *trans (FFQ)*	Q4 vs. Q1; per 1% per 100 g fat/d	Determined by "experienced" staff cardiologist	Matching: none Covariates: age, sex, diabetes, blood pressure, blood lipids	4	Research Support Fund of University of Jordan
Ascherio et al., 1994; United States	58 (10)	78	239/282 [1:1.2]	White men and women aged <76 with no previous history of MI or angina presenting to 6 Boston, MA (USA) coronary care units	Selected at random from resident list of town that gave rise to the case	All C18 *trans,* vegetable *trans,* animal *trans (validated FFQ)*	Q5 vs. Q1 Total *trans*: 6.52 vs. 1.69 g/d Vegetable trans: 5.04 vs. 0.84 g/d Animal *trans*: 1.79 vs. 0.45 g/d	Confirmed from hospital record	Matching: Age, sex, cardiac history	8	Not stated
Clifton et al., 2004	57	80	79/167 [1:2]	First admission for heart disease to 4 major hospitals in Adelaide; free of angina, dyslipidemia, or diabetes	Drawn from a random sample from the electoral roll	16:1 trans; 18:1 trans (total) ; 18:1t9, 18:1t10, 18:1t11 (adipose tissue) Total *trans (validated FFQ)*	Q5 vs. Q1 (diet): 3.7 g vs. 1.6 g/d	Confirmed from hospital chart (clinical history) plus ECG or CK increase	Matching: age, sex, postal code Covariates: energy, saturated fat		Meadow Lea Foods

Study	Follow-up	Diet Method	Diet measured	Unit increase	RR
Nurses' Health Study[66]	14 y	Validated semi-quantitative FFQ	Baseline, 1984, 1986, 1990	2% E	1.30 (1.15, 1.47)
Zutphen Elders Study[30]	10 y	Cross-check diet history	Baseline, 1990, 1995	2% E	1.28 (1.01, 1.61)
ATBC[29]	10 y	Diet history questionnaire	Baseline	2% E	1.14 (0.96, 1.35)
Health Professionals Follow-up Study[2,28]	14 y	Validated semi-quantitative FFQ	Baseline, 1990, 1994, 1998	2% E	1.26 (0.99, 1.61)
Meta-analysis				**2% E**	**1.25 (1.15, 1.36)**

eTable 14. Pooled multivariable RR of CHD associated with a 2% increase in TFA intake at the expense of carbohydrate.

Study	Follow-up	Diet Method	Diet measured	Unit increase	RR
Strong Heart Study (47-59 y)[26]	7 y	24-hour recall	Baseline	2% E	1.25 (0.80, 1.94)
Strong Heart Study (60-79 y)[26]	7 y	24-hour recall	Baseline	2% E	1.12 (0.75, 1.43)
Health Professionals' Followup Study[28,2]	6 y	Validated semi-quantitative FFQ	Baseline, 1990	2% E	0.93 (0.52, 1.66)
ATBC[29]	6.1 y	Validated diet questionnaire	Baseline	2% E[cxiii]	1.41 (1.28, 1.56)
Meta-analysis				**2%E**	**1.31 (1.13, 1.56)**

eTable 15. Pooled multivariable RR of CHD mortality associated with a 2% increase in TFA intake at the expense of carbohydrate.

Study	Follow-up	Diet Method	Diet measured	Unit increase	RR
Nurses' health Study[37]	14 y	Validated semi-quantitative FFQ	Baseline, 1984, 1986, 1990	2% E	1.39 (1.15, 1.67)
ATBC[29]	12 y	Validated diet questionnaire	Baseline	2% E[i]	1.51 (1.04, 2.16)
Meta-analysis				**2%E**	**1.41 (1.20, 1.67)**

eTable 16. Pooled multivariable RR of type 2 diabetes associated with a 2% increase in TFA intake at the expense of carbohydrate.

Study	Follow-up	Diet Method	Diet measured	Unit increase	RR
Health professionals follow-up study[34]	14 y	Validated semi-quantitative FFQ	Baseline, 1990, 1994	2% E	0.86 (0.55, 1.32)
Women's Health Initiative[75]	7.6 y	Validated semi-quantitative FFQ	Baseline, 3 years later	2% E[cxiv]	1.09 (0.77, 1.53)
Meta-analysis				**2%E**	**1.00 (0.76, 1.30)**

eTable 17. Pooled multivariable RR of ischemic stroke associated with a 2% increase in TFA intake at the expense of carbohydrate.

eTable 18. GRADE Evidence Profile for prospective cohort studies of trans-fatty acids and health outcomes limiting analyses to those studies with a "highest" exposure category estimated >1% of dietary energy (Explanatory notes appear at the end of this document)

Quality Assessment									Summary of Findings					
Exposure	**Outcome**	**Participants (# studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rate (%)**	**Absolute - adjusted (per 10,000)[1]**	**Dose-Response**	**Most-adjusted MV RR**	**Least-adjusted MV RR**	**Importance**
Total TFA	Total mortality	18,513 (1 study; 1 comparison)[2]	No serious risk of bias[3]	Not assessed[4]	No serious indirectness	No serious imprecision[5]	Not assessed[6]	⊕⊕◯◯ **LOW[7]**	1,573/18,513 (8.5%)	274 more (from 46 more to 536 more)	Yes[8]	1.24 (1.04 to 1.47)[9]	1.83 (1.57 to 2.15)	CRITICAL
	CHD mortality	70,864 (5 studies; 6 comparisons)[10]	No serious risk of bias[11]	No serious inconsistency[12]	No serious indirectness	No serious imprecision[13]	Not assessed[14]	⊕⊕⊕◯ **MODERATE[15]**	1,234/70,864 (1.7%)	56 more (from 18 more to 101 more)	Yes[16]	1.28 (1.09 to 1.50)	1.34 (1.00 to 1.79)	CRITICAL

Quality Assessment										Summary of Findings				
Exposure	**Outcome**	**Participants (# studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rate (%)**	**Absolute - adjusted (per 10,000)[17]**	**Dose-Response**	**Most-adjusted MV RR**	**Least-adjusted MV RR**	**Importance**
Total TFA	CHD total	145,922 (6 studies; 7 comparisons)[18]	No serious risk of bias[19]	No serious inconsistency[20]	No serious indirectness	No serious imprecision[21]	Not assessed[22]	⊕⊕⊕◯ **MODERATE[23]**	4,579/145,922 (3.1%)	88 more (from 42 more to 139 more)	Yes[24]	1.21 (1.10 to 1.33)	1.31 (1.15 to 1.48)	CRITICAL
	Ischemic Stroke	190,284 (3 studies; 4 comparisons)[25]	No serious risk of bias[26]	Serious inconsistency[27]	No serious indirectness	Serious imprecision[28]	Not assessed[29]	⊕◯◯◯ **VERY LOW[30]**	1,905/190,284 (1.0%)	5 more (from 8 fewer to 20 more)	No[31]	1.07 (0.88 to 1.28)	1.13 (0.94 to 1.37)	CRITICAL
	Type 2 diabetes	230,135(6 studies; 6 comparisons)[32]	Serious risk of bias[33]	Serious inconsistency[34]	No serious indirectness	Serious imprecision[35]	Not assessed[36]	⊕◯◯◯ **VERY LOW[37]**	8,690/230,135 (3.8%)	56 more (from 28 fewer to 151 more)	Unclear[38]	1.10 (0.95 to 1.27)	1.28 (1.05 to 1.55)	CRITICAL

[1] Absolute risk was estimated using the method of Newcombe et al. (*Evid Based Med* 2014;19;6-8). Estimates of baseline risk and associated 95% confidence levels, were obtained from the Emerging Risk Factors Consortium (*Lancet* 2010 Jun 26;375(9733):2215-22) which included 691,872 people from 102 prospective studies. Overall, the mean age of participants at entry was 52 (SD 13) years, and 297,081 (43%) were women. (96%) were in Europe, North America, and Australasia, with the remainder in Japan or the Caribbean. These risks were 11.4% (11.2% to 11.6%) for total mortality; 2.0% (1.9% to 2.2%) for CHD mortality, 4.2% (4.1% to 4.4%) for total CHD: 0.7% (0.5% to 0.8%) for ischemic stroke; and 5.6% (5.5% to 5.8%) for type 2 diabetes.

[2] Included data from 1 prospective cohort study (1 comparison), with 7 years of follow-up, enrolling participants from the United States.

[3] Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score was 8. Fully-adjusted model yielded weaker estimate than minimally-adjusted model, suggesting that these variables captured some important confounders. Since the direction of the bias is likely towards the null, and the pooled estimate exceeded the threshold of harm (>1.2), not downgraded.

[4] Unable to assess with only one study.

[5] Optimal information size met (n= 1,573 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI excludes meaningful benefit.

[6] Unable to assess with only one study.

[7] Data from cohort studies begin with a grade of "LOW". Not downgraded.

[8] P-value for trend of increased risk across quintiles of intake=0.004; the study did not present data for the continuous association. Because only 1 cohort provided data for test for trend, we did not feel confident upgrading for possible dose-response.

[9] Estimate from one study.

[10] Included data from 5 prospective cohort studies (6 comparisons), with a duration of follow-up from 6 to 21.4 years (median=6.6), enrolling participants from 3 different countries (USA, Finland, and the Netherlands).

[11] Possibility of residual confounding always must be considered in observational studies. Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. Newcastle-Ottawa scores of these studies range from 7 to 9 (median=7.5). Diet assessment in 3 studies (Ascherio et al., Pietinen et al., Oomen et al.) was by validated instrument. In Xu et al., a single 24-h recall was used. Using a single dietary assessment may induce misclassification of true diet over the longer term, as during the follow-up period, it is likely that the composition of the food supply changed substantially. Since the direction of the bias is likely towards the null, and the pooled estimate exceeded the threshold of harm (>1.2), not downgraded.

[12] I^2=0%; P_{het}=0.66. 5 studies had point estimates >1.0 and 95% CI and in the 1 study that did not, the 95% CI of this estimate was 0.42 to 1.65.

[13] Optimal information size met (n=1,234 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI bound excludes meaningful benefit.

[14] Due to small number of studies (n<10) risk of publication bias not formally assessed. However, inclusion of additional "underpublished" data from the Iowa Womens' Health study + Finnish Mobile Health Clinics Study (see eFigure 17) results in pooled estimate of 1.22 (95% CI: 1.07 to 1.36; P=0.002; I^2=0%; P_{het}=0.46)

[15] Data from cohort studies begin with a grade of "LOW". Upgraded (+1) due to evidence for dose-response.

[16] Continuous dose-response relationship was assessed in 4 studies (n=1,002 events; RR per 2% increase in TFA at the expense of carbohydrate: 1.31 (1.13 to 1.56).

[17] Estimated using prevalence data from Heart and Stroke Foundation (Canada), American Heart Association (U.S.A.), American Diabetes Association (U.S.A.), World Health Organization (WHO), Centers for Disease Control (U.S.A.)

[18] Included data from 6 prospective cohort studies (7 comparisons), with a duration of follow-up from 1 to 20 years (median=6), enrolling participants from 3 different countries (USA, Finland, Netherlands).

[19] Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores of these studies range from 7 to 9 (median=8). Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. Both studies assessed diet with validated instruments, at multiple time points. Not downgraded.

[20] I^2=0%; P_{het}=0.43. All 7 comparisons reported point estimates >1.0.

[21] Optimal information size met (n=4,579 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI bound excludes meaningful benefit.
[22] Due to small number of studies (n<10) risk of publication bias not formally assessed.
[23] Data from cohort studies begin with a grade of "LOW". Upgraded (+1) due to evidence for dose-response.
[24] Continuous dose-response relationship was assessed in 4 studies (n=1,852 events; pooled mvRR per 2% increase in TFA at the expense of carbohydrate: 1.25 (1.15 to 1.36); meta-analyses of non-referent quantiles found statistically significant increased risk within all quantiles.
[25] Included data from 3 prospective cohort studies (4 comparisons), with a duration of follow-up from 7 to 14 years (median=7.3), enrolling participants from the United States.
[26] Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores for 3 studies ranged from 7 to 8 (median=7.5). Common limitations were failure to control for family history, and unclear attrition rates.
[27] I^2=67%; 2/4 >1.0. Notably, an important inconsistency is that one study (He et al.) suggests important benefit (RR at the lower bound of clinically relevant benefit, RR=0.8) while and another study (Yaemsiri et al.) suggests clinically important harm (RR=1.39, greater than 1.2). The 95% CI of each individual study would exclude the point-estimate of the other.
[28] Optimal information size met (n=1,905 events); summary RR crosses 1.0: lower bound of 95% CI approaches 0.8 and the upper bound is >1.2, which is consistent with is approaching clinically significant benefit and exceeding the upper threshold for harm.
[29] Due to small number of studies (n<10) risk of publication bias not formally assessed
[30] Data from cohort studies begin with a grade of "LOW". Downgraded due to serious inconsistency, and serious imprecision.
[31] Two studies directly assessed dose-response (He et al. and Yaemsiri et al.); no continuous association seen in either study.
[32] Included data from 6 prospective cohort studies (6 comparisons), with a duration of follow-up from 8.8 to 20 years (median=12), enrolling participants from the United States (n=5) and Finland (n=1).
[33] Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores of these studies range from 6 to 9 (median=8). Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. A sensitivity analysis suggested the positive association seen in Salmeron et al. may be attributable to other dietary variables. Pooling the models which did not adjust for fiber and magnesium (Salmeron et al., van Dam et al., Simila et al.), resulted in a MVRR = 1.28 (95% CI: 1.16 to 1.41) though this may reflect failure to adjust for other important confounders. Pooling 5 studies that did not adjust for Mg or Fiber (and other confounders) yields an mVRR = 1.25 (95% CI: 1.15 to 1.36; P<0.001; I^2=0%; P_{het}=0.72)
[34] I^2=66%; P_{het}=0.01. Point estimates for 4 studies >1.0; point estimates for 2 studies <1.0. Upper bound of 95% CI >1.2 but lower bound >0.8.
[35] Optimal information size met (n=8,690 events); summary 95% CI of the RR includes 1.0, but upper bound >1.25, consistent with possible harm. Lower CI excludes meaningful benefit.
[36] Due to small number of studies (n<10) risk of publication bias not formally assessed
[37] Cohort studies start with a GRADE of "LOW". Downgraded for serious risk of bias, inconstancy, and imprecision.
[38] Two studies (n=3,605 cases) directly assessed the dose-response association. In these 2 studies, a 2% increase in energy from trans fatty acids (at the expense of carbohydrate) was associated with a 41% increased risk of type 2 diabetes (MVRR: 1.41; 95% CI: 1.20 to 1.67). However, studies which did not directly assess this association failed to find associations between extreme quintiles.

eTable 19. GRADE Evidence Profile for prospective cohort studies of trans-fatty acids and health outcomes comparing highest vs. Lowest exposure levels, where referent group TFA reported (or estimated to be) <1% of energy.

Quality Assessment									Summary of Findings					
Exposure	**Outcome**	**Participants (# studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rate (%)**	**Absolute - adjusted (per 10,000)[1]**	**Dose-Response**	**Most-adjusted MV RR**	**Least-adjusted MV RR**	**Importance**
Total TFA	Total mortality	0/0	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
	CHD mortality	68,957 (4 studies, 4 comparisons))[2]	No serious risk of bias[3]	No serious inconsistency[4]	No serious indirectness	No serious imprecision[5]	Not assessed[6]	⊕⊕⊕◯ **MODERATE**[7]	1,093/68,957 (1.6%)	56 more (from 18 more to 101 more)	Yes[8]	1.28 (1.09 to 1.50)	1.31 (0.94 to 1.83)	CRITICAL

C:\Users\Russell\Dropbox\WHO Sat and Trans Fat Combined- BMJ\06-01-2015_RESUBMISSION\eTable 19 GRADE ref lt1%.docx

Quality Assessment										Summary of Findings				
Exposure	**Outcome**	**Participants (# studies)**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rate (%)**	**Absolute - adjusted (per 10,000)[9]**	**Dose-Response**	**Most-adjusted MV RR**	**Least-adjusted MV RR**	**Importance**
Total TFA	CHD total	101,499 (4 studies, 4 comparisons)[10]	No serious risk of bias[11]	No serious inconsistency[12]	No serious indirectness	No serious imprecision[13]	Not assessed[14]	⨁⨁⨁◯ **MODERATE[15]**	2,715/101,499 (2.7%)	67 more (from 17 more to 122 more)	Yes[16]	1.16 (1.04 to 1.29)	1.26 (1.10 to 1.44)	CRITICAL
	Ischemic Stroke	86,152 (1 study, 1 comparison)[17]	No serious risk of bias[18]	Not assessed[19]	No serious indirectness	Serious imprecision[20]	Not assessed[21]	⨁◯◯◯ **VERY LOW[22]**	455/86,152 (0.5%)	14 fewer (from 33 fewer to 13 more)	No[23]	0.80 (0.54 to 1.18)	0.93 (0.69 to 1.25)	CRITICAL
	Type 2 diabetes	109,963 (4 studies, 4 comparisons)[24]	Serious risk of bias[25]	Serious inconsistency[26]	No serious indirectness	Serious imprecision[27]	Not assessed[28]	⨁◯◯◯ **VERY LOW[29]**	4,293/109,963 (3.9%)	45 more (from 45 fewer to 157 more)	Unclear[30]	1.08 (0.92 to 1.28)	1.42 (1.20 to 1.69)	CRITICAL

[1] Absolute risk was estimated using the method of Newcombe et al. (*Evid Based Med* 2014;19;6-8). Estimates of baseline risk and associated 95% confidence levels, were obtained from the Emerging Risk Factors Consortium (*Lancet* 2010 Jun 26;375(9733):2215-22) which included 691,872 people from 102 prospective studies. Overall, the mean age of participants at entry was 52 (SD 13) years, and 297,081 (43%) were women. (96%) were in Europe, North America, and Australasia, with the remainder in Japan or the Caribbean. These risks were 11.4% (11.2% to 11.6%) for total mortality; 2.0% (1.9% to 2.2%) for CHD mortality, 4.2% (4.1% to 4.4%) for total CHD: 0.7% (0.5% to 0.8%) for ischemic stroke; and 5.6% (5.5% to 5.8%) for type 2 diabetes.
[2] Included data from 4 prospective cohort studies (4 comparisons), with a duration of follow-up from 6 to 21.4 years (median=6.6), enrolling participants from 2 different countries (USA and Finland).
[3] Possibility of residual confounding always must be considered in observational studies. Fully-adjusted model yielded similar estimates to minimally adjusted models. Newcastle-Ottawa scores of these studies range from 7 to 9 (median=8.5). Diet assessment in 3 studies (Ascherio et al., Pietinen et al., Virtanen et al.) was by validated instrument. In Xu et al., a single 24-h recall was used. Using a single dietary assessment may induce misclassification of true diet over the longer term, as during the follow-up period, it is likely that the composition of the food supply changed substantially. Since the direction of the bias is likely towards the null, and the pooled estimate exceeded the threshold of harm (>1.2), not downgraded.
[4] I^2=0%; P_{het}=0.64. All 4 studies had point estimates >1.0.
[5] Optimal information size met (n=1,093 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI bound excludes meaningful benefit.
[6] Due to small number of studies (n<10) risk of publication bias not formally assessed. However, inclusion of additional "underpublished" data from the Iowa Womens' Health study + Finnish Mobile Health Clinics Study results in pooled estimate of 1.21 (95% CI: 1.05 to 1.40; P=0.008; I^2=4%; P_{het}=0.40)
[7] Data from cohort studies begin with a grade of "LOW". Upgraded (+1) due to evidence for dose-response.
[8] Continuous dose-response relationship was assessed in 3 studies (n=910 events; RR per 2% increase in TFA at the expense of carbohydrate: 1.37 (1.21 to 1.56).
[9] Estimated using prevalence data from Heart and Stroke Foundation (Canada), American Heart Association (U.S.A.), American Diabetes Association (U.S.A.), World Health Organization (WHO), Centers for Disease Control (U.S.A.)
[10] Included data from 4 prospective cohort studies (4 comparisons), with a duration of follow-up from 1 to 7.2 years (median=6), enrolling participants from 2 different countries (USA, Finland).
[11] Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores of these studies range from 8 to 9 (median=8.5). Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. Both studies assessed diet with validated instruments, at multiple time points. Not downgraded.
[12] I^2=0%; P_{het}=0.91. All 4 comparisons reported point estimates >1.0.
[13] Optimal information size met (n=2,719 events); summary RR does not cross 1.0, however upper 95% CI exceeds threshold of harm (>1.2) and lower 95% CI bound excludes meaningful benefit.
[14] Due to small number of studies (n<10) risk of publication bias not formally assessed.
[15] Data from cohort studies begin with a grade of "LOW". Upgraded (+1) due to evidence for dose-response.
[16] Continuous dose-response relationship was assessed in 2 studies (n=2,133 events; pooled mvRR per 2% increase in TFA at the expense of carbohydrate: 1.15 (0.97 to 1.36); meta-analyses of non-referent quantiles found statistically significant increased risk within all quantiles.
[17] Included data from 1 prospective cohort study (1 comparison), with a duration of follow-up of 14 years, enrolling participants from the United States.
[18] Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa score for this study was 7. Limitations were failure to control for family history, and unclear attrition rate.
[19] Not assessed; only 1 study.
[20] Optimal information size met (n=455 events); summary RR crosses 1.0: lower bound of 95% CI exceeds 0.8 and the upper bound is approaching 1.2, which is consistent with is approaching clinically significant benefit and exceeding the upper threshold for harm.
[21] Not assessed; only 1 study.
[22] Data from cohort studies begin with a grade of "LOW". Downgraded due to serious imprecision.
[23]This study directly modeled continuous dose-response; no continuous association was seen.
[24] Included data from 4 prospective cohort studies (4 comparisons), with a duration of follow-up from 8.8 to 20 years (median=12), enrolling participants from the United States (n=3) and Finland (n=1).
[25] Possibility of residual confounding always must be considered in observational studies. Newcastle-Ottawa scores of these studies range from 7 to 9 (median=8). Fully-adjusted model yielded weaker estimates than minimally-adjusted models, suggesting that these variables captured some important confounders. Pooling the models which did not adjust for fiber and magnesium (van Dam et al., Simila et al.), resulted in a MVRR = 1.26 (95% CI: 1.11 to 1.43) though this may reflect failure to adjust for other important

confounders. Pooling 4 estimates that did not adjust for Mg or Fiber (but which did address other potential confounders) yields an mVRR = 1.23 (95% CI: 1.12 to 1.35; P<0.001; I^2=0%; P_{het}=0.67)

[26] I^2=54%; P_{het}=0.09. Point estimates for 3 studies >1.0; point estimates for 1 study <1.0. Upper bound of 95% CI >1.2 but lower bound >0.8.

[27] Optimal information size met (n=4,293 events); summary 95% CI of the RR includes 1.0, but upper bound >1.25, consistent with possible harm. Lower CI excludes meaningful benefit.

[28] Due to small number of studies (n<10) risk of publication bias not formally assessed

[29] Cohort studies start with a GRADE of "LOW". Downgraded for serious risk of bias, inconsistency, and imprecision.

[30] One study (n=1,097 cases) directly assessed the dose-response association. In this study, a 2% increase in energy from trans fatty acids (at the expense of carbohydrate) was associated with a 51% increased risk of type 2 diabetes (MVRR: 1.51; 95% CI: 1.04 to 2.16). However, studies which did not directly assess this association failed to find associations between extreme quintiles.

eTable 20: Reported and estimated dietary intakes of trans fatty acids in cohort studies, according to quantile.

Percent intakes, where not provided (italics) were calculated from grams/d assuming that cohorts of women consumed 1800 kcal/d; and cohorts of men consumed 2100 kcal/d. Highest = fifth quintile, unless another quantile is in bold, in which case that quantile is the highest category.

			% energy						grams				
Study	**figure**	**Measure**	**Lowest**	**Q2**	**Q3**	**Q4**	**Highest**	**Contrast**	**Lowest**	**Q2**	**Q3**	**Q4**	**Highest**
All-Cause Mortality													
Chien	eFigure 11	total tfa	n/r				n/r		n/r				n/r
Kiage	eFigure 11	total tfa	1.60%	2.30%	2.84%	3.45%	4.68%	3.08%					
CHD Mortality													
Ascherio	eFigure 15	total tfa	*0.64%*	*0.94%*	*1.16%*	*1.41%*	*1.84%*	1.20%	1.5	2.2	2.7	3.3	4.3
Pietinen	eFigure 15	total tfa	*0.56%*	*0.73%*	*0.86%*	*1.16%*	*2.40%*	*1.84%*	1.3	1.7	2	2.7	5.6
Oomen	eFigure 15	total tfa					2% contrast	2.00%					
Xu 60-79	eFigure 15	total tfa	1.00%	1.80%	2.60%	**3.90%**	3.90%	2.90%					
Xu 47-59	eFigure 15	total tfa	0.90%	1.80%	2.60%	**4.00%**	4.00%	3.10%					
Virtanen	eFigure 15	total tfa	0.70%	0.90%	1.10%	**1.50%**	1.50%	0.80%					
CHD Mortality (+ unpublished)													
Ascherio	eFigure 17	total tfa	*0.64%*	*0.94%*	*1.16%*	*1.41%*	*1.80%*	1.16%	1.5	2.2	2.7	3.3	4.2
Pietinen	eFigure 17	total tfa	*0.56%*	*0.73%*	*0.86%*	*1.16%*	*2.40%*	*1.84%*	1.3	1.7	2	2.7	5.6
Oomen	eFigure 17	total tfa					2% contrast	2%					
Xu 60-79	eFigure 17	total tfa	1.00%	1.80%	2.60%	**3.90%**	3.90%	2.90%					
Xu 47-59	eFigure 17	total tfa	0.90%	1.80%	2.60%	**4.00%**	4.00%	3.10%					
Robien	eFigure 17	total tfa					1.5% contrast	1.50%					
Knekt 2013	eFigure 17	total tfa (W)	*0.45%*	*0.68%*	*0.85%*	*1.08%*	*1.70%*	1.25%	0.89	1.35	1.69	2.16	3.39
Knekt 2013	eFigure 17	total tfa (M)	*0.56%*	*0.79%*	*0.98%*	*1.23%*	*1.99%*	1.43%	1.3	1.85	2.29	2.87	4.64
Virtanen	eFigure 17	total tfa	0.70%	0.90%	1.10%	**1.50%**	1.50%	0.80%					

Study	figure	Measure	% energy						grams				
			Lowest	Q2	Q3	Q4	Highest	Contrast	Lowest	Q2	Q3	Q4	Highest
CHD total													
Pietinen	eFigure 19	total tfa	*0.56%*	*0.73%*	*0.86%*	*1.16%*	*2.66%*	2.10%	1.3	1.7	2	2.7	6.2
Oomen	eFigure 19	total tfa					2% contrast	2.00%					
Oh >=65	eFigure 19	total tfa	1.30%	1.60%	1.90%	2.20%	2.80%	1.50%	*not reported by age; used whole pop				
Oh <65	eFigure 19	total tfa	1.30%	1.60%	1.90%	2.20%	2.80%	1.50%	*not reported by age; used whole pop				
Xu	eFigure 19	total tfa	0.90%	1.80%	2.60%	**3.90%**	3.90%	3.00%					
Howard	eFigure 19	total tfa	0.55%	**2.50%**			2.50%	1.95%					
Ischemic Stroke													
He	eFigure 21	total tfa	*0.72%*	*1.00%*	*1.23%*	*1.47%*	*1.89%*	1.18%	1.67	2.34	2.86	3.44	4.42
Yaemsiri	eFigure 21	total tfa	*1.10%*	*1.15%*	*1.30%*	*1.70%*	*3.05%*	1.95%	2.2	2.3	2.6	3.4	6.1
Kiage 2014 W	eFigure 21	total tfa					*1.1% contrast*	*1.1%*					2.13
Kiage 2014 M	eFigure 21	total tfa					*0.9% contrast*	*0.9%*					2.13
type 2 diabetes													
Salmeron	eFigure 23	total tfa	1.30%	1.70%	2.00%	2.40%	2.90%	1.60%					
Meyer	eFigure 23	total tfa	*1.10%*	*1.20%*	*1.40%*	*1.75%*	*2.60%*	1.50%	2.2	2.4	2.8	3.5	5.2
van Dam	eFigure 23	total tfa	0.70%	1.00%	1.30%	1.50%	2.00%	1.30%					
Song	eFigure 23	total tfa	*0.56%*	*0.82%*	*1.05%*	*1.33%*	*1.83%*	1.27%	1.12	1.64	2.09	2.65	3.66
Simila	eFigure 23	total tfa					1% energy	1.00%					
Wang	eFigure 23	total tfa					Q4 vs. Q1						
INDUSTRIAL TFA													
all-cause mortality													
Laake M+W	no figure	PHVO	0.08%	0.40%	0.90%	1.40%	2.15%	2.08%					
Laake W+M	no figure	PHFO	0.43%	1.10%	1.60%	2.10%	2.85%	2.43%					
CHD mortality													
Laake M+W	eFigure 25	PHVO	0.08%	0.40%	0.90%	1.40%	2.15%	2.08%					
Laake W+M	eFigure 25	PHFO	0.43%	1.10%	1.60%	2.10%	2.85%	2.43%					
Pietinen	eFigure 25	Vegetable TFA	*0.04%*	*0.17%*	*0.34%*	*0.69%*	*2.19%*	2.14%	0.1	0.4	0.8	1.6	5.1
Pietinen	no figure	elaidic acid	*0.56%*	*0.73%*	*0.86%*	*1.16%*	*2.40%*	1.84%	1.3	1.7	2	2.7	5.6

Study	figure	Measure	% energy						grams				
			Lowest	Q2	Q3	Q4	Highest	Contrast	Lowest	Q2	Q3	Q4	Highest
CHD total													
Willettt	eFigure 29	Vegetable TFA	*0.72%*	*0.97%*	*1.22%*	*1.46%*	*1.71%*	0.99%	1.44	1.935	2.43	2.925	3.42
Oomen	eFigure 29	Manufactured TFA					2% contrast	2%					
RUMINANT TFA													
all-cause mortality													
Laake M	eFigure 33	ruminant TFA	0.20%	0.47%	0.62%	0.77%	1.00%	0.80%					
Laake W	eFigure 33	ruminant TFA	0.20%	0.47%	0.62%	0.77%	1.00%	0.80%					
CHD mortality													
Pietinen	eFigure 35	ruminant TFA	*0.26%*	*0.47%*	*0.64%*	*0.81%*	*1.07%*	0.81%	0.6	1.1	1.5	1.9	2.5
Laake M	eFigure 35	ruminant TFA	0.20%	0.47%	0.62%	0.77%	1.00%	0.80%					
Laake W	eFigure 35	ruminant TFA	0.20%	0.47%	0.62%	0.77%	1.00%	0.80%					
CHD total													
Willett 1993	eFigure 37	ruminant TFA	*0.48%*	*0.65%*	*0.81%*	*0.98%*	*1.14%*	0.66%	0.96	1.29	1.62	1.95	2.28
Oomen 2001	eFigure 37	ruminant TFA					0.75% contrast	0.75%					
Jakobsen W	eFigure 37	ruminant TFA	*0.35%*	*0.55%*	*0.75%*	*0.95%*	*1.35%*	1.00%	0.7	1.1	1.5	1.9	2.7
Jakobsen M	eFigure 37	ruminant TFA	*0.34%*	*0.56%*	*0.77%*	*1.03%*	*1.46%*	1.11%	0.8	1.3	1.8	2.4	3.4
type 2 diabetes													
Mozaffarian 2010	eFigure 41	trans-palmitoleic											
Mozaffarian 2013	eFigure 41	trans-palmitoleic											
Sartaren	eFigure 41	trans-palmitoleic											
Yakoob	eFigure 41	trans-palmitoleic											
Wang	eFigure 41	trans-palmitoleic	0.94%	1.42%	1.89%	2.44%	2.98%		1.8875		3.775		5.95