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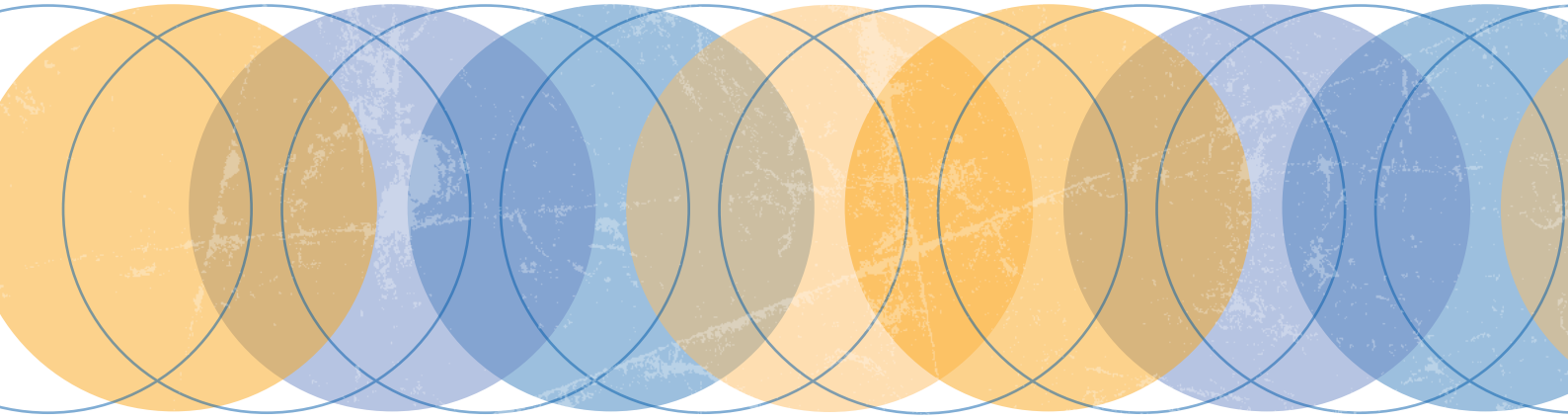

World Health Organization

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Contents

Abbreviations and acronyms

CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
DNL	de novo lipogenesis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MUFA	monounsaturated fats
NCD	noncommunicable disease
PUFA	polyunsaturated fats
RCT	randomized controlled trial
RR	relative risk
SFA	saturated fats/saturated fatty acids
TE	total energy
TFA	*trans*-fats/*trans*-fatty acids
WHO	World Health Organization

Summary

Objectives To examine the evidence from prospective observational studies, to contribute to the evidence base required for dietary recommendations relating to intakes of saturated fats (SFA) and trans-fats (TFA).

Design Systematic review and meta-analysis of studies from database inception to October 2020.

Data sources Medline, Embase, the Cochrane Central Registry of Controlled Trials, Evidence Based Medicine and CINAHL.

Review methods Eligible studies reported on either dietary or tissue measures of SFA or TFA and mortality or noncommunicable disease (NCD) incidence. We considered total SFA or TFA, specific chain lengths or isomers and food sources in extreme quantile, dose–response and replacement analyses where SFA and TFA were replaced with other macronutrients. Searches and data extraction were duplicated. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess quality of evidence.

Results There were 112 publications (3 696 568 participants) relating to SFA and 55 publications (2 227 241 participants) relating to TFA and prespecified health outcomes. Higher dietary intakes of SFA were associated with increased mortality. Mortality reduced when 5% of total energy from SFA was replaced with polyunsaturated fats (PUFA; relative risk [RR] 0.85; 95% confidence interval [CI]: 0.75 to 0.97), monounsaturated fats (MUFA; RR: 0.84; 95% CI: 0.75 to 0.95), plant MUFA (RR: 0.85; 95% CI: 0.82 to 0.88) and carbohydrates (RR: 0.92; 95% CI: 0.86 to 0.99). Coronary heart disease (CHD) incidence reduced with a 5% energy replacement with PUFA (RR: 0.89; 95% CI: 0.81 to 0.98), plant MUFA (RR: 0.83; 95% CI: 0.69 to 1.00) and slowly digested carbohydrates (RR: 0.94; 95% CI: 0.89 to 0.99). Higher tissue measures of total SFA were associated with increased CHD and type 2 diabetes incidence. Higher dietary intakes of TFA were associated with increased mortality, CHD and cardiovascular disease. A 2% replacement of TFA with plant MUFA reduced mortality (RR: 0.90; 95% CI: 0.85 to 0.96) and CHD (RR: 0.80; 95% CI: 0.70 to 0.92). The certainty of evidence was graded from moderate to very low, largely due to the amount of data available.

Conclusions Consideration of the totality of evidence available from prospective observational studies provides convincing evidence that replacing SFA and TFA with other macronutrients may reduce risk of mortality and CHD. These findings reinforce guidelines that SFA and TFA in the diet should be replaced by PUFA, plant MUFA and slowly digested carbohydrates.

Strengths and limitations of this study

- We conducted a systematic review and meta-analysis of prospective studies on the relationship between SFA and TFA intakes and mortality, and incidence of a range of NCDs to address this uncertainty and inform an update of World Health Organization recommendations for intakes of SFA and TFA.
- Our parallel consideration of total amount, dose–response and the replacement of these fats with other macronutrients allowed us to consider this topic in more detail than any other previous work on this topic.
- The approach recommended by the GRADE Working Group has been used to assess the quality of evidence and the importance of the observed associations that influence confidence in nutrition recommendations.

- The major limitation of this work relates to the self-reported dietary assessment methodologies used in cohort studies, an issue that is mitigated (at least in part) by our use of biomarkers in addition to the data generated from a range of dietary assessment methods.
- The relative paucity of data available precluded confidence in the analyses relating to food sources of SFA.

1. Introduction

The association between saturated fat (SFA) intakes and coronary heart disease (CHD) incidence and mortality was first reported in observational studies more than 50 years ago. For example, Keys and colleagues found a strong correlation between percentage of energy from SFA and CHD incidence in the Seven Countries Study *(1)*. This correlation was believed to be largely due to an association between SFA and low-density lipoprotein (LDL) cholesterol concentrations *(2)*. Since then, conflicting results have been reported from multiple prospective observational studies *(3–5)*, and more recently in systematic reviews and meta-analyses *(5–7)*. Variation in data inclusion criteria, approaches to dietary assessment, methods of data analysis and reporting of outcome measures may contribute to the inconsistencies reported to date. Meta-analyses of randomized controlled trials (RCTs) have also not provided conclusive evidence of the association between SFA and CHD *(8)*, a finding that is unsurprising given the difficulty in ensuring long-term compliance with dietary advice in intervention studies.

An increased risk of CHD in relation to trans-fat (TFA) intakes was first reported in the 1990s *(9)*, most likely due to the increase in LDL and reduction in high-density lipoprotein (HDL) cholesterol *(10, 11)*. Although findings in relation to adverse effects of TFA *(12–14)* have generally been more consistent than those reported for SFA *(6, 15–17)*, some uncertainty remains as to whether the effects of naturally occurring TFA, which are found in the fat of ruminant animals, are similar to those of industrially produced TFA consumed as partially hydrogenated vegetable oils (9, 18, 19).

Given the difficulties associated with long-term dietary intervention trials being insufficiently powered to generate conclusive findings relating to clinical outcomes, and the potential benefits of restricting SFA and TFA, the findings of observational studies are especially relevant. Because of inconsistencies in previous reports and newly available data that were not included in earlier meta-analyses, we conducted a meta-analysis to inform World Health Organization (WHO) recommendations for intakes of SFA and TFA. We examined both dietary intakes and the fatty acid composition of relevant tissue and blood lipids as an objective biomarker of intake, because tissue and blood fatty acids are mainly derived from dietary fatty acids *(20)*. We also, for the first time, analysed the effects of replacing SFA or TFA with other macronutrients on a wide range of key health outcomes.

2. Methods

This systematic review and meta-analysis was conducted following the WHO guideline development process *(21)* and reporting standards for systematic reviews and meta-analyses *(22)*. Population, intervention, comparison and outcome (PICO) were agreed by the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health.

2.1 Search strategy and selection criteria

We ran a previously employed *(6)* online search strategy up to October 2020, to identify prospective observational studies reporting on the association between SFA and TFA and critical health outcomes. Measures of SFA and TFA included consideration of specific chain lengths, food sources (i.e. SFA from dairy, SFA from animal, industrially produced TFA and ruminant-derived TFA) and dietary (%total energy [TE] or g/day) or tissue (%mol or % of TFA) measurements. Critical outcomes were all-cause mortality, cardiovascular disease (CVD) or CHD (fatal, non-fatal, or fatal and non-fatal), and incidence of ischaemic stroke or type 2 diabetes. We included data from prospective studies, including cohorts with specific pre-existing conditions. Eligible papers provided quantile comparisons or a higher versus lower intake risk ratio, odds ratio or hazard ratio. Studies that presented continuous estimates were not included in extreme quantile analyses, given the assumption of linearity; however, they were used in replacement analyses per 5% or 2% of TE. The online search strategy is shown in **Annex 1**. Databases searched were Medline, Embase, the Cochrane Central Registry of Controlled Trials, Evidence Based Medicine and CINAHL.

2.2 Study selection

Identification of eligible studies was undertaken independently by two researchers, with discrepancies resolved through discussion with an additional reviewer or first author of a previous review *(6)*. Hand searching of references of systematic reviews, prospective studies and clinical trials was undertaken to supplement the online search. No language restrictions were applied, and foreign language articles were translated. Data were extracted using pretested forms *(23)*. We extracted the most-adjusted effect size values as a conservative estimate of any exposure–outcome associations. If there were multiple publications from the same cohort, we used data for the longest follow-up period or with the most person-years, so that the same participants were not counted twice in the meta-analysis. Non-peer reviewed sources were not considered. A description of the relevant studies is given in **Annex 2**.

2.3 Data extraction and quality assessment

Data extraction for each review was undertaken independently by two researchers, with discrepancies resolved on discussion with an additional reviewer or first author of a previous review *(6)*. Before pooling data from multiple studies, we combined sex-specific or age-range risk estimates when reported separately within the same publication, using a fixed-effect meta-analysis. We did not combine risk estimates for separate cohorts reported in the same publication. We converted low versus high quantile risk estimates into high versus low, so that they could then be pooled with other studies. For studies reporting on cardiovascular outcomes, we used meta-regression techniques to consider whether there was a difference between CHD and CVD risk estimates for fatal, non-fatal, or fatal and non-fatal outcomes. Because we found no statistical evidence of a difference in the association between the exposures and these outcomes, we pooled such studies to comment on total CHD or CVD incidence. Where publications present data

from multiple tissue types (e.g. plasma or serum, red blood cells or adipose tissue), we prioritized plasma measurements because this was the tissue most commonly assessed. We did not extract data only available in hand-drawn figures *(24)*. Data are shown for all comparisons including two or more studies in results tables or the **Annexes 3–12**. We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) protocols *(25)* to assess the certainty of the body of evidence as either high, moderate, low or very low. Absolute risk was calculated using GradePRO software. Full GRADE tables are shown in **Annex 13**.

2.4 Data synthesis and analysis

For studies reporting dietary data in quantiles (SFA or TFA as a %TE or g/day) we pooled the most-adjusted risk estimates of the extreme quantiles with the DerSimonian and Laird random-effects model *(26)* to compare higher and lower intakes. We used the same analysis of quantile data for studies of tissue samples (%mol or % total fat) for studies reporting on specific chain lengths or groups of SFA or TFA, and for studies reporting on food sources of SFA or TFA when available. As a subgroup of these analyses, we also assessed extreme quantile intakes above or below 10%TE for SFA and above or below 1%TE for TFA for each outcome, to better comment on current WHO-recommended dietary targets *(27)*.

For restricted cubic spline dose–response analyses where data were reported in quantile format with SFA or TFA intake as a %TE, we considered dose–response relationships between total SFA or total TFA and outcomes with restricted cubic splines with three knots (at 10%, 50% and 90% of distribution) combined with multivariate meta-analyses *(28)*. The average or midpoint of each defined quantile was used for the dose amount, expressed as %TE intake. Where possible, we calculated %TE for studies reporting absolute intakes in g/day. If the range of the extreme quantiles was not specified, we used half the range of the adjacent quantile to establish the average intake.

Regarding replacement with other macronutrient dose–response analyses, for studies reporting on substitution or replacement of SFA or TFA with other macronutrients (e.g. carbohydrates, polyunsaturated fats [PUFA] or monounsaturated fats[MUFA]), we assumed that the association was linear, and standardized the %TE to a 5% replacement of SFA or a 2% replacement of TFA across studies before pooling them with random-effects *(26)*. Substitution analyses are based on statistical modelling of the data available from prospective observational studies; they are not the same as experimental data where intakes are changed.

Sensitivity analyses made it possible to comment on the robustness of the observed risk estimates. The presence of small study effects was assessed *(29)*, and when an impact was identified it was quantified *(30)*. The effect of each study's findings was considered with an influence analysis, removing one study at a time to consider its impact on the pooled estimate. Heterogeneity was assessed using I^2 *(31)*. A series of dichotomous or categorical meta regressions were undertaken on each analysis to consider factors such as the type of prospective observational study (cohort or nested case control), the dietary data collection method (reported dietary intake or tissue measurement), the tissue type assessed (plasma or serum, red blood cell or adipose tissue) and whether the cohort included the general population or those with a pre-existing disease. Analyses were conducted using Stata statistical software (version 15).

2.5 Role of the funding source

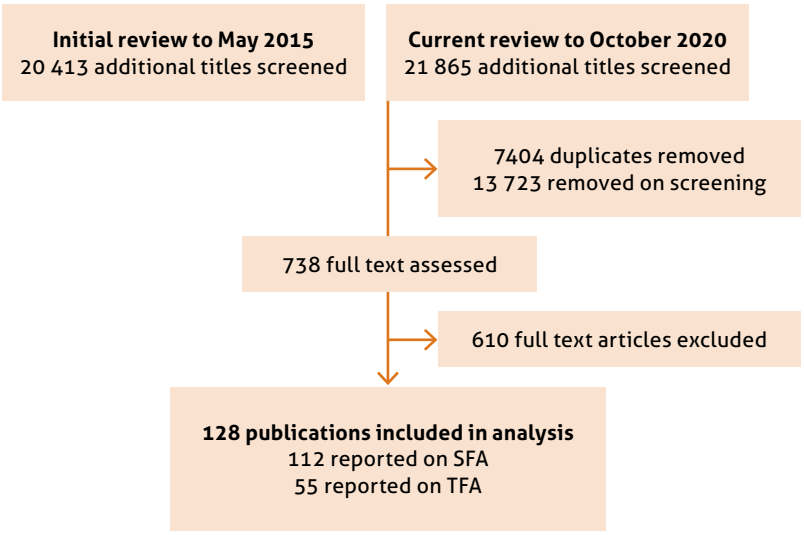
Among the funders, only WHO had a role in study design, data collection, data analysis, data interpretation or writing the report. The research was commissioned by WHO to inform the development of updated recommendations regarding SFA and TFA intake. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

3. Results

We identified 112 publications involving 3 696 568 participants that reported on SFA measures *(3–5, 7, 18, 19, 32–137)* and 55 publications involving 2 227 241 participants that reported on TFA measures and specified health outcomes *(9, 19, 35, 40, 42, 47, 53–55, 57, 59, 61, 62, 64, 66–68, 71–73, 81, 93, 97, 99, 105, 106, 113, 115, 116, 118, 120, 121, 123, 125, 128–130, 134, 136–152)*. Cohorts reporting on SFA were from North America (38%), Europe (28%), Asia (16%), Australia (4%) and the United Kingdom of Great Britain and Northern Ireland (United Kingdom) (4%), with the remainder being from the Middle East or multinational cohorts (11%). Cohorts reporting on TFA were mainly located in North America (60%) or Europe (27%), with the remainder being from Asia, Australia and the United Kingdom. The process of identifying relevant publications is shown in **Fig. 1**. A description of each eligible study is given in **Annex 2**.

Fig. 1. Identification of eligible studies for this review

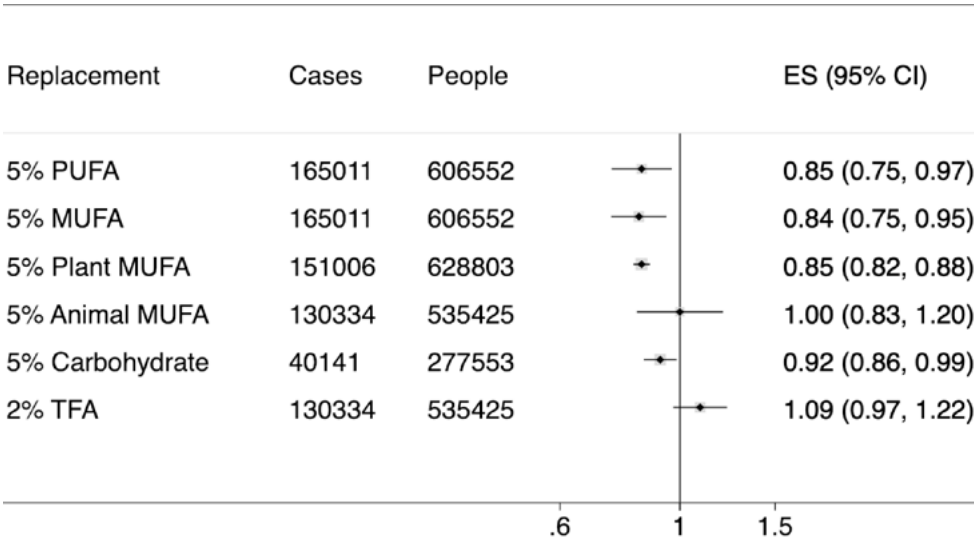


3.1 SFA and all-cause mortality

We identified 32 publications providing 34 data sets of SFA intakes and all-cause mortality. Data were available on 256 508 deaths in 1 509 268 people. Primary analyses relating to all-cause mortality are shown in **Table 1**, and replacement analyses of self-reported dietary intakes of SFA and all-cause mortality in **Fig. 2**. Additional analyses are shown in **Annex 3**.

Higher reported intakes of SFA were associated with increased risk of premature mortality when compared with lower intakes, and when comparing dietary intakes above and below 10%TE. Fewer data were available regarding the source of SFA and tissue measurements, and there was no evidence of a dose–response effect. Reductions in risk of all-cause mortality were observed in analyses where dietary SFA was replaced by PUFA, MUFA (especially plant MUFA) or carbohydrates. Replacements of SFA with MUFA from animal sources or TFA were not associated with a change in the all-cause mortality rate.

Fig. 2. Change in relative risk with replacement of total saturated fat by other macronutrients and all-cause mortality

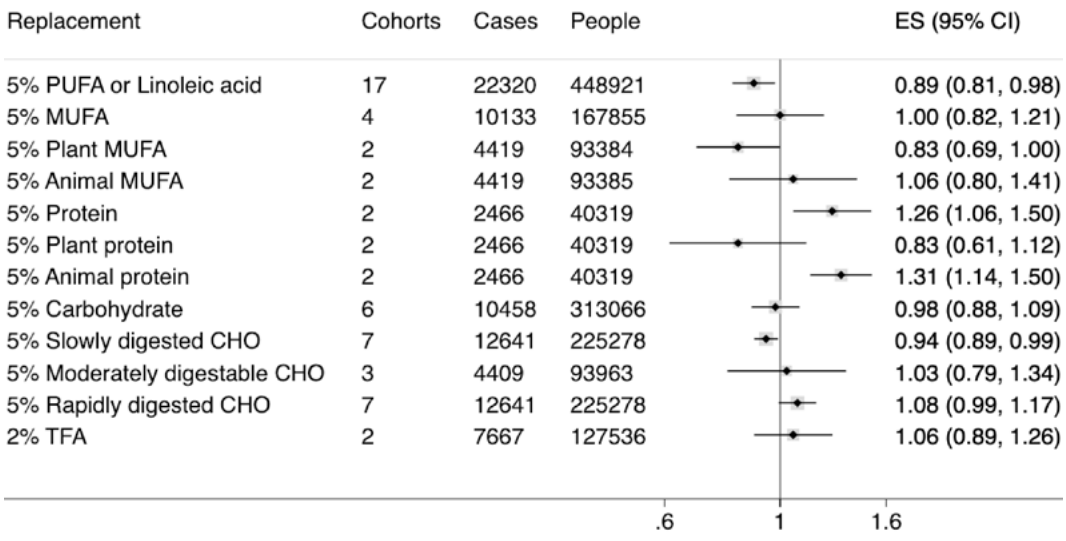


3.2 SFA and NCD outcomes

We identified 38 eligible publications relevant to CHD (66 810 events in 1 534 062 people), 30 to CVD (87 727 events in 1 445 634 people), 13 to ischaemic stroke (10 723 events in 472 933 people) and 34 to type 2 diabetes (118 498 cases in 880 835 people). SFA measurements and noncommunicable disease (NCD) outcomes are shown in **Table 1**, and replacement analyses of self-reported dietary intakes of SFA and CHD risk are shown in **Fig. 3**. Further details are shown in **Annexs 4–7**.

Reductions in CHD incidence were evident from substitution analyses when SFA was replaced in the diet with other macronutrients. Replacing SFA with PUFA, plant MUFA and slowly digested carbohydrates reduced CHD incidence; however, there was no reduction in risk when replacement was with rapidly digested carbohydrates (difference in CHD risk between replacement with slowly

Fig. 3. Change in relative risk with replacement of total saturated fat by other macronutrients and CHD incidence



or rapidly digested carbohydrates, *P*=0.047). Replacing SFA with protein (specifically, animal protein) was associated with increased CHD incidence. Fewer substitution data were available for other NCD outcomes; however, replacing SFA with PUFA or plant MUFA decreased CVD incidence. Data on SFA chain lengths and NCD outcomes are detailed in **Annexes 4–7**. No individual chain length of SFA (C12:0–C24:0) was significantly associated with a change in CHD incidence. Higher tissue measurements of C16:0 were associated with higher CVD and type 2 diabetes incidence when compared with lower tissue measurements. Lower tissue measurements of C15:0, C17:0 and SFA more than 20 carbons in length were associated with lower incidence of type 2 diabetes when compared with higher tissue measurements.

3.3 TFA and all-cause mortality

Thirteen publications relating to TFA intakes and all-cause mortality were available, providing information on 184 397 deaths in 770 780 people. Primary outcome data are shown in **Table 2** and additional analyses are shown in **Annex 8**.

Higher reported intakes of TFA were associated with increased premature mortality when compared with lower intakes, and when comparing dietary intakes above and below 1%TE. Restricted cubic spline analysis indicated a dose–response relationship between total TFA intakes and premature mortality (RR 1.14; 95% CI: 1.04 to 1.26) based on 167 453 deaths over 11 million person-years from seven cohorts. A dose–response was also observed with premature mortality when replacing 2%TE TFA in the diet with plant MUFA (RR: 0.90; 95% CI: 0.85 to 0.96). Tissue measurements of TFA were not associated with all-cause mortality.

3.4 TFA and NCD outcomes

We identified 19 relevant publications to CHD (28 667 events in 617 268 people), 15 to CVD (59 860 events in 871 673 people), four to ischaemic stroke (3634 events in 262 731 people) and 18 to type 2 diabetes (49 243 cases in 609 005 people). TFA measurements and NCD outcomes are shown in **Table 2**. Further details are shown in **Annexes 9–12**.

Higher dietary intakes of total TFA were associated with higher CHD and CVD incidence when compared with lower intakes, and when comparing intakes above and below 1%TE. Higher intakes of industrially produced TFA were also associated with increased CHD incidence. Restricted cubic spline analysis indicated a dose–response relationship between total TFA intakes and CHD incidence (RR: 0.25; 95% CI: 1.15 to 1.36) based on 10 132 deaths over 3 million person-years from seven cohorts. Furthermore, a 2%TE replacement of TFA with plant MUFA reduced CHD incidence (RR: 0.80; 95% CI: 0.70 to 0.92). Assessment of tissue measurements of total and individual TFA isomers is detailed in **Annexes 9–12**.

Table 1. Extreme quantile analyses of saturated fat measurements and all-cause mortality or noncommunicable disease incidence

Data source	Exposure	Cohorts	Cases	People	RR (95% CI)	Absolute risk (95% CI)	GRADE
ALL-CAUSE MORTALITY							
Dietary intake	Total SFA	21	213 579	1 211 729	1.08 (1.00 to 1.17)	14 more per 1000 (0 fewer to 30 more)	Low
Dietary intake	>10 vs <10%TE SFA[a]	13	194 456	1 095 528	1.09 (1.01 to 1.18)	16 more per 1000 (2 more to 32 more)	Low
Dietary intake	Animal SFA	2	724	17 530	1.05 (0.82 to 1.35)	2 more per 1000 (7 fewer to 14 more)	Very low
Dietary intake	Dairy SFA	2	6982	137 739	1.05 (0.64 to 1.71)	3 more per 1000 (18 fewer to 36 more)	Very low
Tissue measurements	C16:0	2	3832	4722	1.18 (0.91 to 1.53)	146 more per 1000 (73 fewer to 422 more)	Very low
CHD INCIDENCE (FATAL AND NON-FATAL)							
Dietary intake	Total SFA	18	19 263	570 326	1.04 (0.98 to 1.12)	1 more per 1000 (1 fewer to 4 more)	Low
Dietary intake	>10 vs <10%TE SFA[a]	5	10 538	268 221	1.00 (0.87 to 1.14)	0 more per 1000 (4 fewer to 4 more)	Low
Dietary intake	Animal SFA	3	3509	85 917	1.06 (0.96 to 1.17)	2 more per 1000 (2 fewer to 7 more)	Very low
Dietary intake	Dairy SFA	2	3464	75 425	1.00 (0.98 to 1.02)	0 per 1000 (1 fewer to 1 more)	Very low
Tissue sample	Total SFA	4	3916	24 108	1.46 (1.09 to 1.94)	75 more per 1000 (15 more to 153 more)	Low
Tissue measurements	C16:0	3	3155	8882	1.06 (0.92 to 1.23)	21 more per 1000 (28 fewer to 82 more)	Very low
CVD INCIDENCE (FATAL AND NON-FATAL)							
Dietary intake	Total SFA	16	68 232	1 088 501	1.07 (0.99 to 1.17)	4 more per 1000 (1 fewer to 11 more)	Low
Dietary intake	>10 vs <10%TE SFA[a]	11	61 329	969 859	1.10 (0.99 to 1.22)	6 more per 1000 (1 fewer to 14 more)	Very low
Dietary intake	Dairy SFA	2	6103	137 739	0.92 (0.75 to 1.12)	4 fewer per 1000 (11 fewer to 5 more)	Low

Data source	Exposure	Cohorts	Cases	People	RR (95% CI)	Absolute risk (95% CI)	GRADE
Tissue measurements	C16:0	2	2004	4722	1.12 (1.01 to 1.25)	51 more per 1000 (4 more to 106 more)	Very low
ISCHAEMIC STROKE INCIDENCE (FATAL AND NON-FATAL)							
Dietary intake	Total SFA	9	6400	402 847	0.98 (0.87 to 1.12)	0 per 1000 (2 fewer to 2 more)	Low
Dietary intake	>10 vs <10%TE SFA[a]	3	3048	172 688	0.91 (0.67 to 1.24)	2 fewer per 1000 (6 fewer to 4 more)	Very low
Tissue measurements	C16:0	2	699	7739	1.19 (0.93 to 1.52)	17 more per 1000 (6 fewer to 47 more)	Very low
TYPE 2 DIABETES INCIDENCE							
Dietary intake	Total SFA	13	15 727	351 134	1.02 (0.95 to 1.10)	1 more per 1000 (2 fewer to 4 more)	Low
Dietary intake	>10 vs <10%TE SFA[a]	5	7294	118 400	1.01 (0.82 to 1.23)	1 more per 1000 (11 fewer to 14 more)	Very low
Tissue sample	Total SFA	8	2599	18 867	1.30 (1.06 to 1.59)	41 more per 1000 (8 more to 81 more)	Very low
Tissue measurements	C16:0	23	18 094	75 922	1.41 (1.21 to 1.64)	98 more per 1000 (50 more to 153 more)	Very low

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RR: relative risk; SFA: saturated fats; TE: total energy; WHO: World Health Organization.

[a] Threshold analyses based on current WHO recommendations.

Table 2. Extreme quantile analyses of trans-fat measurements and all-cause mortality or noncommunicable disease incidence

Analyses	Exposure	Cohorts	Cases	People	RR (95% CI)	Absolute risk (95% CI)	GRADE
ALL-CAUSE MORTALITY							
Dietary intake	Total TFA	6	164 951	673 830	1.11 (1.02 to 1.20)	27 more per 1000 (5 more to 49 more)	Moderate
Dietary intake	>1% vs <1%TE TFA[a]	3	33 637	127 159	1.11 (1.00 to 1.24)	29 more per 1000 (0 to 63 more)	Very low
Tissue sample	Total TFA as %TF	6	2626	11 315	1.28 (0.90 to 1.82)	65 more per 1000 (23 fewer to 190 more)	Very low
Tissue sample	Ruminant-derived TFA	3	959	5427	1.23 (0.87 to 1.74)	41 more per 1000 (23 fewer to 131 more)	Very low
Tissue sample	Industrially produced TFA	3	959	5427	1.43 (0.70 to 2.93)	76 more per 1000 (53 fewer to 341 more)	Low
CHD INCIDENCE (FATAL AND NON-FATAL)							
Dietary intake	Total TFA	7	10 311	185 664	1.17 (1.09 to 1.27)	9 more per 1000 (5 more to 15 more)	Moderate
Dietary intake	>1% vs <1%TE TFA[a]	4	6575	67 739	1.14 (1.04 to 1.25)	14 more per 1000 (4 more to 24 more)	Low
Dietary intake	Ruminant-derived TFA	4	4311	177 659	0.93 (0.75 to 1.15)	2 fewer per 1000 (6 fewer to 4 more)	Very low
Dietary intake	Industrially produced TFA	3	4213	177 090	1.28 (1.10 to 1.50)	7 more per 1000 (2 more to 12 more)	Low
Tissue sample	Total TFA as %TF	3	3767	8722	0.98 (0.92 to 1.05)	9 fewer per 1000 (35 fewer to 22 more)	Low
CVD INCIDENCE (FATAL AND NON-FATAL)							
Dietary intake	Total TFA	6	47 406	675 673	1.14 (1.04 to 1.25)	10 more per 1000 (3 more to 18 more)	Very low
Dietary intake	>1% vs <1%TE TFA[a]	2	7878	126 233	1.20 (1.08 to 1.33)	12 more per 1000 (5 more to 21 more)	Low
Tissue sample	Total TFA as %TF	6	1430	11 315	1.08 (0.67 to 1.74)	10 more per 1000 (42 fewer to 94 more)	Very low

Analyses	Exposure	Cohorts	Cases	People	RR (95% CI)	Absolute risk (95% CI)	GRADE
Tissue sample	Ruminant-derived TFA	2	35	3439	0.48 (0.15 to 1.57)	5 fewer per 100 (9 fewer to 6 more)	Very low
Tissue sample	Industrially produced TFA	2	35	3439	0.52 (0.14 to 1.86)	5 fewer per 1000 (9 fewer to 9 more)	Very low
ISCHAEMIC STROKE INCIDENCE (FATAL AND NON-FATAL)							
Dietary intake	Total TFA as %TE or g/day	3	1889	257 437	1.09 (0.80 to 1.48)	1 more per 1000 (1 fewer to 4 more)	Very low
TYPE 2 DIABETES INCIDENCE							
Dietary intake	Total TFA	9	11 049	275 402	1.05 (0.95 to 1.16)	2 more per 1000 (2 fewer to 6 more)	Low
Dietary intake	>1% vs <1%TE TFA[a]	3	3286	81 231	1.02 (0.85 to 1.23)	1 more per 1000 (6 fewer to 9 more)	Very low
Tissue sample	Total TFA as %TF	4	1668	10 645	0.77 (0.40 to 1.48)	36 fewer per 1000 (94 fewer to 75 more)	Very low

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RR: relative risk; TE: total energy; TFA: trans-fats; WHO: World Health Organization.

[a] Threshold analyses based on current WHO recommendations.

4. Discussion

The most consistent findings of our pooled analyses of SFA intakes relate to health benefits when reducing intakes in the context of the overall macronutrient profile of the diet. Substitution of 5% of total energy derived from SFA with PUFA or MUFA from plant sources was associated with risk reductions in all-cause mortality, and in CHD or CVD incidence. Reduced risk of all-cause mortality and CHD were also observed when SFA were replaced with slowly digested carbohydrates, such as whole grains and other high-fibre carbohydrate-containing foods. Replacement of SFA with carbohydrates where the source was not specified, where the glycaemic index was moderate or high, or where the source was sugars was not associated with risk reduction. When not taking the overall macronutrient profile of the diet into account, a comparison of those in the highest compared with the lowest quantiles of SFA intake demonstrated an increased risk of all-cause mortality in those with the highest intakes. Some evidence supporting the potential benefits of a lower intake of SFA was also seen when considering tissue measurements and incidence of clinical outcomes.

Extreme quantile analysis indicated that higher dietary intakes of TFA were associated with increased all-cause mortality, and with both CVD and CHD incidence when compared with lower intakes. A clear dose–response relationship was observed for TFA intake and CHD incidence, regardless of the source of replacement energy. Although fewer data were available, replacement of energy intake from TFA with MUFA from plant sources reduced all-cause mortality and CHD incidence. Our analyses provide some support for a specific adverse effect of industrially produced TFA; however, we could not rule out a comparable effect of ruminant TFA based on the data available. Given that ruminant-derived TFA contribute only a small proportion of total dietary TFA, it seems appropriate to consider adverse health consequences in relation to total TFA intakes, regardless of source, for which there are clear outcomes and the most data are available.

We identified 128 studies published over the past 50 years that reported on the relationship between SFA or TFA levels and all-cause mortality or NCD incidence. Recently, numerous systematic reviews and meta-analyses have attempted to aggregate these findings *(5, 6, 12–18, 50, 66, 67, 92, 146, 153–158)*. Most previous meta-analyses have reported on the association between dietary intakes of total SFA and TFA, typically derived from food frequency questionnaires, and a single NCD outcome or all-cause mortality *(12, 14, 16, 17, 153–156)*. Fewer systematic reviews and meta-analyses have reported on the effects of individual SFA and TFA isomers *(50, 66, 67)*, or the effects of both dietary intakes and tissue markers of SFA or TFA *(15)*. Three meta-analyses have examined the relationship between intake and multiple disease outcomes *(5, 6, 13)*, and three recently published meta-analyses have considered macronutrient replacement (18, 92, 158). Although many previous reports have concluded that a high consumption of SFA or TFA is associated with adverse health outcomes *(50, 66, 146, 153, 155, 157, 158)*, several others have reported no effects *(6, 14–17, 92, 154)* or even benefits from higher intakes *(5, 12–14, 18, 67, 157)*. Our findings confirm and extend the findings of previous meta-analyses that have reported adverse clinical consequences of select SFA and TFA intakes and health outcomes *(50, 66, 146, 153, 155, 157, 158)*. Using various measures of intake, multiple health outcome measures and different analytical approaches, we have considered the totality of evidence from prospective observational studies.

A 2009 study by Jakobsen and colleagues based on data from 11 cohorts provided a possible explanation as to why some meta-analyses of SFA and CHD may have failed to find an association between SFA and CHD. The authors used individual-patient data from these cohorts and reported that a 5% replacement of energy intake from SFA with PUFA reduced the risk of both CHD

events and death *(159)*. For a 5% lower energy intake from SFA and a concomitant higher intake of carbohydrates, risk of coronary events but not coronary deaths was marginally increased. Those choosing a higher intake of MUFA had no difference in CHD rates. These findings show the importance of considering the effects of SFA in the context of the overall macronutrient content of the diet, although that study did not consider the sources or nature of these replacement nutrients. A subsequent meta-analysis that also considered the issue of replacement energy showed similar reductions in risk, based on extreme quantile comparison and dose–response relationships, when dietary linoleic acid replaced a proportion of energy provided by SFA *(18)*. We confirm and extend these observations in our considerably expanded meta-analysis. Our data confirm that PUFA replacement of SFA has the potential to be associated with a reduced risk of CHD; they also demonstrate comparable benefits when MUFA derived from plant sources and slowly digested carbohydrates replace SFA.

The fatty acid composition of adipose tissue and blood lipids has increasingly been used as an objective biomarker of dietary fat intake *(20)*. This is particularly appropriate in the case of long-chain n-3 and n-6 fatty acids, which are essential nutrients and for which blood concentrations reflect dietary intake *(20)*. Tissue and blood levels of SFA represent a combination of dietary SFA and those produced endogenously by de novo lipogenesis (DNL), such as palmitic acid (C16:0) *(160)*. The contribution of DNL-derived C16:0 in fasting is low (~10%) in healthy adults and higher (up to 22%) in individuals with insulin resistance or fatty liver disease *(161–163)*. Therefore, for most individuals it is likely that most tissue C16:0 would be derived from dietary fat sources. This fatty acid contributes up to 30% of the total fatty acid composition of red blood cells and serum lipids *(20)*, indicating that it may also be considered partially reflective of dietary intake. In our meta-analysis, extreme quantile comparisons demonstrated an appreciable increase in risk of CHD and type 2 diabetes incidence among those with high levels of total SFA or C16:0. Comparable findings have been reported from a recent meta-analysis of circulating fatty acid measured in individuals participating in five cohorts based in the United Kingdom and one matched case–control study *(3)*.

An association first demonstrated over 30 years ago between TFA and all-cause mortality and CHD *(9)* has been a consistent finding, despite TFA contributing a relatively small proportion of TE intake. Our extreme quantile analyses, dose–response data and macronutrient replacement analyses provide strong confirmation of previous findings. The striking adverse effects of TFA intakes are even more remarkable given that, in the countries from which most data were derived, regulatory measures have resulted in a reduction of TFA intake, to the extent that baseline measurements from cohorts do not reflect intakes over the period of observation. A recent consideration of two independent National Health and Nutrition Examination Survey (NHANES) cohorts indicated that dietary intakes of industrially produced fatty acids had halved over time following the introduction of public health regulation to remove them from the food supply, appreciably reducing any association between TFA intake and all-cause mortality *(152)*. Thus, it seems possible, indeed likely, that risk estimates associated with TFA may represent an underestimate of the true effect of sustained intakes.

This systematic review and meta-analysis has several strengths. For the first time, our approach has involved the examination of the relationships between SFA and TFA intakes (estimated from dietary assessment methods and tissue biomarkers) and multiple disease outcomes. We have used a range of analytical approaches and followed prescribed guidelines and protocols, which enable the findings to be used by WHO and other organizations that employ the GRADE approach to inform dietary recommendations. Furthermore, we have examined the associations in the context of intakes of other macronutrients, an approach first suggested by Jakobsen in 2009 and rarely employed since then *(18, 159)*. The estimates provided in our analyses are conservative. We analysed the most-adjusted risk estimates available from each study, many of which were adjusted for known mediators of the health outcomes considered. It may be that more judicious adjustments of confounders rather than moderators in future cohort reporting would better reflect the relationship between fatty acid exposure and health outcomes.

The major limitation of this work relates to the self-reported dietary assessment methodologies used in cohort studies, an issue which was mitigated (at least in part) by our use of biomarkers in addition to the data generated from a range of dietary assessment methods. The GRADE assessment that some of the associations were based on "low quality" evidence may also be considered a weakness. However, GRADE guidelines generally require the availability of data derived from RCTs for evidence to be considered "high quality". Given the difficulties associated with large long-term trials requiring a high level of dietary compliance, observational studies become more relevant , and when findings are consistent and compatible with experimental approaches they may lead to strong recommendations. The relative paucity of data available precluded confidence in the analyses relating to food sources of SFA. For example, the risk estimates suggesting a null effect in relation to the health consequences of dairy and animal sources of SFA are associated with wide confidence intervals and could not be further examined in relation to substitution with other foods. In addition, findings concerning foods are country or culture specific. It was our intention in this systematic review and meta-analysis to generate results that were likely to be broadly applicable and could be translated into a range of dietary patterns best suited to individuals and populations.

Our findings are consistent with experimental data that provide convincing evidence of a deleterious effect of SFA and TFA on clearly established risk factors for CVDs, notably total and LDL cholesterol *(164, 165)*. There are limitations associated with the long-term clinical trials that have attempted to determine the clinical consequences of restricting SFAs, but meta-analyses from the Cochrane Collaboration suggest that a reduced risk of coronary events is associated with the replacement of some dietary SFA with PUFA *(8)*. We consider that these findings pooled from 128 cohort studies make a substantial contribution to the totality of evidence indicating improved health outcomes when reducing total SFA and TFA in the diet. Promoting a reduction in SFA intake without an isocaloric replacement with other macronutrients may have the additional benefit of reducing energy intakes in the global obesity pandemic *(166)*. Our findings strongly reinforce the guidance that, when replacement energy is required, it should be provided by PUFA, plant sources of MUFA and slowly digested carbohydrates. Thus, dietary fats should come largely from seeds, nuts or liquid vegetable oil (olive, canola) rather than hydrogenated vegetable fats or land animal fats and coconut oil.

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- ANR reports receiving grants from the World Health Organization (WHO), grants from the Riddet Institute Centre of Research Excellence and personal fees from the National Heart Foundation of New Zealand during the conduct of the study;
- RdS reports receiving personal fees and non-financial support from WHO during the conduct of the study; personal fees from the Canadian Institutes of Health Research/Health Canada; grants from the Canadian Foundation for Dietetic Research; grants from the Canadian Institutes for Health Research; personal fees from McMaster Children's Hospital; grants from Hamilton Health Sciences Corporation/Population Health Research Institute; other from the College of Family Physicians of Canada, Royal College; and other from The Helderleigh Foundation outside the submitted work;
- JM reports receiving personal fees from Healthier Lives National Science Challenge during the conduct of the study; and
- the other authors report no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing Search strategy and eligible studies are shown in the annexes. Data used in analyses are available from the original publications.

Ethics statement No ethical approval is needed as data were from published studies.

[1] See www.icmje.org/coi_disclosure.pdf.

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Annexes

ANNEX 1.

Search terms

These searches were initially conducted up to 2015, as part of a previous systematic review. We ran the same searches in the same databases from 2015 up to 1 October 2020. Below is an example of the terms used for the saturated fats (SFA) and ***trans***-fats (TFA) searches.

For SFA intakes

1 Fatty Acids/

2 fatty acid*.tw.

3 Dietary Fats/

4 (saturated adj2 fat*).tw.

5 Butyric Acid/

6 ((butyric or butanoic) adj acid*).tw.

7 ((caproic or hexanoic) adj acid*).tw.

8 ((caprylic or octanoic) adj acid*).tw.

9 exp Decanoic Acids/

10 ((capric or decanoic) adj acid*).tw.

11 exp Lauric Acids/

12 ((lauric or docadecanoic) adj acid*).tw.

13 exp Myristic Acids/

14 ((myristic or tetradecanoic) adj acid*).tw.

15 exp Palmitic Acids/

16 ((palmitic or hexadecanoic) adj acid*).tw.

17 exp Stearic Acids/

18 ((stearic or octadecanoic) adj acid*).tw.

19 Diet, Carbohydrate-Restricted/

20 Diet, Fat-Restricted/

21 Diet, High-Fat/

22 Diet, Protein-Restricted/

23 diet*.tw.

24 ((low or restricted or free or high) adj1 fat).tw.

25 23 and 24

26 Dairy Products/

27 Butter/

28 Cheese/

29 Ice Cream/

30 exp Milk/

31 Meat/

32 Meat Products/

33 exp Poultry/

34 (butter or milk* or cheese* or cream* or meat*).tw.

35 Plant Oils/

36 (palm adj2 (oil or oils)).tw.

37 (lard or lards or tallow).tw.

38 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

39 Cardiovascular Diseases/

40 exp Heart Diseases/

41 exp Vascular Diseases/

42 Cerebrovascular Disorders/

43 exp Brain Ischemia/

44 exp Carotid Artery Diseases/

45 exp Dementia, Vascular/

46 exp Intracranial Arterial Diseases/

47 exp "Intracranial Embolism and Thrombosis"/

48 exp Intracranial Hemorrhages/

49 exp Stroke/

50 (coronar* adj5 (bypas* or graft* or disease* or event*)).tw.

51 (cerebrovasc* or cardiovasc* or mortal* or angina* or stroke or strokes).tw.

52 (myocardi* adj5 (infarct* or revascular* or ischaemi* or ischemi*)).tw.

53 (morbid* adj5 (heart* or coronar* or ischaem* or ischem* or myocard*)).tw.

54 (vascular* adj5 (peripheral* or disease* or complication*)).tw.

55 (heart* adj5 (disease* or attack* or bypass*)).tw.

56 Diabetes Mellitus/

57 exp Diabetes Mellitus, Type 2/

58 diabetes.mp. or diabetic.tw. [mp=ti, ot, ab, sh, hw, kw, tx, ct]

59 Mortality/

60 "Cause of Death"/

61 Fatal Outcome/

62 Hospital Mortality/

63 Mortality, Premature/

64 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63

65 38 and 64

66 exp case control study/

67 control group/

68 statistical analysis/

69 ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

70 cohort.ti,ab.

71 cohort analysis/

72 longitudinal study/

73 longitudinal.ti,ab.

74 prospective study/

75 prospective.ti,ab.

76 retrospective study/

77 retrospective.ti,ab.

78 epidemiology/

79 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 86 or 77 or 78

80 65 and 79

81 Animals/ not (Humans/ and Animals/)

82 80 not 81

For TFA intakes

1 fatty acids/ or exp fatty acids, unsaturated/

2 exp Diet/

3 infant formula/ or exp food/

4 exp plants, edible/ or vegetables/ or plants, genetically modified/

5 exp plant oils/ or corn oil/ or safflower oil/ or soybean oil/

6 dietary fats/ or butter/ or margarine/ or fats, unsaturated/

7 Or/1–6

8 exp Cardiovascular Diseases/

9 exp Stroke/

10 diabetes mellitus/ or exp diabetes mellitus, type 1/ or exp diabetes mellitus, type 2/ or diabetes, gestational/ or prediabetic state/

11 mortality/ or "cause of death"/ or fatal outcome/ or hospital mortality/ or mortality, premature/

12 Or/8–11

13 (conjugat* or unsaturat* or "trans fat*" or ruminant* or bovin* or rumenic* or "animal fat" or (trans adj2 fatty adj2 acid*) or (Trans adj2 isomer*) or "transfat*" or (fat* adj2 intake)).mp.

14 7 and 12 and 13

15 Animals/ not (Humans/ and Animals/)

16 14 not 15

ANNEX 2. Description of relevant studies

Table A1. Studies of SFA intakes and health outcomes included in meta-analyses

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Akter 2017 **Japan** *(1)*	Hitachi Health Study	1014 adults followed for 5 years	Total SFA and chain lengths	– Type 2 diabetes	Serum	– Extreme quantile tissue measures
Alhazmi 2013 **Australia** *(2)*	Longitudinal study on women's health	8370 women followed for 6 years	Total SFA	– Type 2 diabetes	DietHx	– Extreme quantile self-reported – Dose response
Ardisson Korat 2020 **USA** *(3)*	NHS and HPFS	2854 adults followed for 17.1 or 11.1 years	SFA chain lengths	– Type 2 diabetes	Diet FFQ	– Extreme quantile tissue measures
Ascherio 1996 **USA** *(4)*	HPFS	43 528 men followed for 6 years	Total SFA	– Fatal CHD – Total CHD	Diet FFQ	– Extreme quantile self-reported
Blekkenhorst 2015 **Australia** *(5)*	Perth Western Australian Study	1469 women followed for 10 years	Total SFA	– Fatal CVD	Diet FFQ	– Extreme quantile self-reported
Booth 2016 **USA** *(6)*	REGARDS	5709 adults followed for 5.8 years	Total SFA	– All-cause mortality – Total CVD	Diet FFQ	– Extreme quantile self-reported
Campmans-Kuijpers 2016 **Europe** *(7)*	EPIC	6192 adults followed for 9.2 years	Total SFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Replacement analyses
Chei 2018 **Japan** *(8)*	CIRCS	12 840 adults followed for 11 years	Total SFA and chain lengths	– Total CHD	Serum	– Extreme quantile tissue measures
Chien 2013 **Taiwan, China** *(9)*	Chin-Shan	3098 adults followed for 9.6 years	Total SFA	– All-cause mortality – Total CVD	Plasma phospholipids	– Extreme quantile tissue measures
Clarke 2009 **UK** *(10)*	Whitehall	355 men followed for 6.8 years	Total SFA	– Fatal CHD	Plasma phospholipids	– Extreme quantile tissue measures
de Oliveira Otto 2012 **USA** *(11)*	MESA	5209 adults followed for 7 years	Total SFA	– Total CVD	Diet FFQ	– Extreme quantile self-reported

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
de Oliveira Otto 2018 **USA** *(12)*	CHS	2907 adults followed for 22 years	SFA chain lengths	– All-cause mortality – Total CHD – Fatal CHD – Total CVD – Fatal CVD – Non-fatal CVD	Plasma phospholipids	– Extreme quantile tissue measurement
Dehghan 2017 **Multinational** *(13)*	PURE	135 335 adults followed for 7.4 years	Total SFA	– All-cause mortality – Fatal CVD – Total CVD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Dehghan 2018, **Multinational** *(14)*	PURE	130 701 adults followed for 9.1 years	SFA from dairy	– All-cause mortality – Total CVD	Diet FFQ	– Extreme quantile self-reported
Deshmukh 2018 **USA** *(15)*	NHANES	1191 adults followed for 17.2 years	Total SFA	– All-cause mortality	Diet 24hr recall	– Extreme quantile self-reported
Dominguez 2018 **Spain** *(16)*	SUN	9793 adults followed for 9.5 years	Total SFA	– All-cause mortality	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Dow 2016 **France** *(17)*	E3N	71 334 women followed for 18 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported – Dose response
Ericson 2015 **Sweden** *(18)*	Malmö	26 930 adults followed for 14 years	Total SFA and chain lengths	– Type 2 diabetes	Diet 7DDR and FFQ	– Extreme quantile self-reported – Dose response
Farvid 2014 **Multinational** *(19)*	11 cohorts	310 602 adults from 11 cohorts	Total SFA	– Fatal CHD	Diet FFQ and DietHx	– Replacement analyses
Forouhi 2014 **Europe** *(20)*	EPIC InterAct	27 296 adults	SFA chain length	– Type 2 diabetes	Plasma phospholipids	– Extreme quantile tissue measurement
Fretts 2016 **USA** *(21)*	CHS	3941 adults followed for 11.6 years	SFA chain length	– All-cause mortality – Fatal CHD – Fatal CVD	Plasma phospholipids	– Extreme quantile tissue measurement

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Fretts 2019 **Multinational** *(22)*	12 cohorts	51 431 adults	SFA chain length	– Type 2 diabetes	RBC, total plasma, plasma phospholipids	– Extreme quantile tissue measurement
Gillman 1997 **USA** *(23)*	Framingham	832 men followed for 20 years	Total SFA	– Fatal CHD	Diet 24hr recall	– Extreme quantile self-reported
Guasch-Ferré 2015 **Spain** *(24)*	PREDIMED	7038 adults followed for 6 years	Total SFA, food sources	– All-cause mortality Total CVD	Diet FFQ	– Extreme quantile self-reported – Dose response
Guasch-Ferré 2017 **Spain** *(25)*	PREDIMED	3349 adults followed for 4.3 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported – Dose response
Guasch-Ferré 2019 **USA** *(26)*	NHS and HPFS	93 378 adults followed for 22 years	Total SFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Replacement analyses
Harris 2016 **USA** *(27)*	Women's Health Initiative Memory study	6379 women followed for 11 years	SFA chain lengths	– Type 2 diabetes	RBC membrane	– Extreme quantile tissue measurement
He 2003 **USA** *(28)*	HPFS	43 732 men followed for 14 years	Total SFA	– Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported
Ho 2020 **UK** *(29)*	UK Biobank	195 658 adults followed for 10.6 years	Total SFA	– All-cause mortality	Diet 24HR	– Extreme quantile self-reported
Hodge 2007 **Australia** *(30)*	MCCS	3737 adults followed for 4 years	Total SFA and chain lengths	– Type 2 diabetes	Plasma phospholipids	– Extreme quantile tissue measurement
Hosseini-Esfahani 2020 **Iran** *(31)*	Tehran LGS	5102 adults followed for 5.3 years	Total SFA	– Total CVD	Diet FFQ	– Replacement analyses
Houston 2011 **USA** *(32)*	Health ABC	1,941 adults followed for 9 years	Total SFA	– Total CVD	Diet FFQ	– Extreme quantile self-reported
Howard 2006 **USA** *(33)*	WHI	32 728 women followed for 8.1 years	Total SFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported
Hu 1997 **USA** *(34)*	NHS	80 082 women followed for 13.2 years	Total SFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Hu 1999 **USA** *(35)*	NHS	80 082 women followed for 14 years	SFA chain lengths	– Total CHD	Diet FFQ	– Extreme quantile self-reported
Iggman 2016 **Sweden** *(36)*	Uppsala	853 men followed for 14.8 years	SFA chain lengths	– All-cause mortality – Fatal CVD	Buttock adipose	– Extreme quantile tissue measurement
Imamura 2018 **Multinational** *(37)*	12 cohorts	46 107 adults	SFA chain lengths	– Type 2 diabetes	Tissue measurements	– Extreme quantile tissue measurement
Imamura 2020 **Multinational** *(38)*	17 cohorts	62 225 adults	SFA chain lengths	– Type 2 diabetes	Tissue measurements	– Extreme quantile tissue measurement
Iso 2001 **USA** *(39)*	NHS	85 764 women followed for 14 years	Total SFA	– Ischaemic stroke	Diet FFQ	– -Extreme quantile self-reported
Jakobsen 2004 **Denmark** *(40)*	MONICA 1, MONICA II	3686 adults followed for 16 years	Total SFA	– Total CHD	Diet 7DDR	– Replacement analyses
Jakobsen 2010 **Denmark** *(41)*	DCHS	53 644 adults followed for 12 years	Total SFA	– Total CHD	Diet FFQ	– Replacement analyses
Jiao 2019 **USA** *(42)*	NHS and HPFS	11 264 adults followed for 11 years	Total SFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Khaw 2012 **UK** *(43)*	EPIC Norfolk	7354 adults followed for 13 years	Total SFA	– Total CHD	Plasma phospholipids	– Extreme quantile tissue measurement
Kröger 2011 **Germany** *(44)*	EPIC Potsdam	272 adults followed for 7 years	Total SFA and chain lengths	– Type 2 diabetes	Erythrocyte and Diet FFQ as a % of total fat	– Extreme quantile tissue measurement
Lai 2019 **USA** *(45)*	CHD	3869 adults followed 13 years	SFA chain lengths	– All-cause mortality – Fatal CVD – Total CHD – Total CVD – Ischaemic stroke	Plasma phospholipids	– Extreme quantile tissue measurement

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Lankinen 2015 **Finland** *(46)*	METSIM	1302 men followed for 5.9 years	Total SFA and chain lengths	– Type 2 diabetes	Plasma phospholipids, cholesteryl esters, Triacylglycerols	– Extreme quantile tissue measurement
Larsson 2012 **Sweden** *(47)*	SMC	34 670 women followed for 10.4 years	Total SFA	– Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported
Laursen 2018 **Denmark** *(48)*	DDCH	5294 adults followed for 12.8 years	Total SFA	– Ischaemic stroke	Adipose tissue	– Extreme quantile tissue measurement
Lemaitre 2015 **USA** *(49)*	CHS	3179 adults followed for 10.3 years	Total SFA and chain lengths	– Type 2 diabetes	Plasma phospholipids	– Extreme quantile tissue measurement
Leosdottir 2005 **Sweden** *(50)*	Malmö	27 190 adults followed for 6.6 years	Total SFA	– All-cause mortality – Fatal CVD	7DDR and FFQ	– Extreme quantile self-reported – Dose response
Lesodottir 2007 **Sweden** *(51)*	Malmö	28 098 adults followed for 8.4 years	Total SFA	– Total CHD – Total CVD – Ischaemic stroke	Diet 7DDR and FFQ	– Extreme quantile self-reported
Li 2015 **USA** *(52)*	NHS and HPFS	127 536 adults followed 30 (NHS) and 24 (HPFS) years	Total SFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Lin 2018 **China** *(53)*	GNHS	2683 adults followed for 5.6 years	Total SFA and chain lengths	– Type 2 diabetes	Erythrocyte	– Extreme quantile tissue measurement
Lindström 2006 **Finland** *(54)*	DPS	500 adults followed for 4.1 years	Total SFA	– Type 2 diabetes	Diet 3DDR	– Extreme quantile self-reported – Dose response
Liu 2019 **Netherlands** *(55)*	EPIC Netherlands	37 421 adults followed for 10.1 years	Total SFA and chain lengths	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported – Replacement analyses
Lu 2018 **Singapore** *(56)*	SCHS	320 adults	SFA chain lengths	– Type 2 diabetes	Serum	– Extreme quantile tissue measurement

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Ma 2015 **USA** *(57)*	CHS	4221 adults followed for 10.2 years	SFA chain lengths	– Type 2 diabetes	Diet FFQ and plasma phospholipids	– Extreme quantile self-reported – Extreme quantile tissue measurement
Malik 2015 **USA** *(58)*	HPFS and NHS	2,027 adults	SFA chain lengths	– Total CHD	Plasma phospholipids and erythrocytes	– Extreme quantile tissue measurement
Mandalazi 2016 **Sweden** *(59)*	Malmö	26 868 adults followed for 17 years	Total SFA	– Type 2 diabetes	Diet 7DDR and FFQ	– Extreme quantile self-reported
Mann 1997 **UK** *(60)*	Oxford cohort	10 492 adults followed for 13.3 years	SFA from food sources	– All-cause mortality – Fatal CHD	Diet FFQ	– Extreme quantile self-reported
Mao 2019 **China** *(61)*	China Health and Nutrition Survey	14 305 adults followed for 14 years	Total SFA	– All-cause mortality	Diet 3DDR	– Replacement analyses
Matthan 2014 **USA** *(62)*	WHI	3559 women	Total SFA and chain lengths	– Total CHD	Plasma phospholipids	– Extreme quantile tissue measurement
Mazidi 2020 **USA** *(63)*	NHANES	24 144 adults followed for 12 years	Total SFA	– All-cause mortality – CHD mortality	Diet 24HR	– Extreme quantile self-reported
Meyer 2001 **USA** *(64)*	IWHS	35 988 women followed for 11 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported
Merino 2020 **Multinational** *(65)*	15 cohorts	61 795 adults	Total SFA	– Type 2 diabetes	Self-reported	– Replacement analyses
Mirmiran 2018 **Iran** *(66)*	Tehran LGS	2139 adults followed for 5.8 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported
Nagata 2012 **Japan** *(67)*	Takayama	28 356 adults followed for 16 years	Total SFA	– All-cause mortality – CVD mortality	Diet FFQ	– Extreme quantile self-reported – Dose response
Neelakantan 2018 **Singapore** *(68)*	SCHS	57 078 adults followed for 17 years	Total SFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported
Oh 2005 **USA** *(69)*	NHS	78 778 women followed for 20 years	Total SFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported – Dose response

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Otsuka 2019 **Japan** *(70)*	NILS-LSA	1054 adults followed for 11.7 years	Total SFA	– All-cause mortality	Diet 3DDR	– Extreme quantile self-reported
Patel 2010 **UK** *(71)*	EPIC Norfolk	383 adults followed for 13 years	Total SFA and chain lengths	– Type 2 diabetes	FFQ, plasma phospholipids, erythrocyte	– Extreme quantile tissue measurement
Pietinen 1997 **Finland** *(72)*	ATBC	21,930 men followed for 6.1 years	Total SFA and chain lengths	– Fatal CHD – Total CHD	Diet FFQ	– Extreme quantile self-reported
Praagman 2016 **Netherlands** *(73)*	EPIC Netherlands	35 597 adults followed for 12.2 years	Total SFA	– Total CHD	Diet FFQ	– Replacement analyses
Praagman 2016 **Netherlands** *(74)*	Rotterdam Study	4722 adults followed for 16.3 years	Total SFA	– Total CHD	Diet FFQ	– Replacement analyses
Praagman 2018 **Europe** *(75)*	EPIC Denmark and Norfolk	75 425 adults followed 13.6 (Denmark) or 18.8 (UK) years	SFA food sources and chain lengths	– Total CHD	Diet FFQ	– Extreme quantile self-reported
Puaschitz 2015 **Norway** *(76)*	WENBIT	2412 adults followed for 4.8 years	Total SFA	– All-cause mortality – Fatal CHD – Total CHD	Diet FFQ	– Extreme quantile self-reported – Dose response
Ricci 2018 **USA** *(77)*	NHANES	18 372 adults followed for 6.1 years	Total SFA	– All-cause mortality – Fatal CVD	Diet 24hr recall	– Extreme quantile self-reported – Replacement analyses – Dose response
Salmerón 2001 **USA** *(78)*	NHS	84 204 women followed 14 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported – Dose response
Santiago 2018 **Spain** *(79)*	SUN	19 341 adults followed 10.1 years	Total SFA	– Total SFA	Diet FFQ	– Extreme quantile self-reported – Dose response
Sauvaget 2004 **Japan** *(80)*	Adult Health Study	3731 adults followed for 14 years	Total SFA	– Ischaemic stroke	Diet 24hr recall	– Extreme quantile self-reported – Dose response
Savolainen 2017 **Sweden** *(81)*	Gothenburg	399 women followed for 5.5 years	SFA chain lengths	– Type 2 diabetes	Plasma phospholipids	– Extreme quantile tissue measurement

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Schoenaker 2012 **Europe** *(82)*	EURODIAB	2108 adults followed for 7.3 years	Total SFA	– All-cause mortality – Total CVD	Diet 3DDR	– Extreme quantile self-reported – Replacement analyses – Dose response
Seino 1997 **Japan** *(83)*	Shibita	2283 adults followed for 15.5 years	Total SFA	– Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported – Dose response
Siri-Tarino 2009 **Multinational** *(84)*	Four cohorts	16 395 adults followed in four cohorts	Total SFA	– Total CHD	Various	– Extreme quantile self-reported
Sluijs 2017 **Netherlands** *(85)*	EPIC Netherlands	36 520 adults followed for 15 years	Total SFA	– Total CHD – Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported – Dose response
Solfrizzi 2005 **Italy** *(86)*	ILSA	278 adults followed for 8.5 years	Total SFA	– All-cause mortality	Diet FFQ	– Extreme quantile self-reported – Dose response
Song 2004 **USA** *(87)*	WHS	37 309 women followed for 8.8 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported
Sugihiro 2019 **USA** *(88)*	Japanese living in Haiwaii cohort	765 adults followed for 10.7 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported
Sun 2007 **USA** *(89)*	NHS	493 women	SFA chain lengths	– Total CHD	Plasma phospholipids and erythrocytes	– Extreme quantile tissue measurement
Sun 2016 **Singapore** *(90)*	SCHS	1454 adults followed for 11 years	SFA chain lengths	– Total CHD	Plasma phospholipids	– Extreme quantile tissue measurement
Takkunen 2015 **Finland** *(91)*	DPS	383 adults followed for 11 years	Total SFA and chain lengths	– Type 2 diabetes	Serum	– Extreme quantile tissue measurement
Tanasescu 2004 **USA** *(92)*	NHS	5672 women followed for 10.1 years	Total SFA	– Non-fatal CVD – Fatal CVD – Total CVD	Diet FFQ	– Extreme quantile self-reported – Dose response
Trevisan 2020 **Italy** *(93)*	ANA	5049 men followed for 7 years	Total SFA	– All-cause mortality	Diet FFQ	– Extreme quantile self-reported

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Van Blarigan 2015 **USA** *(94)*	PHS	926 men followed for 10 years	Total SFA	– All-cause mortality	Diet FFQ	– Extreme quantile self-reported – Dose response
van Dam 2002 **USA** *(95)*	HPFS	42 504 men followed for 12 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Extreme quantile self-reported – Dose response
Venø 2017 **Denmark** *(96)*	DDCH	57 053 adults followed for 13.5 years	Total SFA	– Ischaemic stroke	Diet FFQ	– Replacement analyses
Virtanen 2014 **Finland** *(97)*	KIHD	1,981 men followed for 10 years	Total SFA	– Non-fatal CHD – Fatal CHD	Diet 4DDR	– Extreme quantile self-reported – Replacement analyses – Dose response
Wakai 2014 **Japan** *(98)*	JACC	58 672 adults followed for 19.3 years	Total SFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported – Dose response
Wang 2016 **USA** *(99)*	HPFS and NHS	126 233 adults followed for 32 (NHS) and 26 (HPFS) years	Total SFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Wang 2018 **China** *(100)*	Harbin	6641 adults followed for 6.7 years	Total SFA	– Type 2 diabetes	Serum	– Extreme quantile tissue measurement
Wu 2011 **USA** *(101)*	CHD	2890 adults followed for 7 years	SFA chain lengths	– Total CHD	Plasma phospholipids	– Extreme quantile tissue measurement
Xu 2006 **USA** *(102)*	Strong Heart Study	2938 adults followed for 7.2 years	Total SFA	– Non-fatal CHD – Fatal CHD	Diet 24hr recall	– Extreme quantile self-reported – Dose response
Yaemsiri 2012 **USA** *(103)*	WHI	87 025 women followed for 7.6 years	Total SFA	– Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported – Dose response
Yakoob 2016 **USA** *(104)*	HPFS and NHS	3333 adults followed for 12.9 years	SFA chain lengths	– Type 2 diabetes	Plasma phospholipids and erythrocytes	– Extreme quantile tissue measurement

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Yamagishi 2010 **Japan** *(105)*	JACC	58 453 adults followed for 14.1 years	Total SFA	– CHD mortality – CVD mortality	Diet FFQ	– Extreme quantile self-reported
Yamagishi 2013 **Japan** *(106)*	JPHC	81 932 adults followed for 11.1 years	Total SFA	– Total CHD – Total CVD – Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported – Dose response
Yamagishi 2013 **USA** *(107)*	ARIC	3870 adults followed for 19.9 years	Total SFA	– Ischaemic stroke	Plasma phospholipids	– Extreme quantile tissue measurement
Zhuang 2019 **USA** *(108)*	NIH AARP DHS	521 120 adults followed for 16 years	Total SFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Zhuang 2019 **China** *(109)*	China Health and Nutrition Survey	14 383 adults followed for 14 years	Total SFA and chain lengths	– All-cause mortality	Diet 3DDR	– Extreme quantile self-reported – Replacement analyses – Dose response
Zong 2016 **USA** *(110)*	HPFS and NHS	115 782 adults followed for 25.3 (NHS) and 20.2 (HPFS) years	SFA chain lengths	– Total CHD	Diet FFQ	– Extreme quantile self-reported
Zong 2018 **USA** *(111)*	HPFS and NHS	93 384 adults followed for 20.1 (NHS) or 19.7 (HPFS) years	Total SFA	– Total CHD	Diet FFQ	– Replacement analyses
Zong 2019 **USA** *(112)*	NHS and HPFS	214 029 adults followed for 23 years	Total SFA	– Type 2 diabetes	Diet FFQ	– Replacement analyses

ABC: Health, Aging and Body Composition Study; ANA: Associazione Nazionale Alpini; ARIC: Atherosclerosis Risk in Communities; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CIRCS: Circulatory Risk in Communities Study; CVD: cardiovascular disease; DCHS: Diet, Cancer, and Health Study; DDCH: Danish Diet, Cancer, and Health; DDR: day diet record; DPS: Diabetes Prevention Study; EPIC: European Prospective Investigation into Cancer and Nutrition; E3N: Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; FFQ: food frequency questionnaire; EURODIAB: EURODIAB Prospective Complications Study; GNHS: Guangzhou Nutrition and Health Study; HPFS: Health Professionals Follow-Up Study; ILSA: Italian Longitudinal Study on Aging; IWHS: Iowa Women's Health Study; JACC: Japan Collaborative Cohort Study; JPHC: Japan Public Health Centre; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; LGS: Lipid and Glucose Study; MCCS: Melbourne Collaborative Cohort Study; MESA: Multi-Ethnic Study of Atherosclerosis; METSIM: Metabolic Syndrome in Men Study; MONICA: Monitoring of Trends and Determinants in Cardiovascular Disease; NHANES: National Health and Nutrition Examination Survey; NIH AARP DHS: National Institutes of Health-American Association of Retired Persons Diet and Health Study; NILS-LSA: National Institute for Longevity Sciences-Longitudinal Study of Aging; NHS: Nurses' Health Study; PHS: Physicians' Health Study; PREDIMED: Prevención con Dieta Mediterránea; PURE: Prospective Urban Rural Epidemiology; REGARDS: Reasons for Geographic and Racial Differences in Stroke; RBC: red blood cell; SCHS: Singapore Chinese Health Study; SFA: saturated fatty acids; SMC: Swedish Mammography Cohort; SUN: Seguimiento Universidad de Navarra; TFA: trans-fatty acids; WENBIT: Western Norway B-Vitamin Intervention Trial; WHI: Women's Health Initiative; WHS: Women's Health Study.

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Table A2. Studies of TFA intakes and health outcomes included in meta-analyses

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Ascherio 1996 **USA** (1)	HPFS	43 023 men followed for 6 years	Total TFA	– Total CHD – Fatal CHD	Diet FFQ	– Extreme quantile self-reported
Borgeraas 2016 **Norway** (2)	BECAC	1364 adults followed for 5.8 years	Total TFA and isomers	– All-cause mortality – Total CHD – Fatal CVD	Serum and plasma	– Extreme quantile tissue measure
Chandra 2018 **Norway** (3)	Norwegian Renal Patients	1,988 adults followed for 9.6 years	Total TFA and food sources	– All-cause mortality – Fatal CVD	Plasma	– Extreme quantile tissue measure
Chien 2013 **Taiwan, China** (4)	Chin-Shan	1265 adults followed for	Total TFA	– All-cause mortality – Total CVD	Plasma	– Extreme quantile tissue measure
de Oliveira Otto 2018 **USA** (5)	CHS	2907 adults followed for 22 years	TFA isomers	– All-cause mortality – Total CHD – Fatal CHD – Total CVD	Plasma	– Extreme quantile tissue measure
Dow 2016 **France** (6)	E3N	71 334 women followed for 18 years	Total TFA	– T2 diabetes	Diet FFQ	– Extreme quantile self-reported – Dose response
Guasch-Ferré 2015 **Spain** (7)	PREDIMED	7038 adults followed for 6 years	Total TFA	– All-cause mortality – Total CVD	Diet FFQ	– Extreme quantile self-reported – Dose response
Guasch-Ferré 2017 **Spain** (8)	PREDIMED	3349 adults followed for 4.3 years	Total TFA	– T2 diabetes	Diet FFQ	– -Extreme quantile self-reported – Dose response
Guasch-Ferré 2019 **USA** (9)	NHS and HPFS	93 378 adults followed for 22 years	Total TFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Replacement analyses
He 2003 **USA** *(10)*	HPFS	85 697 men followed for 14 years	Total TFA	– Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported
Hodge 2007 **Australia** *(11)*	MCCS	3737 adults followed for 4 years	Total TFA	– T2 diabetes	Diet FFQ and plasma	– Extreme quantile self-reported – Extreme quantile tissue measure

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Houston 2011 **USA** *(12)*	Health ABC	1,941 adults followed for 9 years	Total TFA	– Total CVD	Diet FFQ	– Extreme quantile self-reported
Howard 2006 **USA** *(13)*	WHI	32 728 women followed for 8.1 years	Total TFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported
Hu 1997 **USA** *(14)*	NHS	80 082 women followed for 13.2 years	Total TFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported – Dose response – Replacement analyses
Imamura 2018 **Multinational** *(15)*	16 cohorts	63 682 adults followed in multiple cohorts	TFA isomers	– T2 diabetes	Plasma, red blood cell	– Extreme quantile tissue measure
Imamura 2020 **Multinational** *(16)*	16 cohorts	60 387 adults followed in multiple cohorts	TFA isomers	– T2 diabetes	Plasma, red blood cell	– Extreme quantile tissue measure
Iso 2001 **USA** *(17)*	NHS	85 764 women followed for 14 years	Total TFA	– Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported
Jakobsen 2018 **Denmark** *(18)*	DDCH	3156 adults followed for 14 years	TFA isomers	– Total CHD	Adipose	– Extreme quantile tissue measure
Jiao 2019 **USA** *(19)*	NHS and HPFS	11 264 adults followed for 11 years	Total TFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported – Dose response
Khaw 2012 **UK** *(20)*	EPIC Norfolk	4930 adults followed for 13 years	Total TFA and isomers	– Total CHD	Plasma	– Extreme quantile tissue measure
Kiage 2013 **USA** *(21)*	REGARDS	18 513 adults followed for 7 years	Total TFA	– All-cause mortality	Diet FFQ	– Extreme quantile self-reported – Dose response
Kleber 2016 **Germany** *(22)*	LURIC	3259 adults followed for 10 years	Total TFA and isomers	– All-cause mortality – Fatal CVD	Erythrocyte membrane	– Extreme quantile tissue measure
Kröger 2011 **Germany** *(23)*	EPIC Potsdam	2724 adults followed for 7 years	Total TFA and isomers	– T2 diabetes	Erythrocyte membrane	– Extreme quantile tissue measure
Laake 2011 **Norway** *(24)*	Norwegian Countries Study	71 464 adults followed for 25.8 years	TFA isomers	– All-cause mortality – Fatal CHD – Fatal CVD	Diet FFQ	– Extreme quantile self-reported

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Laursen 2019 **Denmark** *(25)*	DDCH	5294 adults followed for 12.8 years	TFA isomers	– Ischaemic stroke	Adipose	– Extreme quantile tissue measure
Li 2015 **USA** *(26)*	NHS and HPFS	127 536 adults followed for 30 or 24 years	Total TFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Liu 2018 **USA** *(27)*	NHANES	3801 adults for unstated time	Total TFA and isomers	– T2 diabetes	Plasma	– Extreme quantile tissue measure
Liu 2019 **USA** *(28)*	WHI	2428 women followed for 4.5 years	TFA isomers	– Total CHD	Plasma and erythrocyte	– Extreme quantile tissue measure
Meyer 2001 **USA** *(29)*	IWHS	34 078 women followed for 11 years	Total TFA	– T2 diabetes	Diet FFQ	– Extreme quantile self-reported
Mozaffarian 2010 **USA** *(30)*	CHS	3736 adults followed for 14 years	TF isomers	– T2 diabetes	Plasma	– Extreme quantile tissue measure
Mozaffarian 2013 **USA** *(31)*	MESA	2281 adults followed for 4.8 years	TF isomers	– T2 diabetes	Plasma	– Extreme quantile tissue measure
Oh 2005 **USA** *(32)*	NHS	41 990 women followed for 20 years	Total TFA	– Total CHD	Diet FFQ	– Extreme quantile self-reported – Dose response
Oomen 2001 **Netherlands** *(33)*	Zutphen	569 men followed for 10 years	Total TFA, isomer, and food source	– Total CHD	Diet FFQ	– Extreme quantile self-reported – Dose response
Patel 2010 **UK** *(34)*	EPIC Norfolk	383 adults followed for 13 years	Total TFA and isomers	– T2 diabetes	Diet FFQ, plasma, erythrocyte	– Extreme quantile self-reported – Extreme quantile tissue measure
Pietinen 1997 **Finland** *(35)*	ATBC	20,531 men followed for 6 years	Total TFA, isomers, food sources	– Total CHD – Fatal CHD	Diet FFQ	– Extreme quantile self-reported – Dose response
Salmerón 2001 **USA** *(36)*	NHS	81 697 women followed for 14 years	Total TFA	– T2 diabetes	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Santiago 2018 **Spain** *(37)*	SUN	19 341 adults followed for 10.1 years	Total TFA	– Total CVD	Diet FFQ	– Extreme quantile self-reported – Dose response
Similä 2012 **Finland** *(38)*	ATBC	24,846 men followed for 12 years	Total TFA	– T2 diabetes	Diet FFQ	– Replacement analyses
Song 2004 **USA** *(39)*	WHS	35 751 women followed for 8.8 years	Total TFA	– T2 diabetes	Diet FFQ	– Extreme quantile self-reported
Sun 2007 **USA** *(40)*	NHS	493 women followed for 6 years	TFA isomers	– Total CHD	Plasma and erythrocyte	– Extreme quantile tissue measure
Sun 2016 **Singapore** *(41)*	SCHS	493 adults in a nested case control	TFA isomers	– Total CHD	Plasma	– Extreme quantile tissue measure
Tanasescu 2004 **USA** *(42)*	NHS	5672 women followed for 10.1 years	Total TFA	– Total CVD	Diet FFQ	– Extreme quantile self-reported
Van Blarigan 2015 **USA** *(43)*	PHS	926 men followed for 10 years	Total TFA	– All-cause mortality	Diet FFQ	– Extreme quantile self-reported – Dose response
van Dam 2002 **USA** *(44)*	HPFS	41 273 men followed for 12 years	Total TFA	– T2 diabetes	Diet FFQ	– Extreme quantile self-reported – Dose response
Virtanen 2014 **Finland** *(45)*	KIHD	1798 men followed for 21.4 years	Total TFA	– Fatal CHD – – Non-fatal CHD	4DDR	– Extreme quantile self-reported – Dose response
Wang 2016 **USA** *(46)*	NHS and HPFS	126 233 adults followed for 26 years	Total TFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported – Dose response – Replacement analyses
Wang 2015 **USA** *(47)*	CHS	3800 adults followed for 20 years	Total TFA and isomers	– T2 diabetes	Diet FFQ and plasma	– Extreme quantile self-reported – Extreme quantile tissue measure
Wang 2020 **USA** *(48)*	NHANES	3439 adults followed for 9.8 years	Total TFA, food sources, and isomers	– All-cause mortality – Fatal CVD	Plasma	– Extreme quantile tissue measure

ID	Cohort	Participants	Exposure	Outcomes	Measurement	Which analyses was this used in
Willett 1993 **USA** *(49)*	NHS	85 095 women followed for 8 years	Total TFA and food sources	– Total CHD	Diet FFQ	– Extreme quantile self-reported
Xu 2006 **USA** *(50)*	Strong Heart Study	2502 adults followed for 7.2 years	Total TFA	– Total CHD – Fatal CHD – Non-fatal CHD	24HR recall	– Extreme quantile self-reported – Dose response
Yaemsiri 2012 **USA** *(51)*	WHI	85 976 women followed for 7.6 years	Total TFA	– Ischaemic stroke	Diet FFQ	– Extreme quantile self-reported
Yakoob 2016 **USA** *(52)*	NHS and HPFS	1864 adults followed for 12.9–16.9 years	TFA isomers	– T2 diabetes	Plasma and erythrocyte	– Extreme quantile self-reported
Zhuang 2019 **USA** *(53)*	NIH AARP DHS	521 120 adults followed for 16 years	Total TFA	– All-cause mortality – Fatal CVD	Diet FFQ	– Extreme quantile self-reported – Replacement analyses – Dose response
Zong 2019 **USA** *(54)*	NHS and HPFS	214 029 adults followed for 23 years	Total TFA	– T2 diabetes	Diet FFQ	– Replacement analyses
Zong 2018 **USA** *(55)*	NHS and HPFS	63 442 adults followed for 20 years	Total TFA	– Total CHD	Diet FFQ	– Replacement analyses

ABC: Health, Aging and Body Composition Study; ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BECAC: Bergen Coronary Angiography Cohort; CHD: coronary heart disease; CHS: Cardiovascular Health Study; CVD: cardiovascular disease; DDCH: Danish Diet, Cancer, and Health; DDR: day diet record; EPIC: European Prospective Investigation into Cancer and Nutrition; E3N: Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale; FFQ: food frequency questionnaire; HPFS: Health Professionals Follow-Up Study; IWHS: Iowa Women's Health Study; KIHD: Kuopio Ischemic Heart Disease Risk Factor Study; LURIC: Ludwigshafen Risk and Cardiovascular Health study; MCCS: Melbourne Collaborative Cohort Study; MESA: Multi-Ethnic Study of Atherosclerosis; NHANES: National Health and Nutrition Examination Survey; NIH AARP DHS: National Institutes of Health-American Association of Retired Persons Diet and Health Study; NHS: Nurses' Health Study; PHS: Physicians' Health Study; PREDIMED: Prevención con Dieta Mediterránea; REGARDS: Reasons for Geographic and Racial Differences in Stroke; SCHS: Singapore Chinese Health Study; SUN: Seguimiento Universidad de Navarra; TFA: trans-fatty acids; WHI: Women's Health Initiative; WHS: Women's Health Study.

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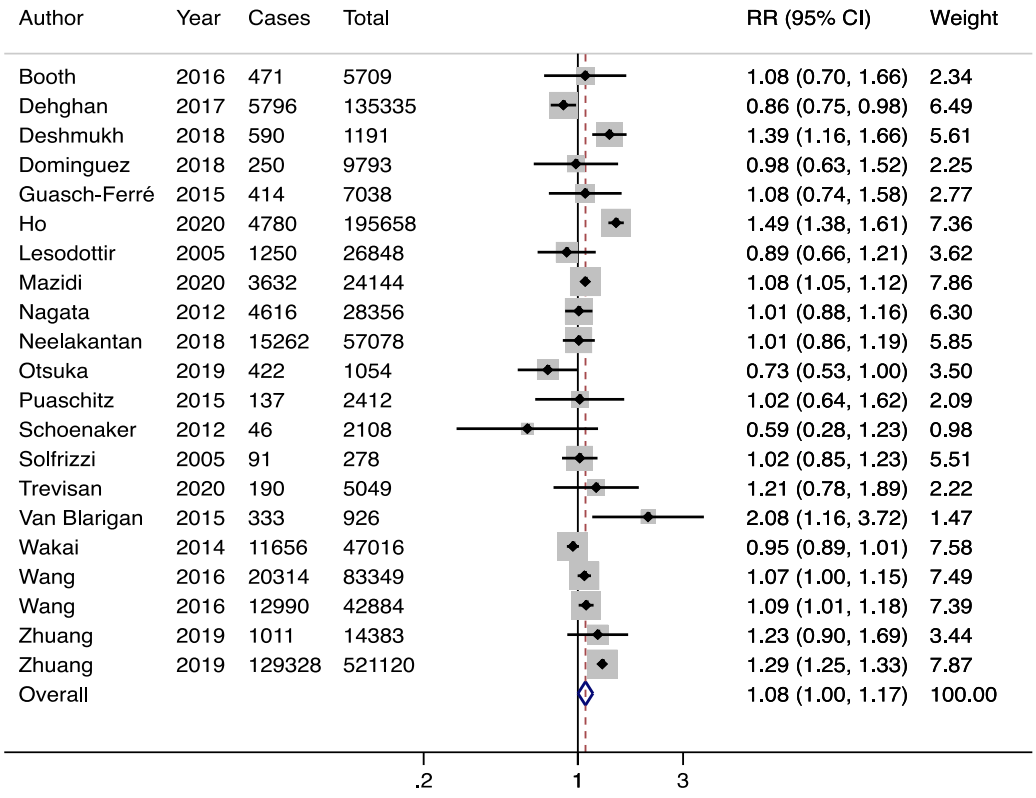
ANNEX 3.

SFA intakes and all-cause mortality

Dietary intakes

Fig. A3.1. Self-reported intakes of total SFA and all-cause mortality

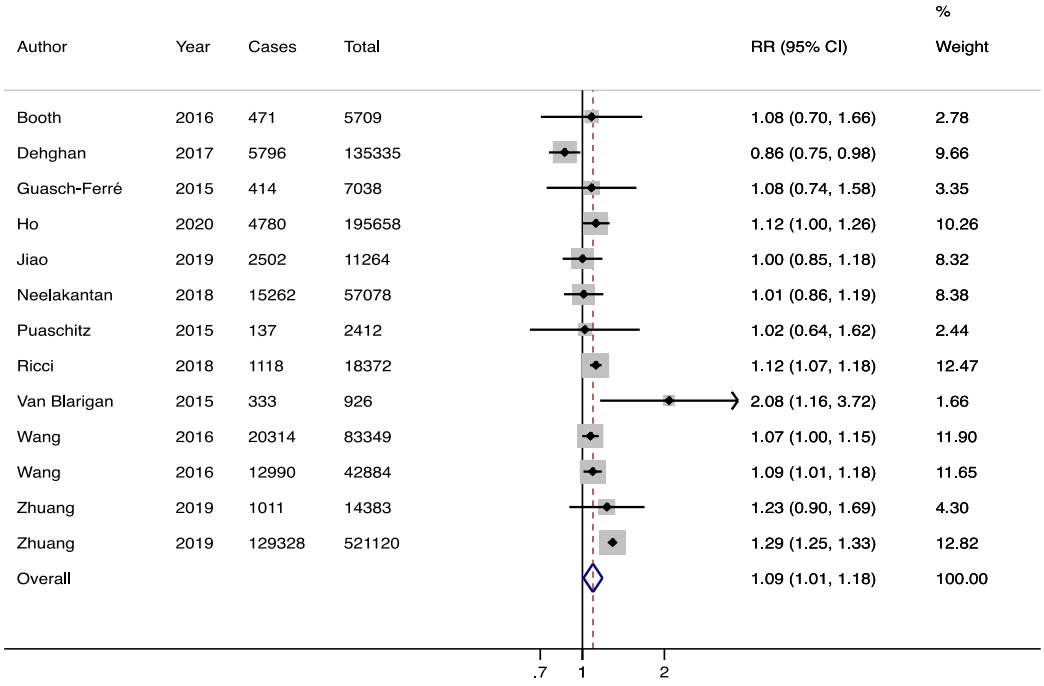
Initial heterogeneity was high (I^2 90%). Influence analysis indicated that two studies (Zhuang 2019 *(1)* and Mazidi 2020 *(2)*) influenced the pooled effect size. Without Mazidi 2020, the RR was 1.08 (95% CI: 0.99 to 1.18) and heterogeneity remained high (I^2 98%). Without Zhuang 2019, the RR was 1.07 (95% CI: 0.99 to 1.15) and heterogeneity remained high (I^2 84%). Without either Mazidi 2020 or Zhuang 2019, the RR was 1.06 (95% CI: 0.97 to 1.17) and heterogeneity remained high (I^2 84%). The Egger test did not indicate a small study effect (*P*=0.289), and neither the study type (*P*=0.280) nor the presence of a pre-existing condition (*P*=0.217) appeared to influence the pooled result.



CI: confidence interval; RR: relative risk; SFA: saturated fats.

Fig. A3.2. Self-reported intakes of <10% total SFA with >10% SFA and all-cause mortality

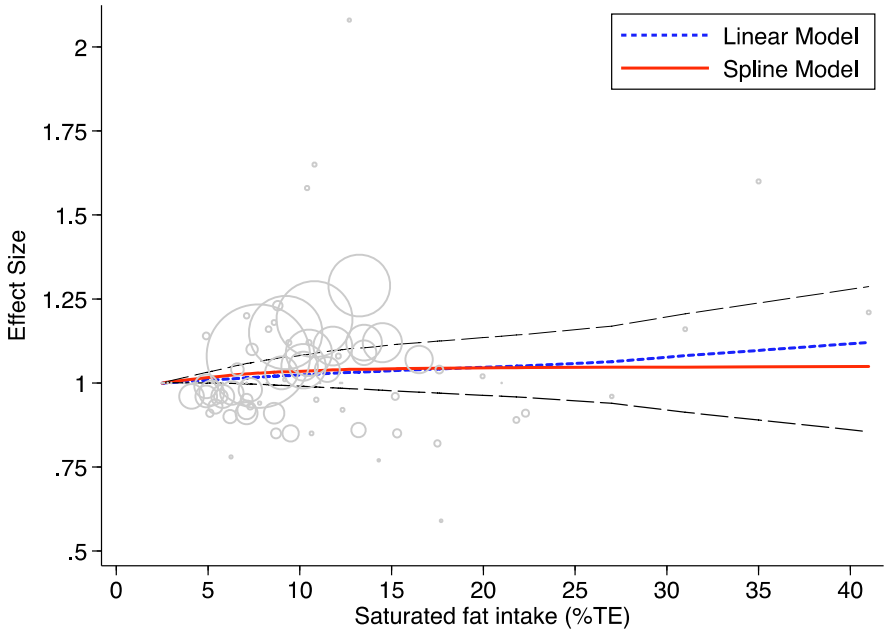
Initial heterogeneity was high (I^2 85%). One study (Zhuang 2019 *(1)*) influenced the pooled result. The pooled result without Zhuang 2019 remained significant RR 1.06 (95% CI: 1.01 to 1.13) and heterogeneity was reduced (I^2 48%). There was no evidence of a small study effect (*P*=0.107).



CI: confidence interval; RR: relative risk.

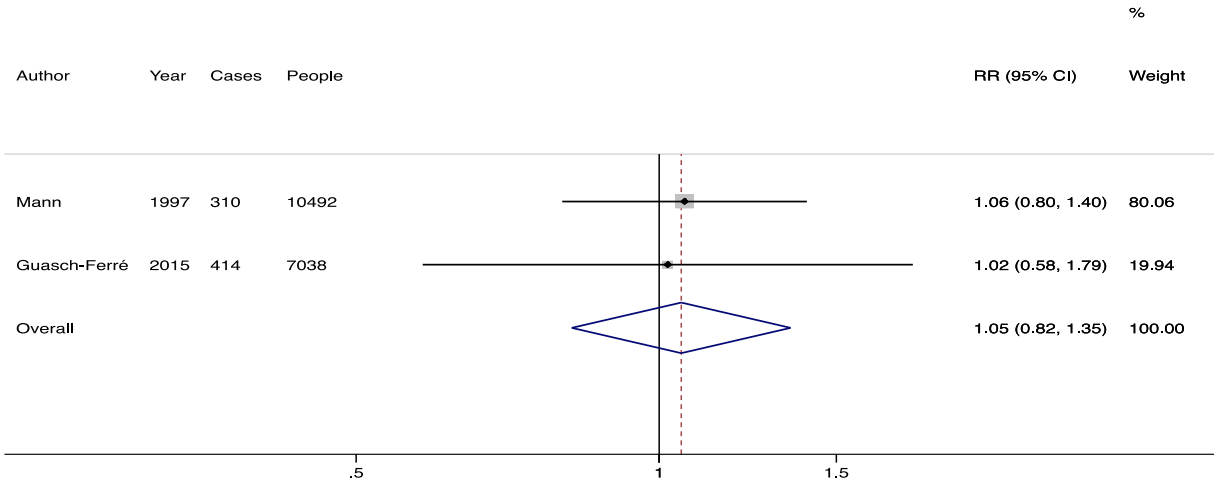
Fig. A3.3. Cubic spline dose response between self-reported total SFA intake (%TE) and all-cause mortality

Data were available from 19 cohorts of 189 298 cases during 15 809 006 PY. Assuming linearity, the relative risk per 5% increase in TE from SFA was 1.03 (95% CI: 0.98 to 1.09).



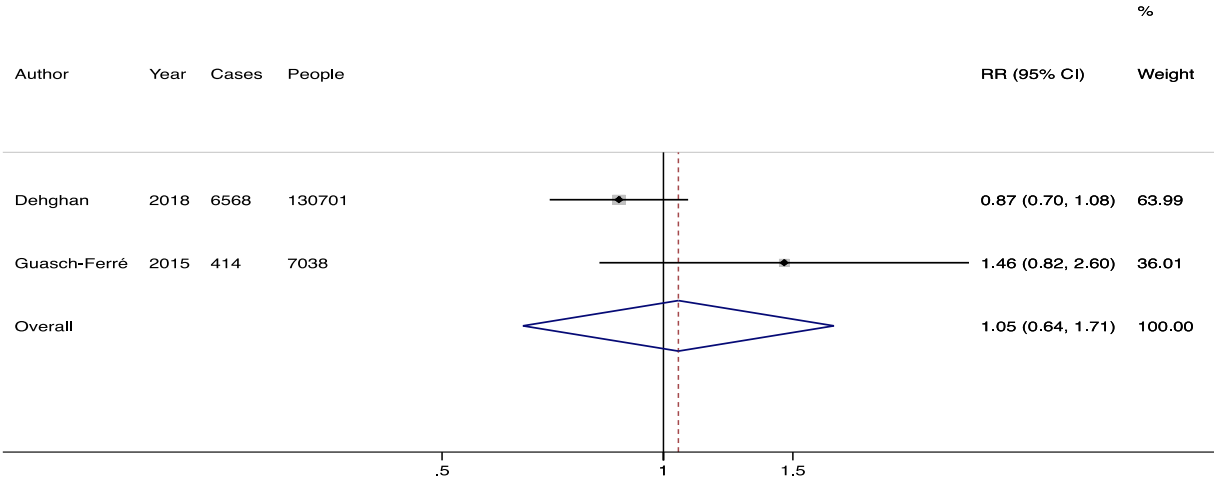
CI: confidence interval; PY: person years; SFA: saturated fatty acids; TE: total energy.

Fig. A3.4a. Self-reported intakes of SFA from animal sources and all-cause mortality



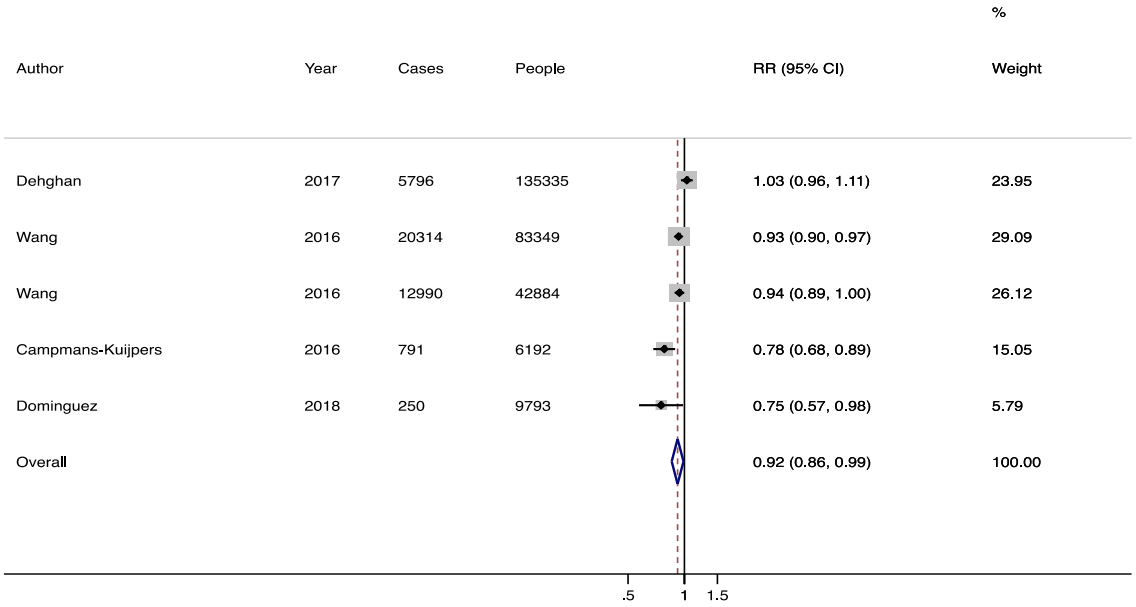
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A3.4b. Self-reported intakes of SFA from dairy sources and all-cause mortality



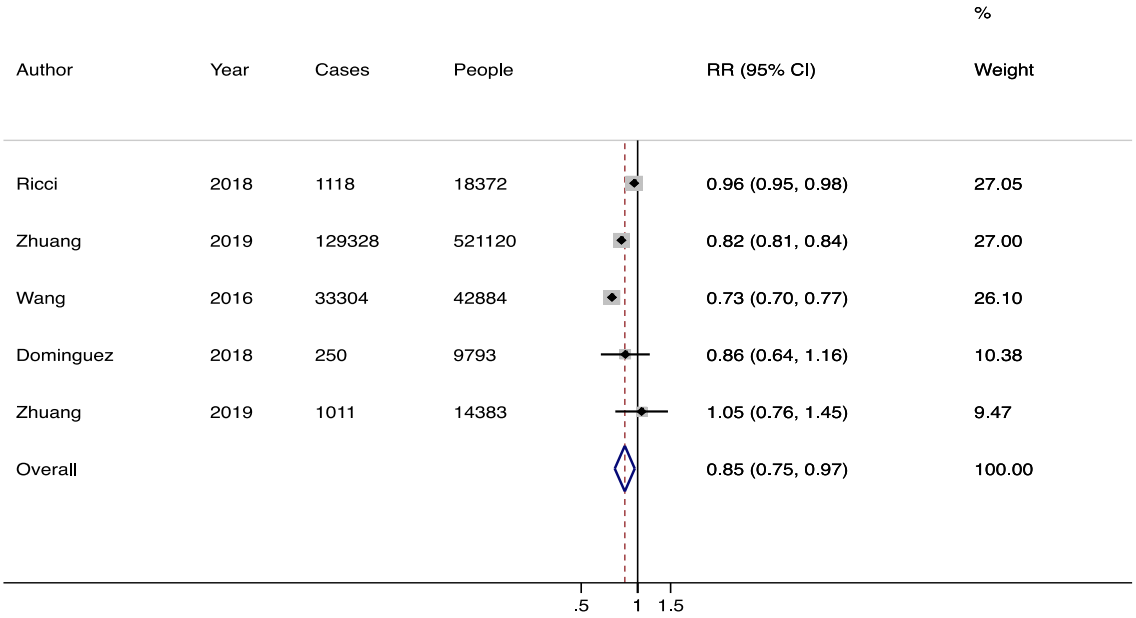
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A3.5a. Replacement of self-reported total SFA intakes with 5% CHO and all-cause mortality



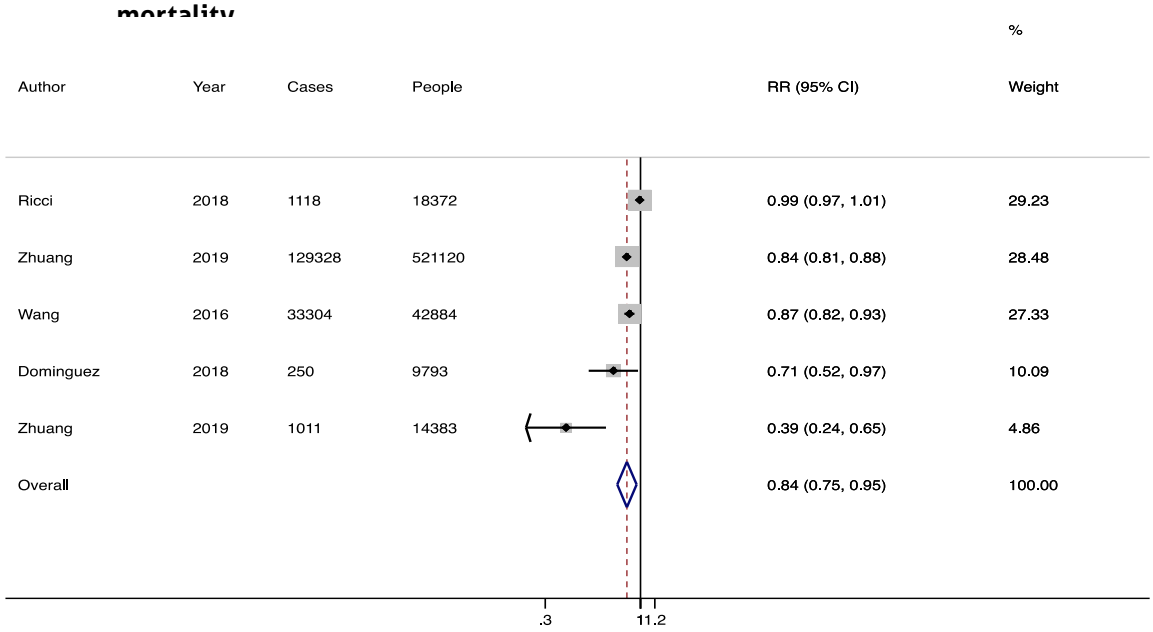
CHO: carbohydrate; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A3.5b. Replacement of self-reported total SFA intakes with 5% PUFA and all-cause mortality



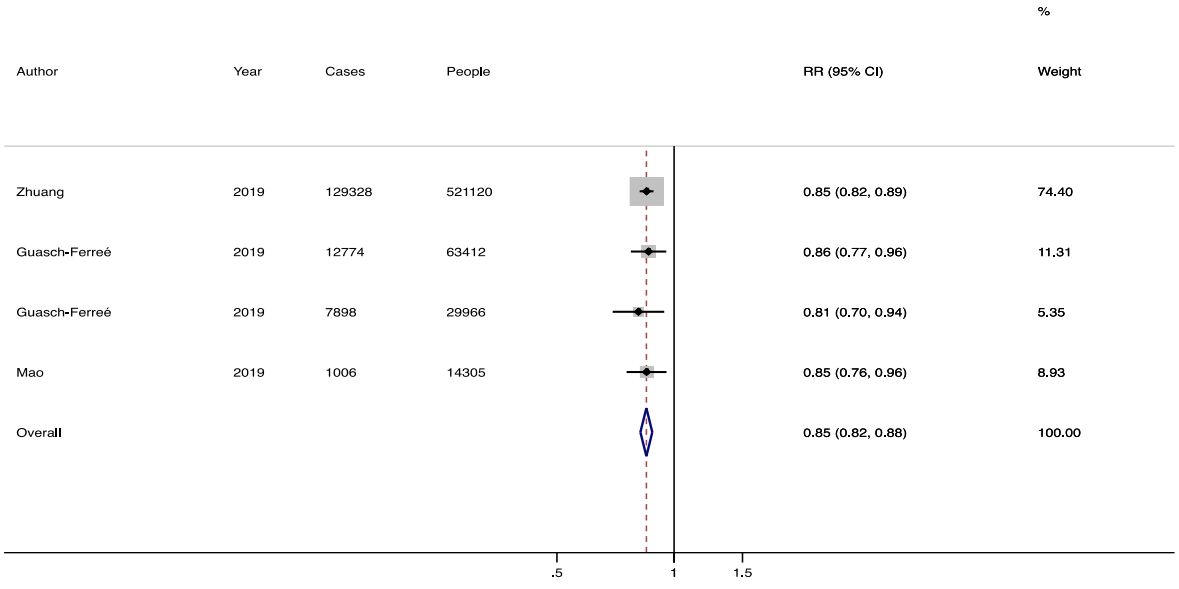
CI: confidence interval; PUFA: polyunsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A3.5c. Replacement of self-reported total SFA intakes with 5% MUFA and all-cause mortality



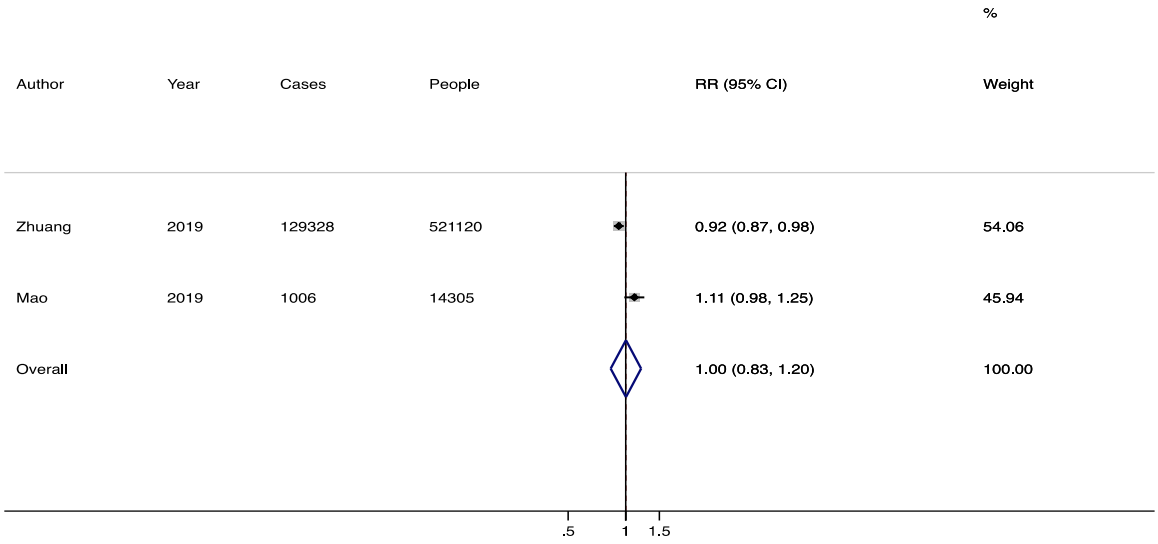
CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids

Fig. A3.5d. Replacement of self-reported total SFA intakes with 5% Plant MUFA and all-cause mortality



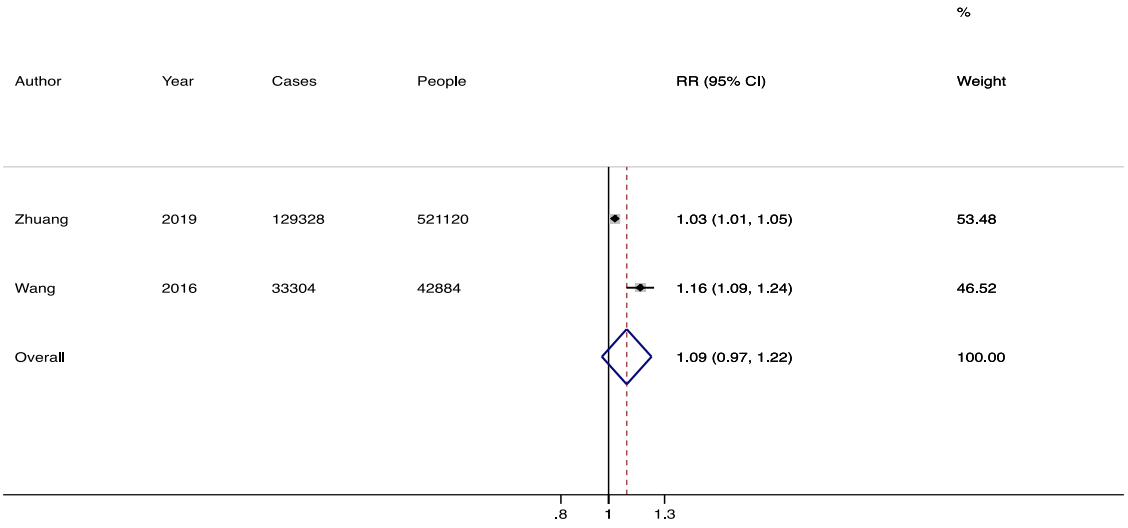
CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A3.5e. Replacement of self-reported total SFA intakes with 5% animal MUFA and all-cause mortality



CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

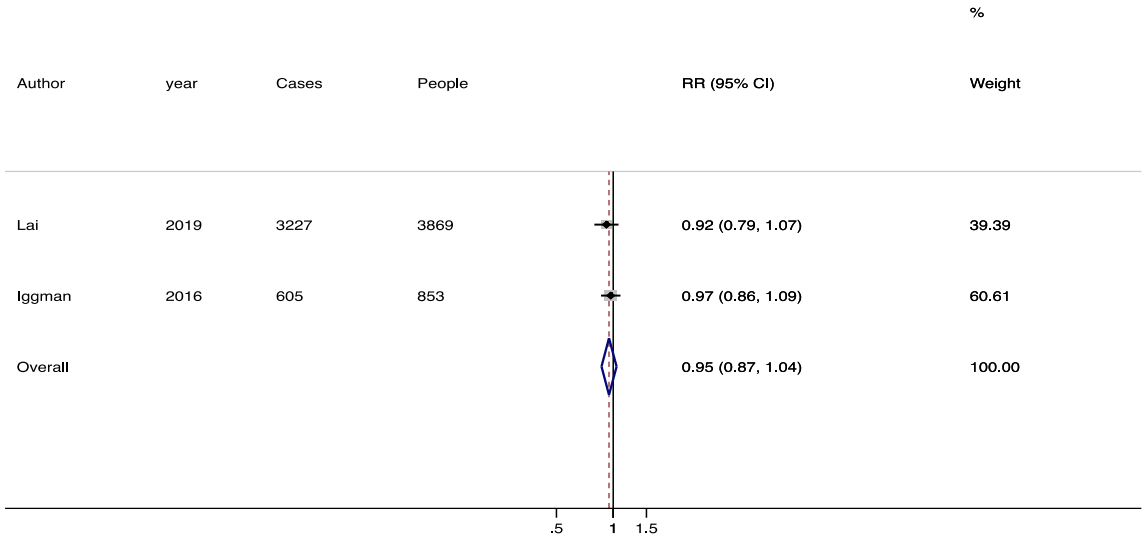
Fig. A3.5f. Replacement of self-reported total SFA intakes with 2% TFA and all-cause mortality



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids; TFA: *trans*-fatty acids.

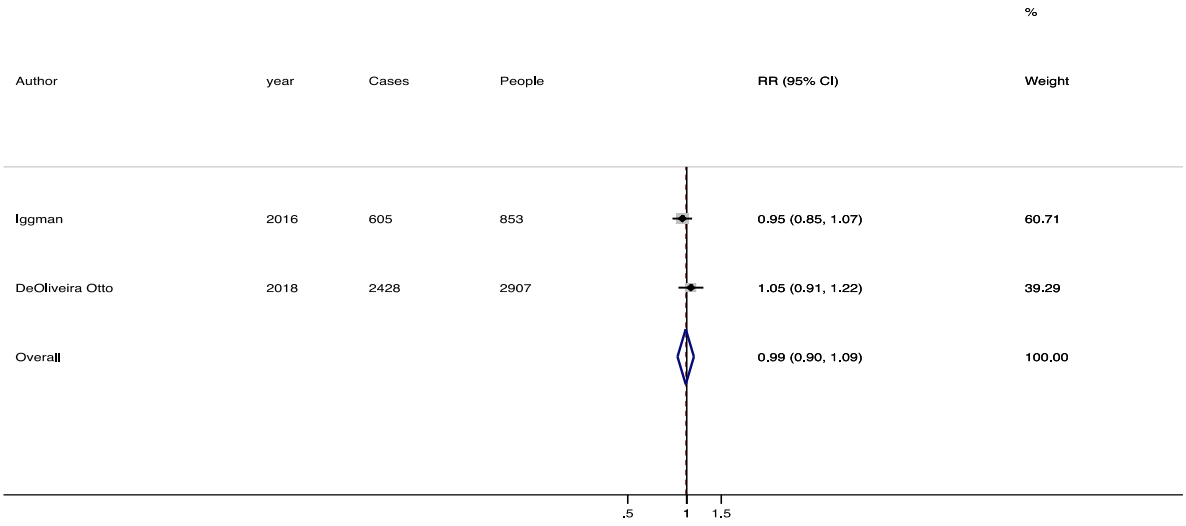
Tissue samples

Fig. A3.6a. Tissue measurements of C14:0 and all-cause mortality



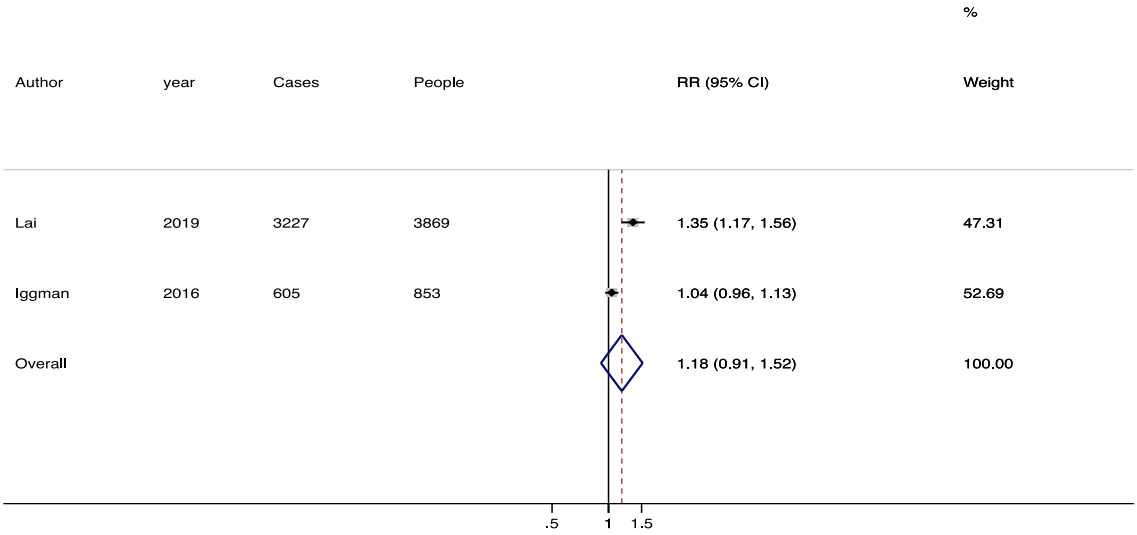
CI: confidence interval; RR: relative risk.

Fig. A3.6b. Tissue measurements of C15:0 and all-cause mortality



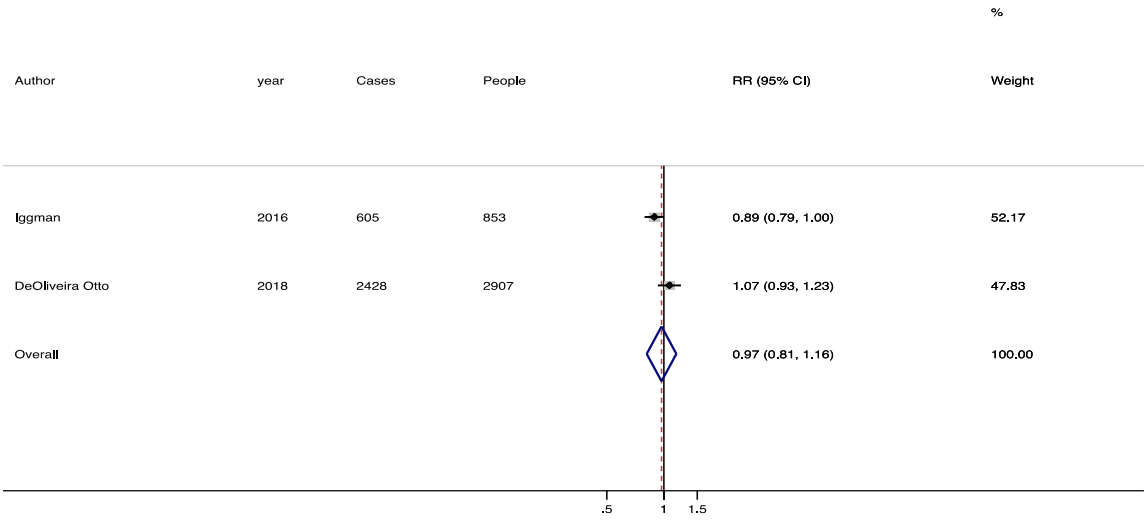
CI: confidence interval; RR: relative risk.

Fig. A3.6c. Tissue measurements of C16:0 and all-cause mortality



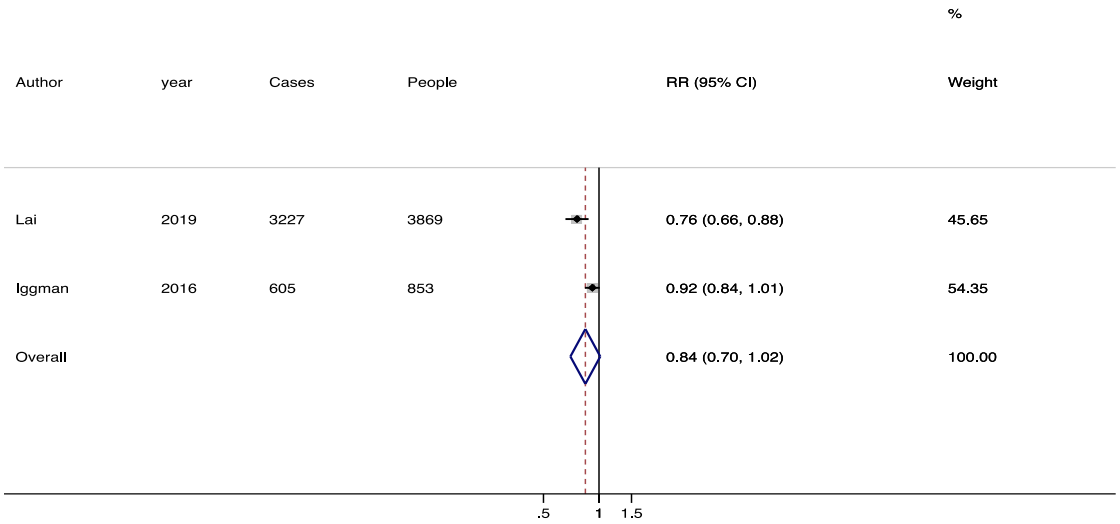
CI: confidence interval; RR: relative risk.

Fig. A3.6d. Tissue measurements of C17:0 and all-cause mortality



CI: confidence interval; RR: relative risk.

Fig. A3.6e. Tissue measurements of C18:0 and all-cause mortality



CI: confidence interval; RR: relative risk.

References for Annex 3

1 Zhuang P, Zhang Y, He W, Chen X, Chen J, He L et al. Dietary fats in relation to total and cause-specific mortality in a prospective cohort of 521,120 individuals with 16 years of follow-up. Circ Res. 2019;124(5):757–68.

2 Mazidi M, Mikhailidis DP, Sattar N, Toth PP, Judd S, Blaha MJ et al. Association of types of dietary fats and all-cause and cause-specific mortality: a prospective cohort study and meta-analysis of prospective studies with 1,164,029 participants. Clin Nutr. 2020.

ANNEX 4.

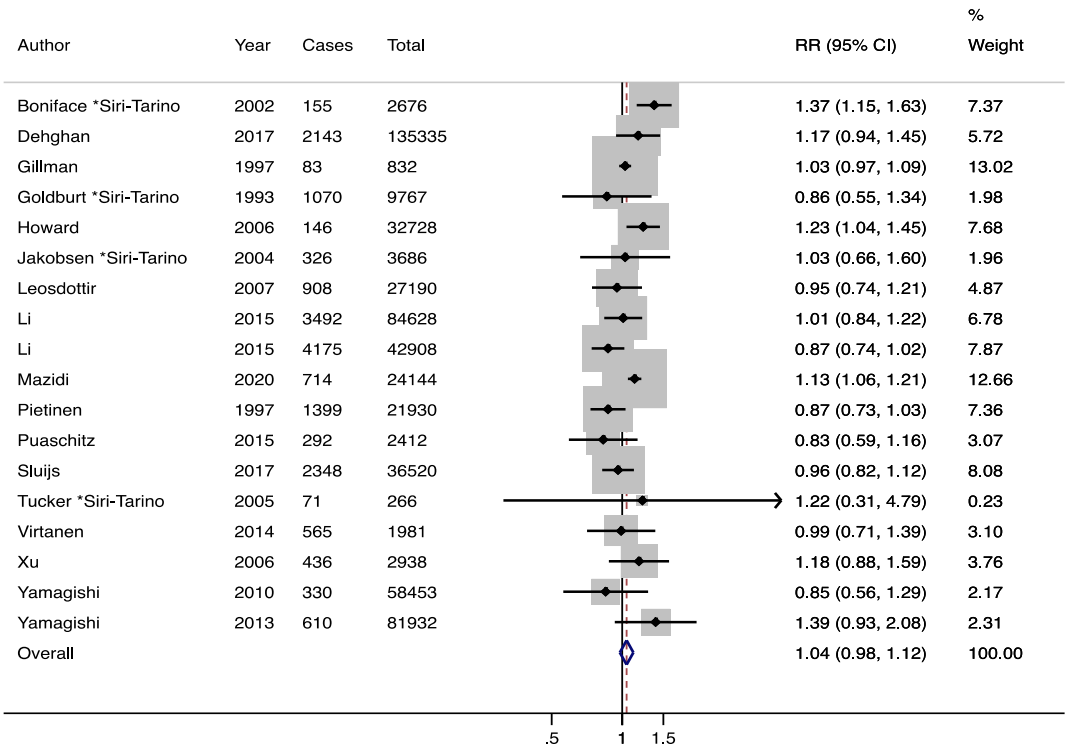
SFA intakes and coronary heart disease occurrence

Dietary intakes

Estimates for fatal coronary heart disease (CHD), non-fatal CHD, and combined fatal and non-fatal CHD were run and then considered with a categorical meta-regression to see whether effect size estimates varied by which outcome was reported. *P* values (*P*>0.468) indicated there was no difference between outcome type, so estimates were run together, without duplication of the same participants, to comment on CHD occurrence.

Fig. A4.1. Self-reported intakes of total SFA and CHD occurrence

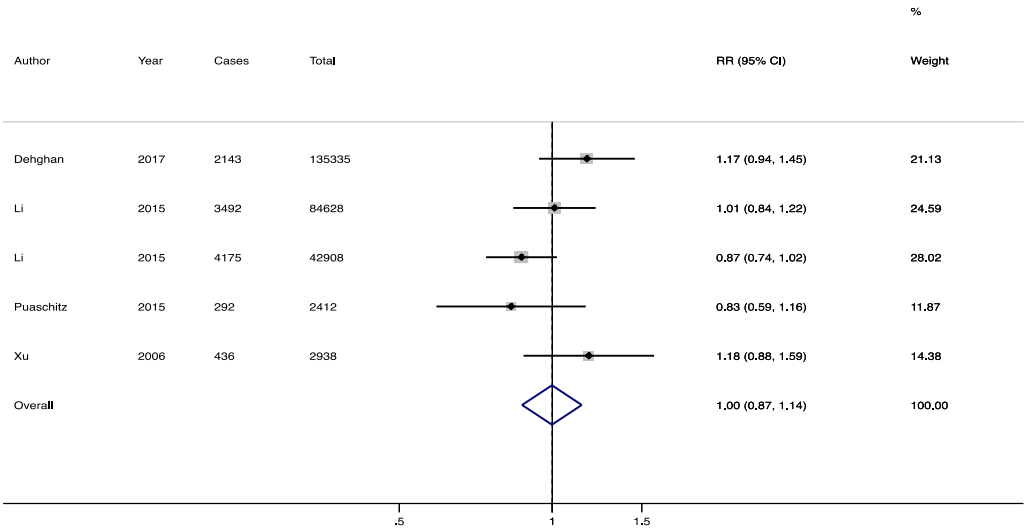
Initial heterogeneity was high (I^2 54%). Influence analysis did not indicate that any study unduly influenced the pooled result. There was no evidence of a small study effect (Egger *P*=0.597). The presence of pre-existing conditions (*P*=0.271) or study design (*P*=0.716) did not appreciably influence the pooled result.



CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids

Fig. A4.2. Self-reported intakes of <10% total SFA intakes with >10% total SFA intakes and CHD occurrence

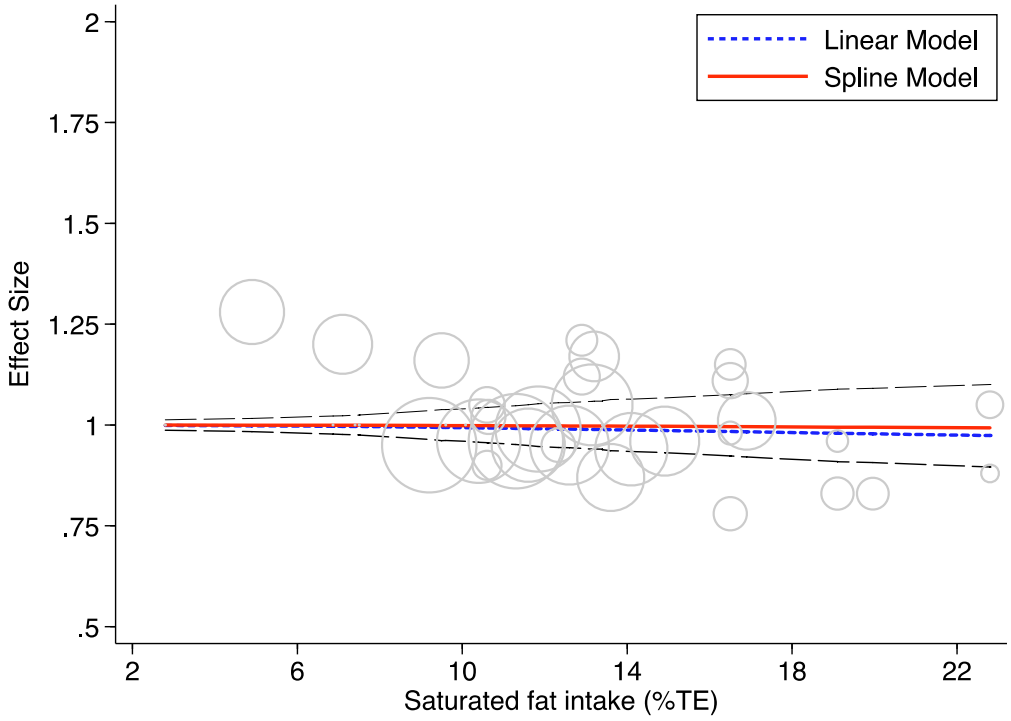
Initial heterogeneity was low (I^2 45%).



CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

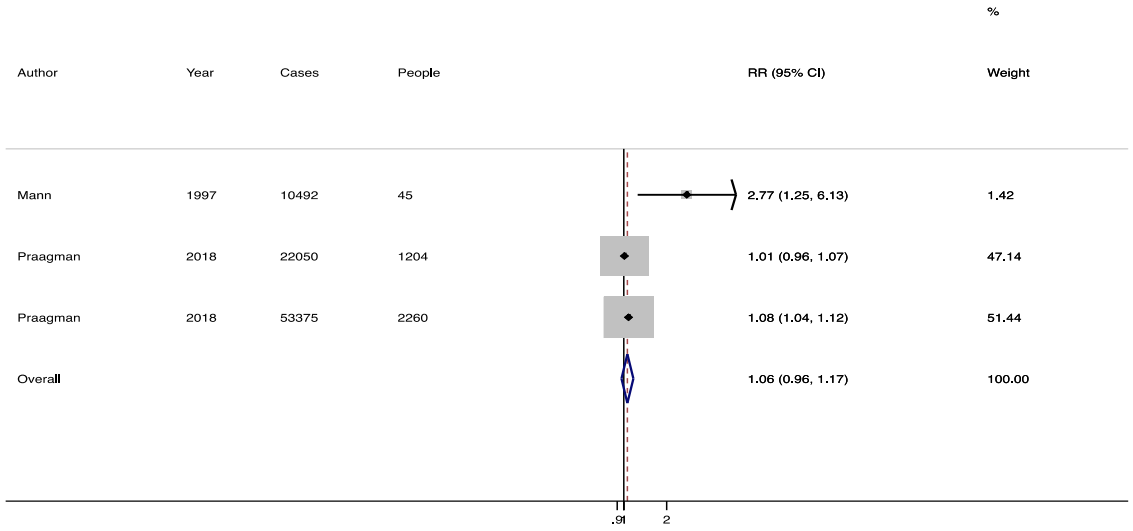
Fig. A4.3. Cubic spline dose response between self-reported total TFA intake (%TE) and CHD occurrence

Data were available from nine cohorts of 13 716 cases during 5 207 754 PY. Assuming linearity, the relative risk of a 5% increase in SFA was 0.99 (95% CI: 0.94 to 1.03).



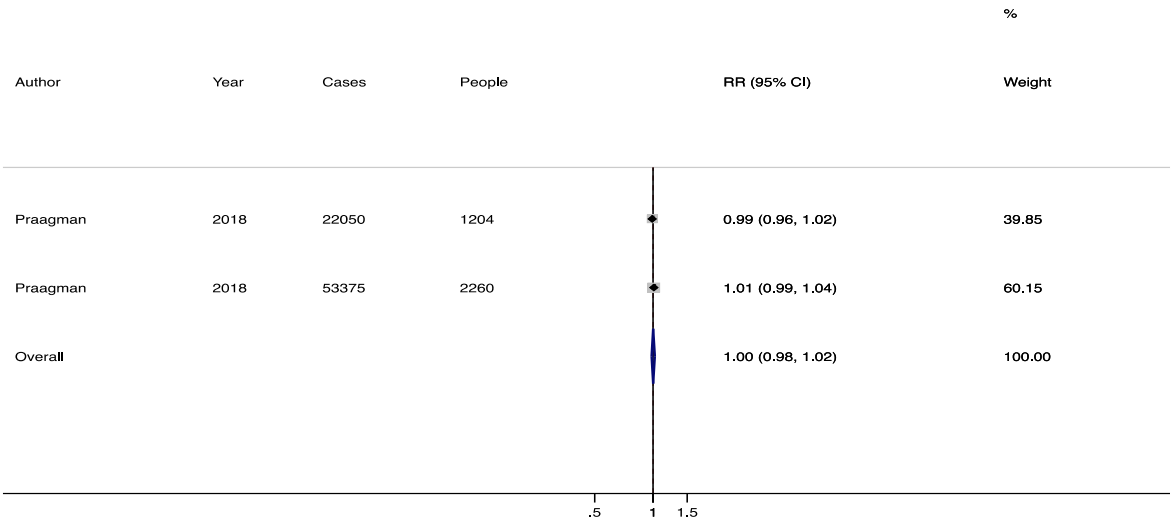
CHD: coronary heart disease; CI: confidence interval; PY: person years; SFA: saturated fatty acids; TE: total energy; TFA: *trans*-fatty acids.

Fig. A4.4a. Self-reported intakes of SFA from animal sources and CHD occurrence



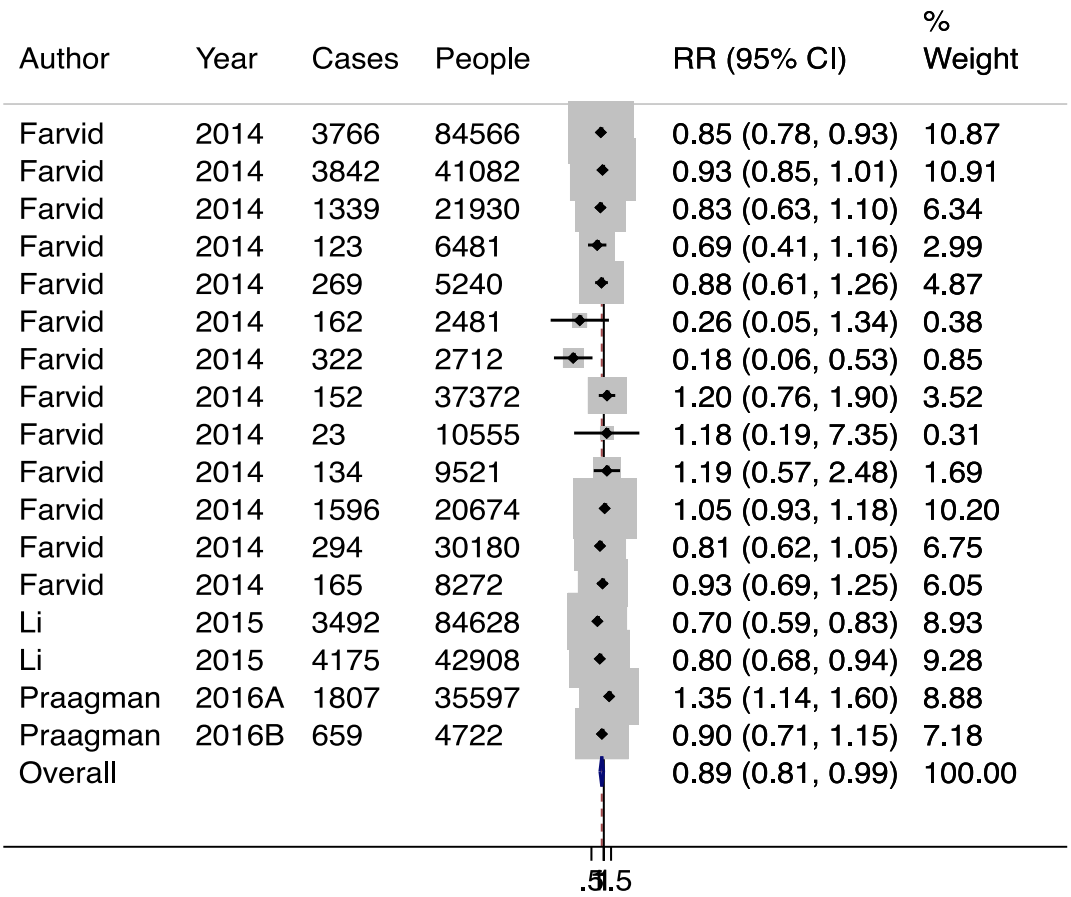
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.4b. Self-reported intakes of SFA from dairy sources and CHD occurrence



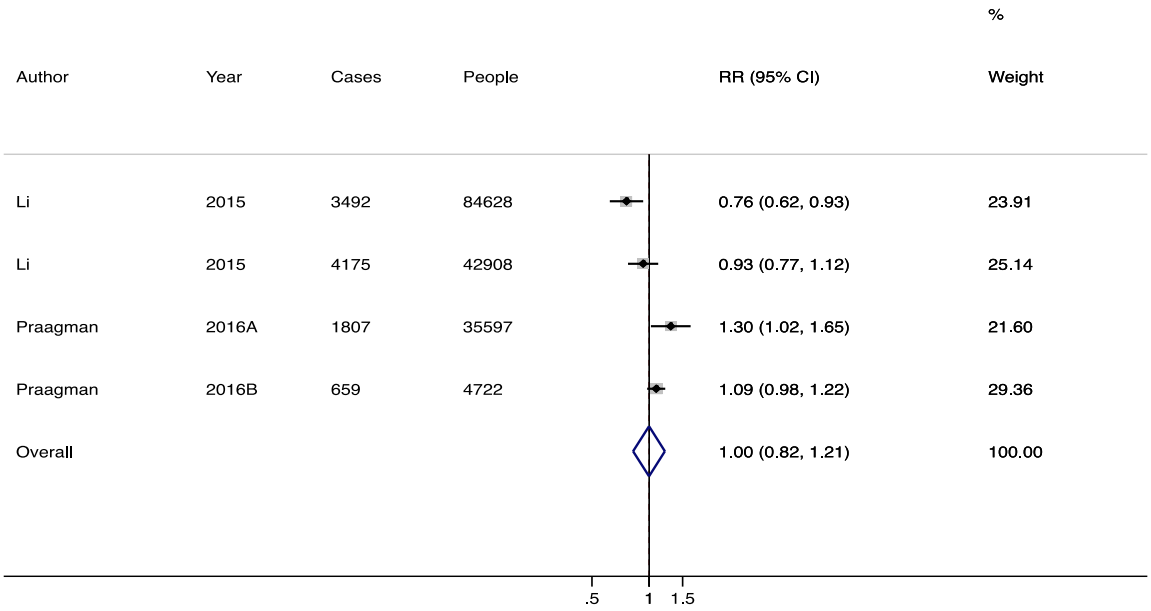
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5a. Replacement of self-reported total SFA intakes with 5% PUFA or linoleic acid and CHD occurrence



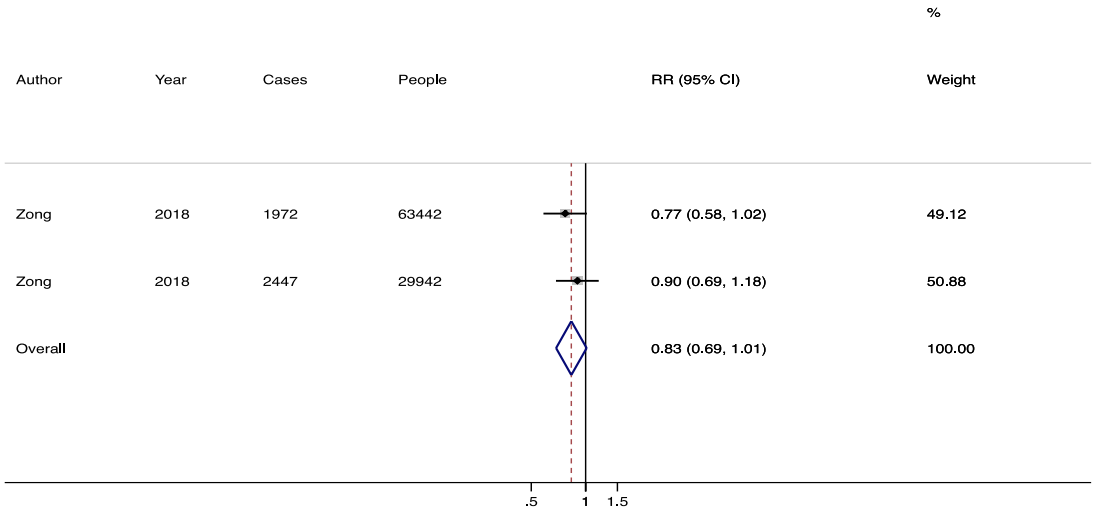
CHD: coronary heart disease; CI: confidence interval; PUFA: polyunsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5b. Replacement of self-reported total SFA intakes with 5% MUFA and CHD occurrence



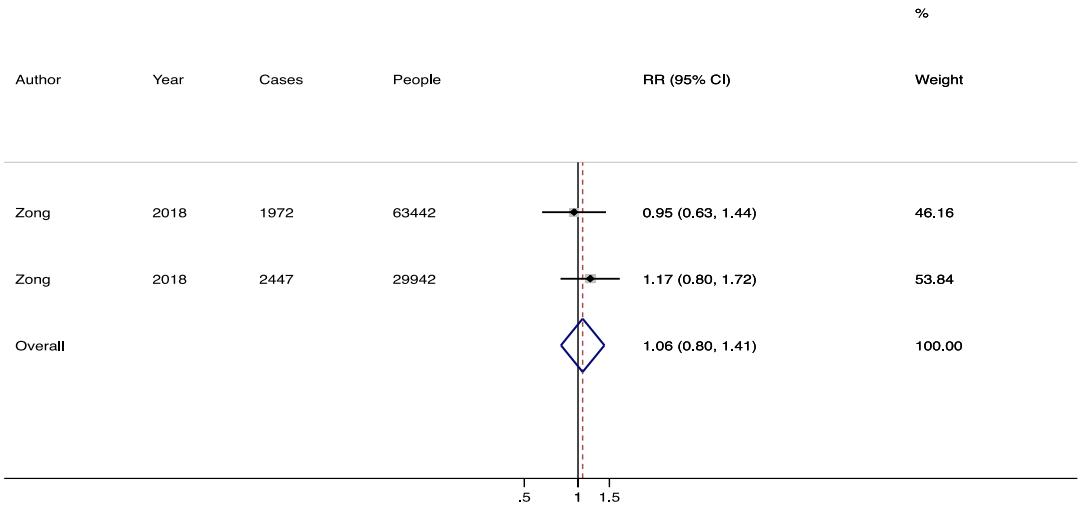
CHD: coronary heart disease; CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5c. Replacement of self-reported total SFA intakes with 5% plant MUFA and CHD occurrence



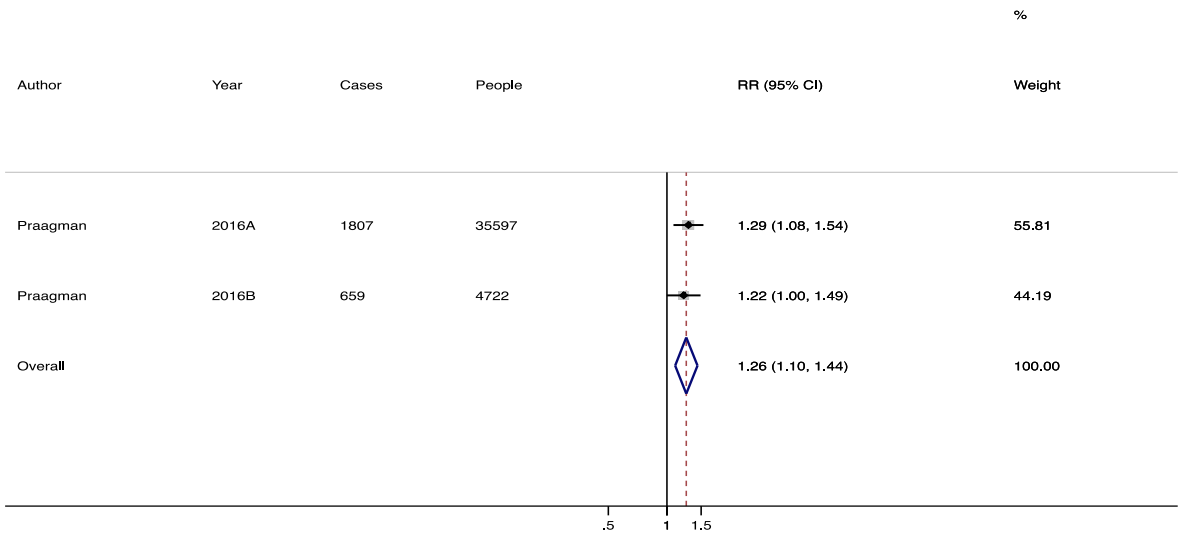
CHD: coronary heart disease; CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5d. Replacement of self-reported total SFA intakes with 5% animal MUFA and CHD occurrence



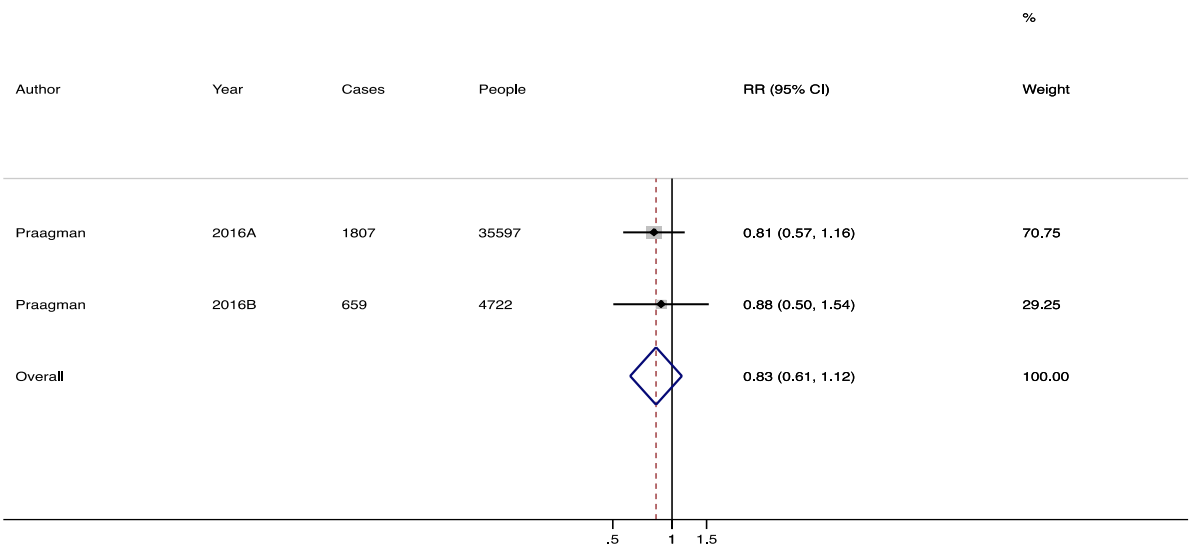
CHD: coronary heart disease; CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5e. Replacement of self-reported total SFA intakes with 5% protein and CHD occurrence



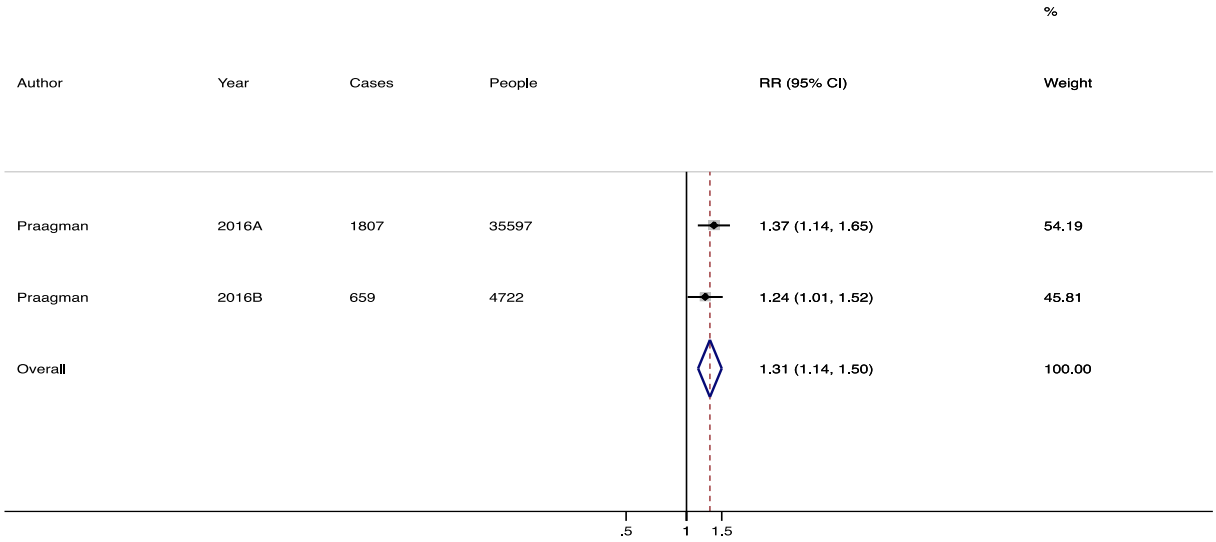
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids

Fig. A4.5f. Replacement of self-reported total SFA intakes with 5% plant protein and CHD occurrence



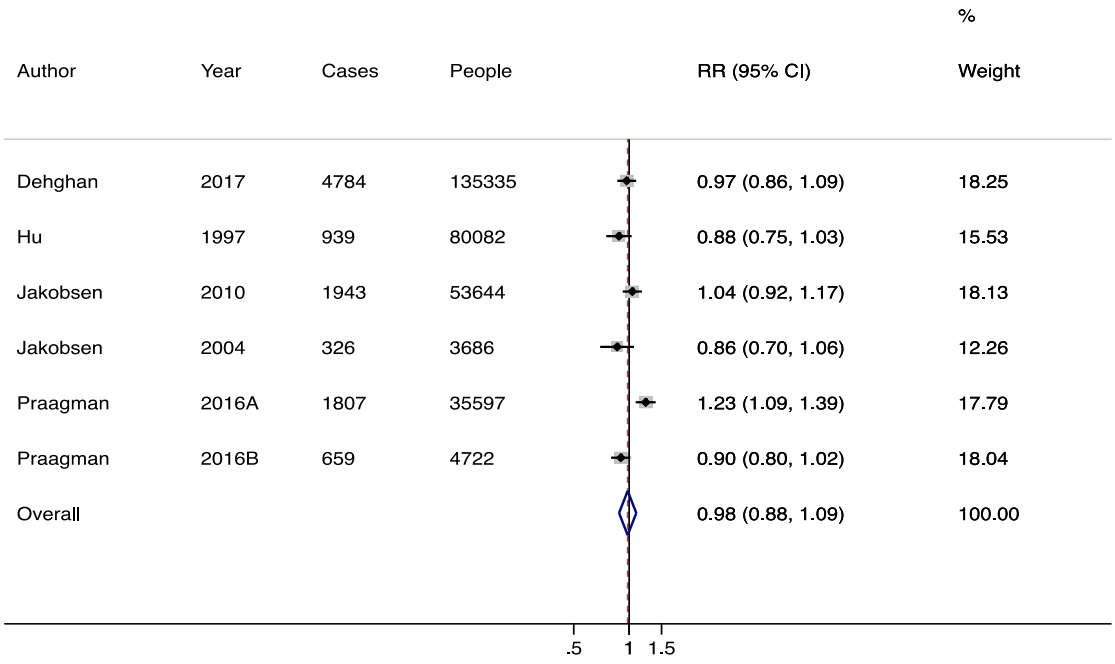
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5g. Replacement of self-reported total SFA intakes with 5% animal protein and CHD occurrence



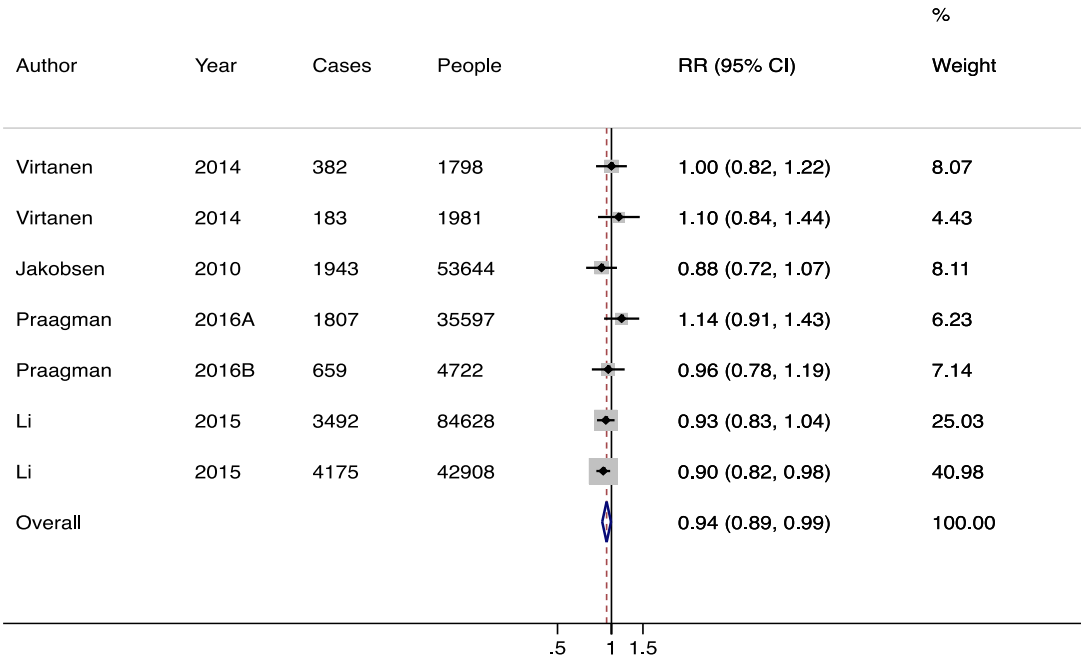
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5h. Replacement of self-reported total SFA intakes with 5% CHO and CHD occurrence



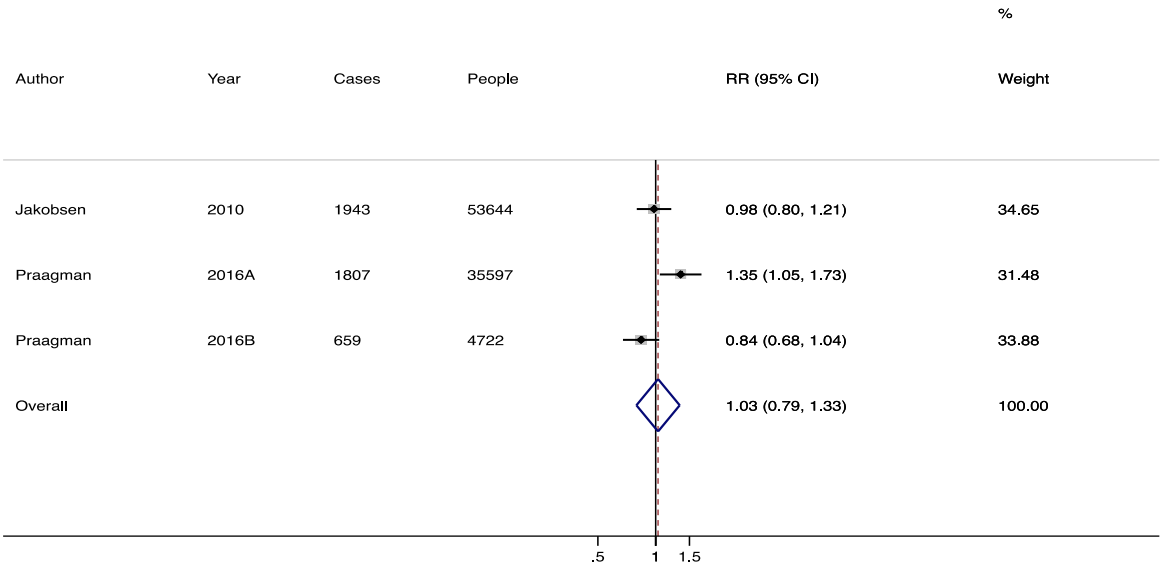
CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5i. Replacement of self-reported total SFA intakes with 5% slowly digested CHO (whole grains or low GI) and CHD occurrence



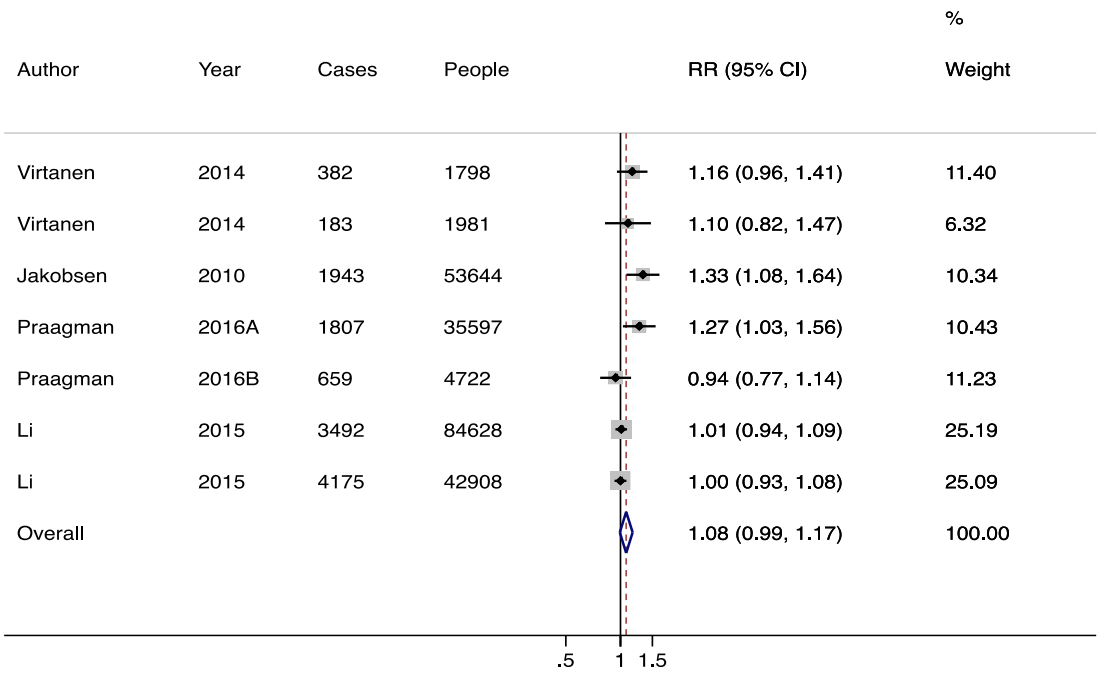
CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; GI: glycemic index; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5j. Replacement of self-reported total SFA intakes with 5% moderately digestible CHO (medium GI) and CHD occurrence



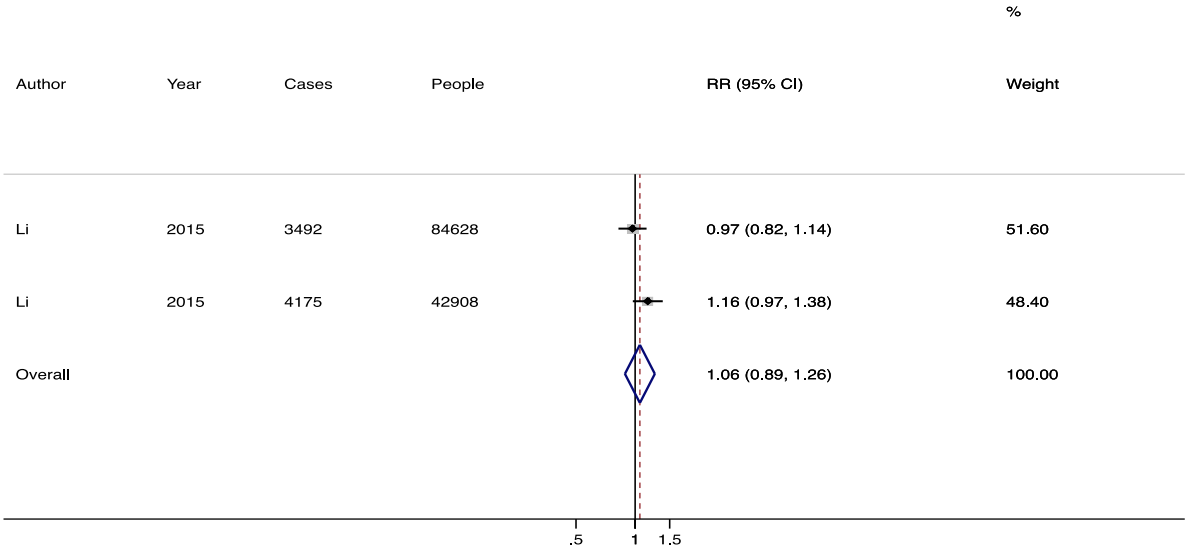
CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; GI: glycemic index; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5k. Replacement of self-reported total SFA intakes with 5% rapidly digested CHO (sugars or high GI) and CHD occurrence



CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; GI: glycemic index; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.5l. Replacement of self-reported total SFA intakes with 2% TFA and CHD occurrence

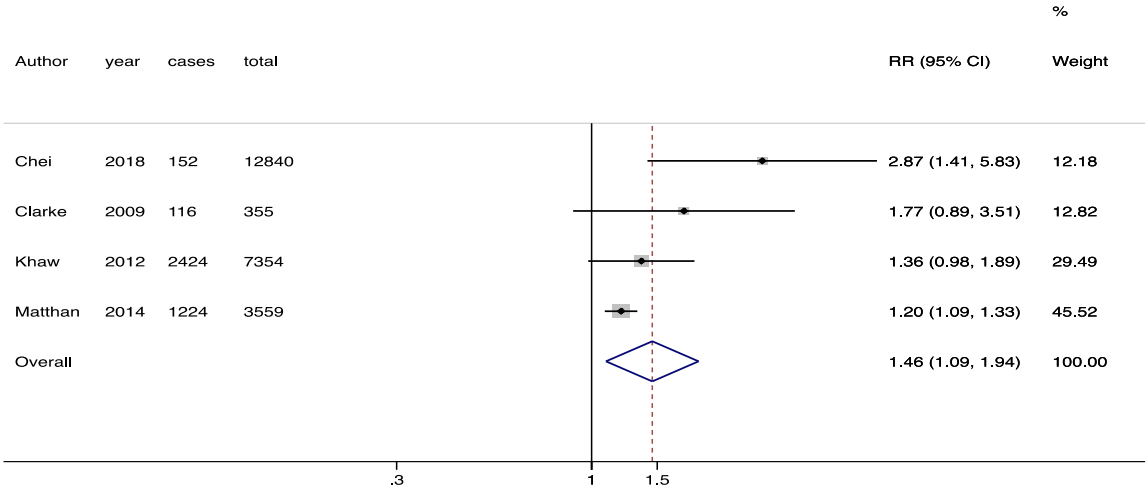


CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids; TFA: *trans*-fatty acids.

Tissue samples

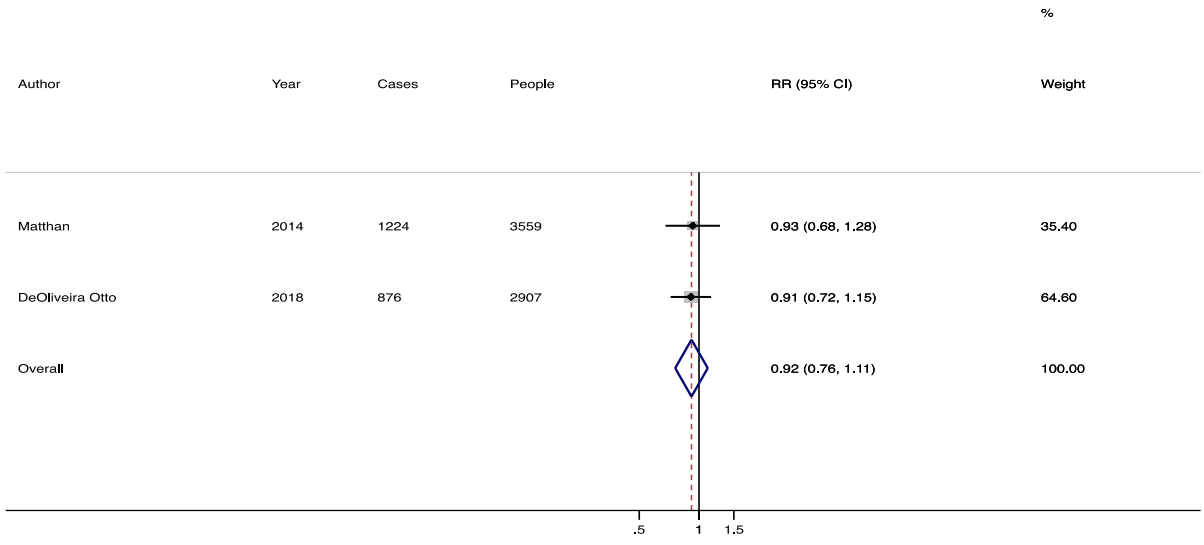
Fig. A4.6. Total SFA from tissue measurements and CHD occurrence

Initial heterogeneity was high (I^2 58%). Influence analysis indicated that one study, Matthan 2014 *(1)*, appreciably influenced the pooled result. The analysis without Matthan 2014 was RR 1.74 (95% CI: 1.13 to 2.68) and reduce heterogeneity (I^2 44%). There was no evidence of a small study effect (*P*=0.086) and tissue type assessed did not influence the results (*P*=0.144).



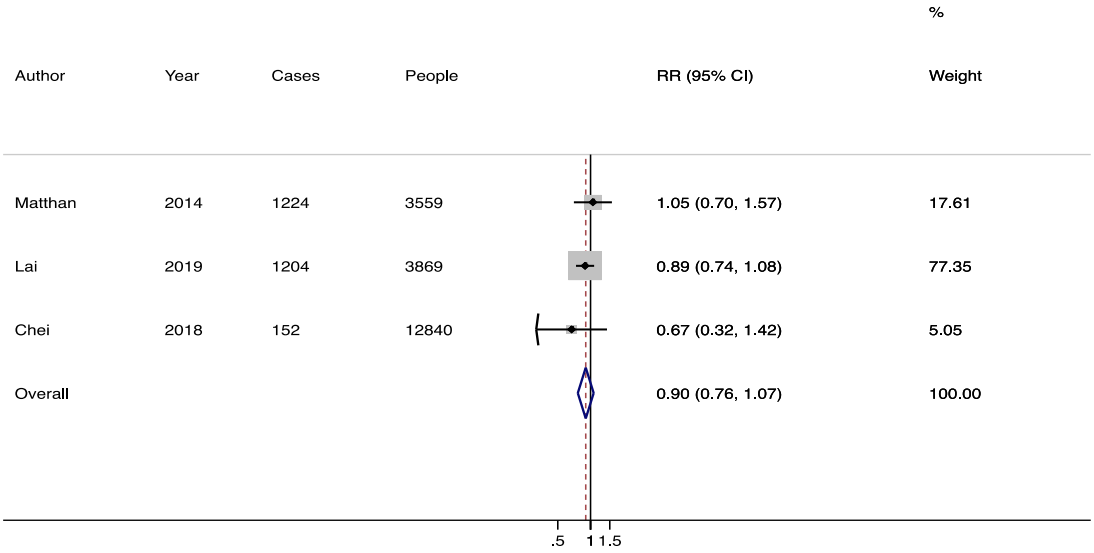
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7a. SFA by chain length from tissue measurements of C12:0 and CHD occurrence



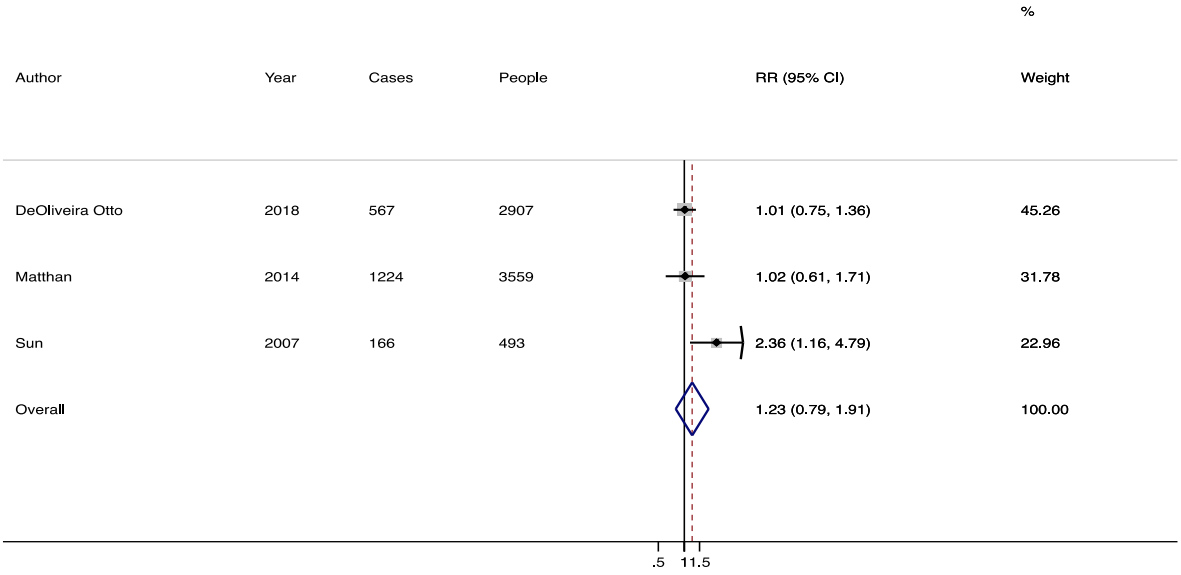
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7b. SFA by chain length from tissue measurements of C14:0 and CHD occurrence



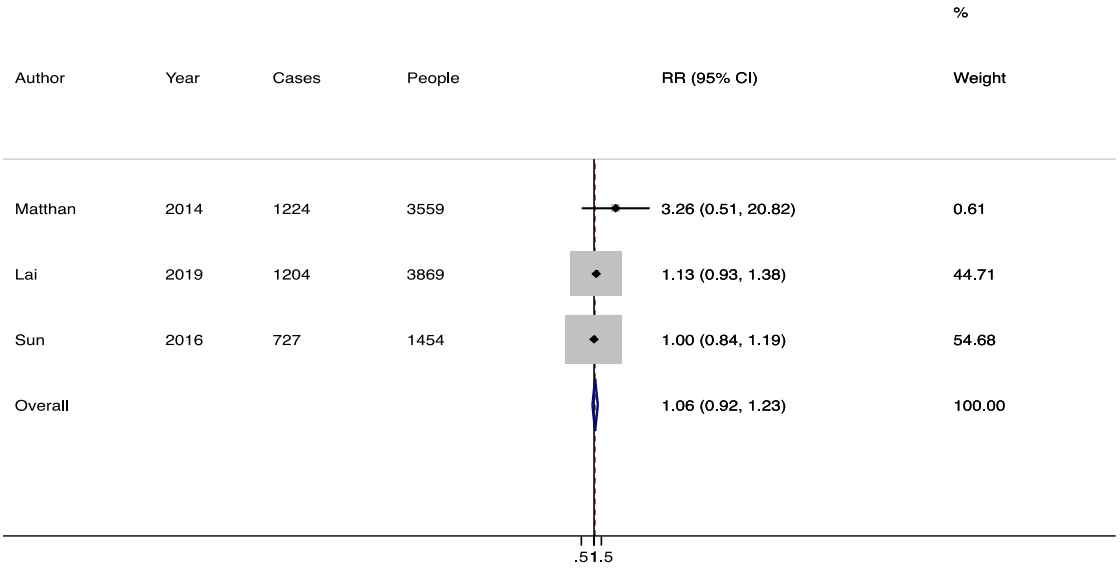
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7c. SFA by chain length from tissue measurements of C15:0 and CHD occurrence



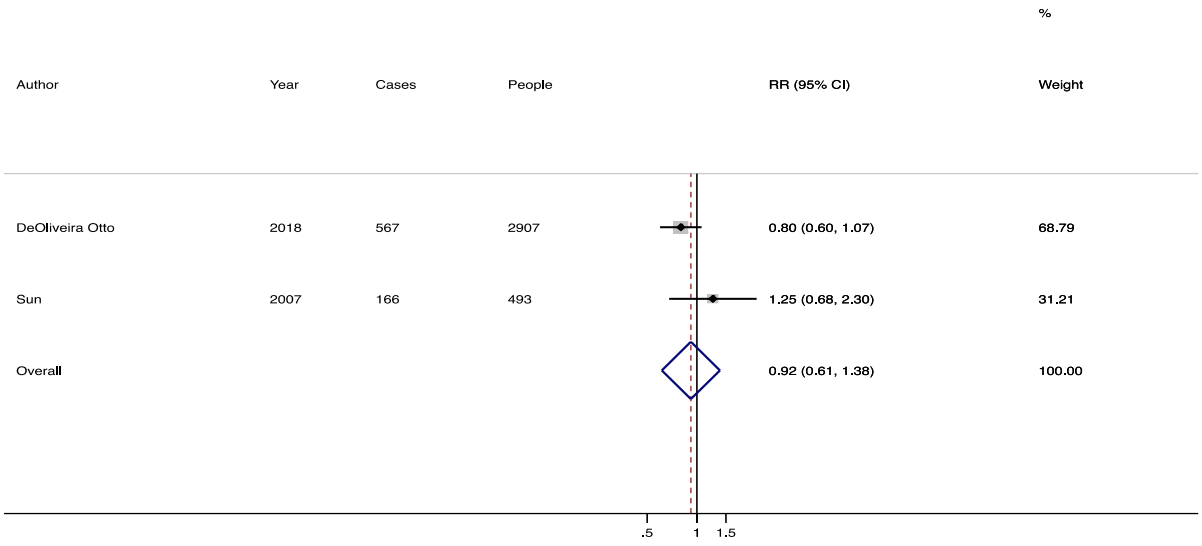
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7d. SFA by chain length from tissue measurements of C16:0 and CHD occurrence



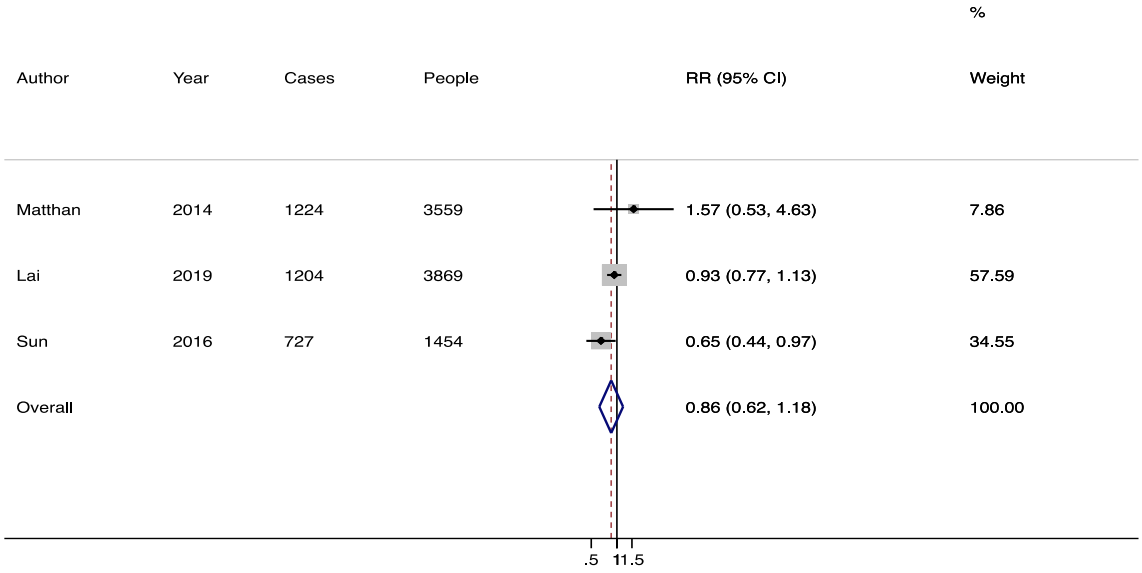
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7e. SFA by chain length from tissue measurements of C17:0 and CHD occurrence



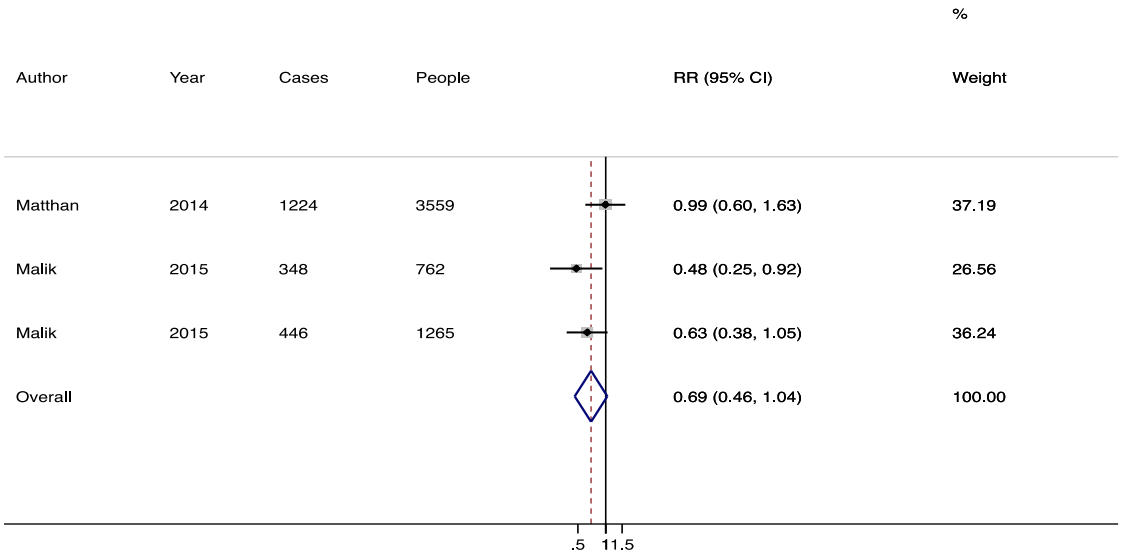
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7f. SFA by chain length from tissue measurements of C18:0 and CHD occurrence



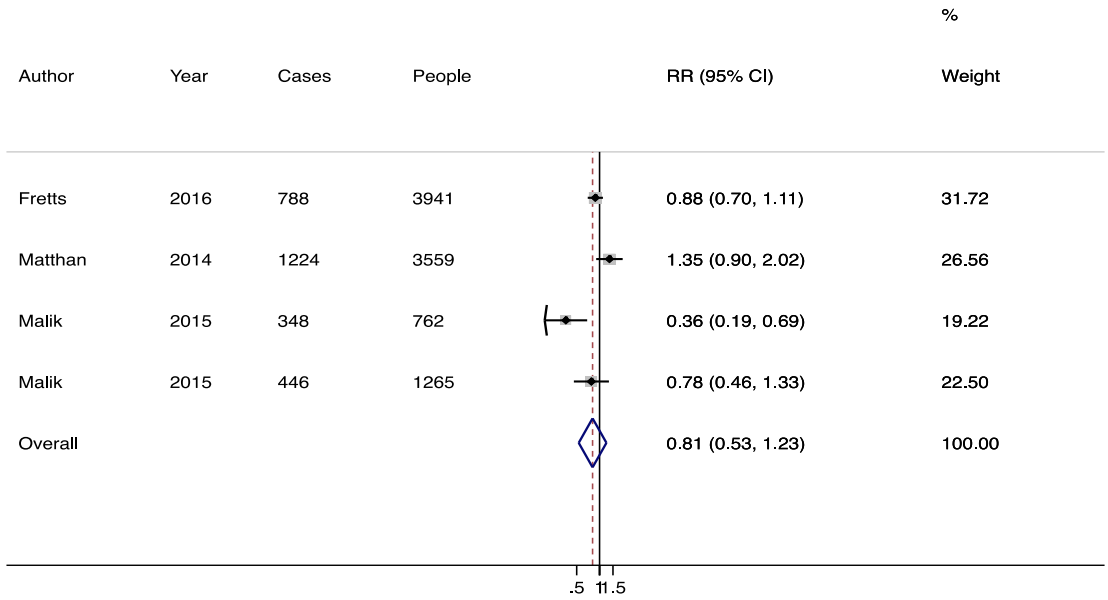
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7g. SFA by chain length from tissue measurements of C20:0 and CHD occurrence



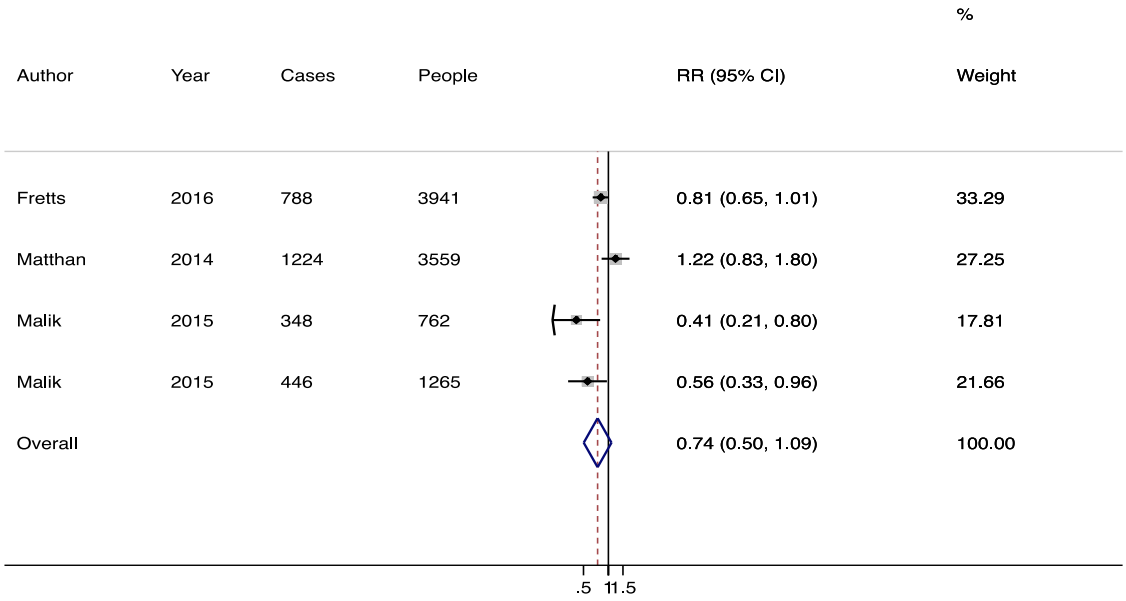
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7h. SFA by chain length from tissue measurements of C22:0 and CHD occurrence



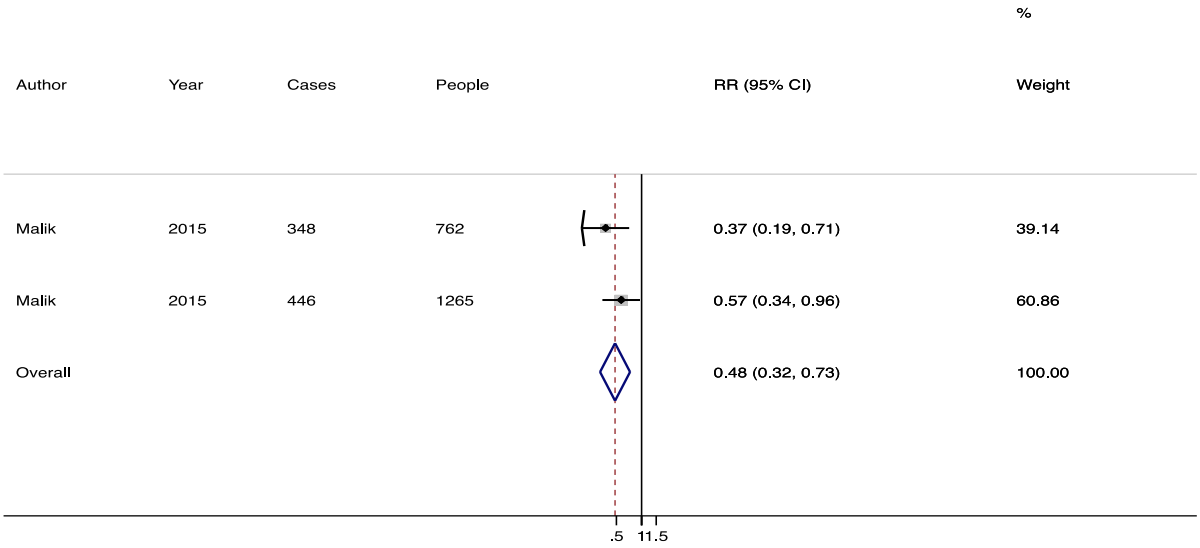
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7i. SFA by chain length from tissue measurements of C24:0 and CHD occurrence



CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A4.7j. SFA by chain length from tissue measurements of >C19:0 and CHD occurrence



CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Reference for Annex 4

1 Matthan NR, Ooi EM, Van Horn L, Neuhouser ML, Woodman R, Lichtenstein AH. Plasma phospholipid fatty acid biomarkers of dietary fat quality and endogenous metabolism predict coronary heart disease risk: a nested case-control study within the Women's Health Initiative observational study. J Am Heart Assoc. 2014;3(4).

ANNEX 5.

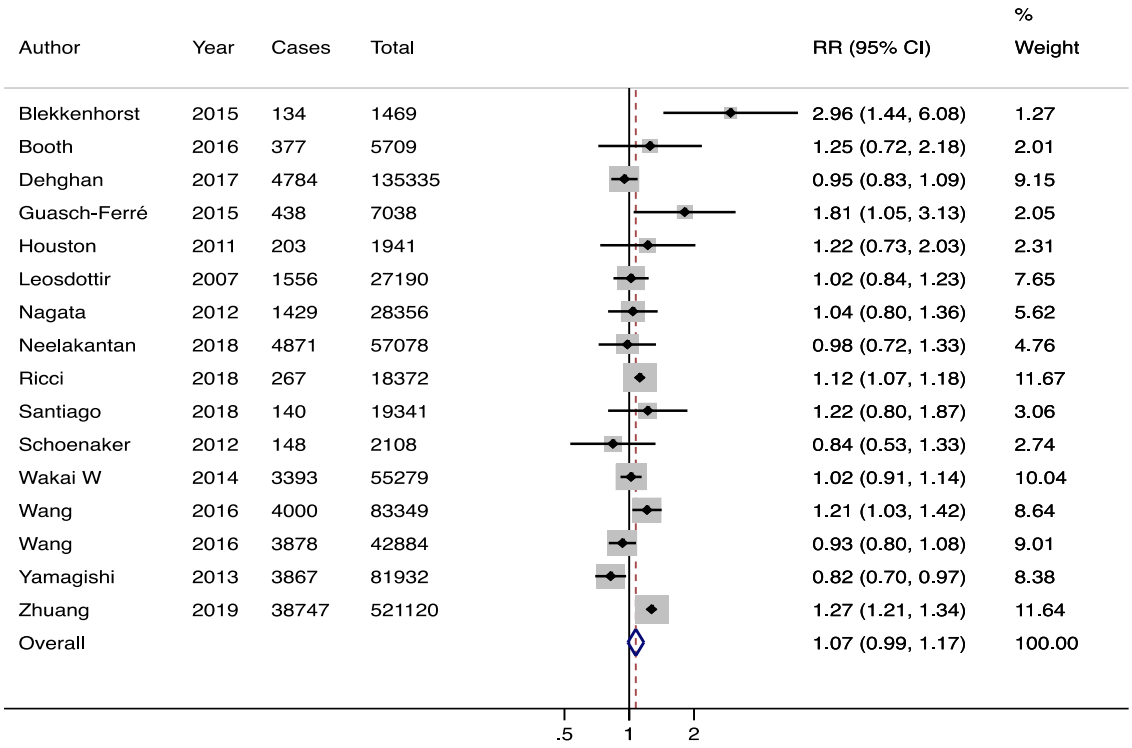
SFA intakes and cardiovascular disease occurrence

Dietary intakes

Estimates for fatal cardiovascular disease (CVD), non-fatal CVD, and combined fatal and non-fatal CVD were run and then considered with a categorical meta-regression to see whether effect size estimates varied by which outcome was reported. *P* values (*P*>0.693) indicated that there were no differences between outcome type, so estimates were run together, without duplication of the same participants, to comment on CVD occurrence.

Fig. A5.1. Self-reported intakes of total SFA and CVD occurrence

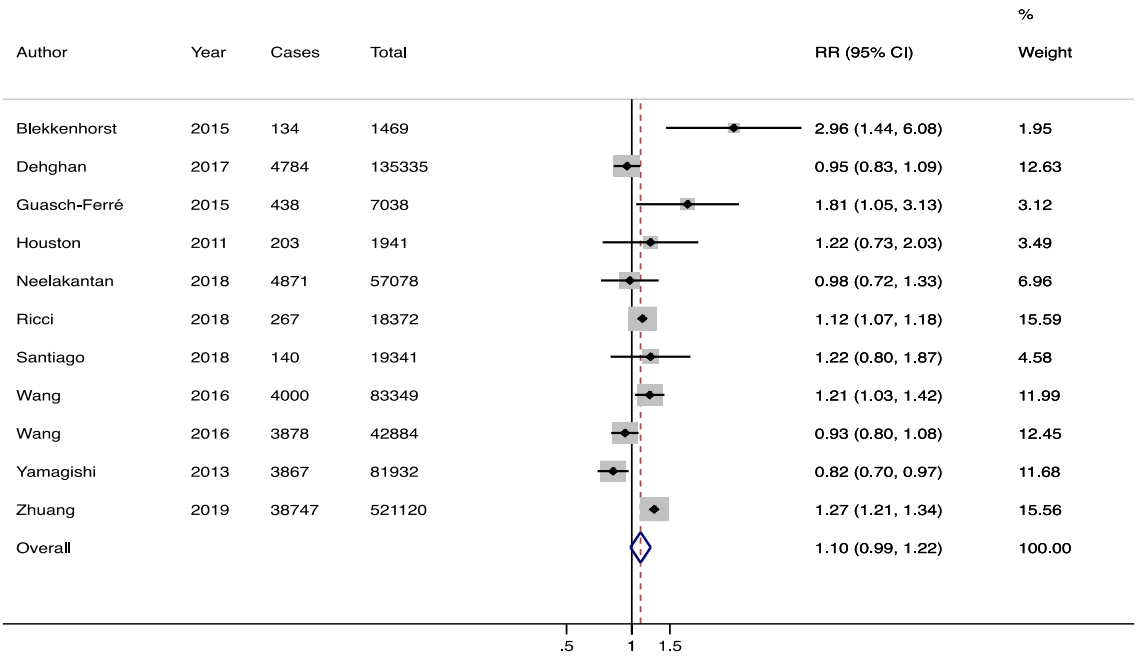
Initial heterogeneity was high (I^2 77%). One study (Zhuang 2019 *(1)*) was found to appreciably influence the pooled result. The effect size estimate without Zhuang 2019 was RR 1.05 (95% CI: 0.96 to 1.14) and heterogeneity remained high (I^2 62%). There was no evidence of a small study effect (*P*=0.411). Cohorts of those with pre-existing conditions were not found to influence the pooled result (*P*=0.424).



CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.2. Self-reported intakes of <10% and >10% SFA and CVD occurrence

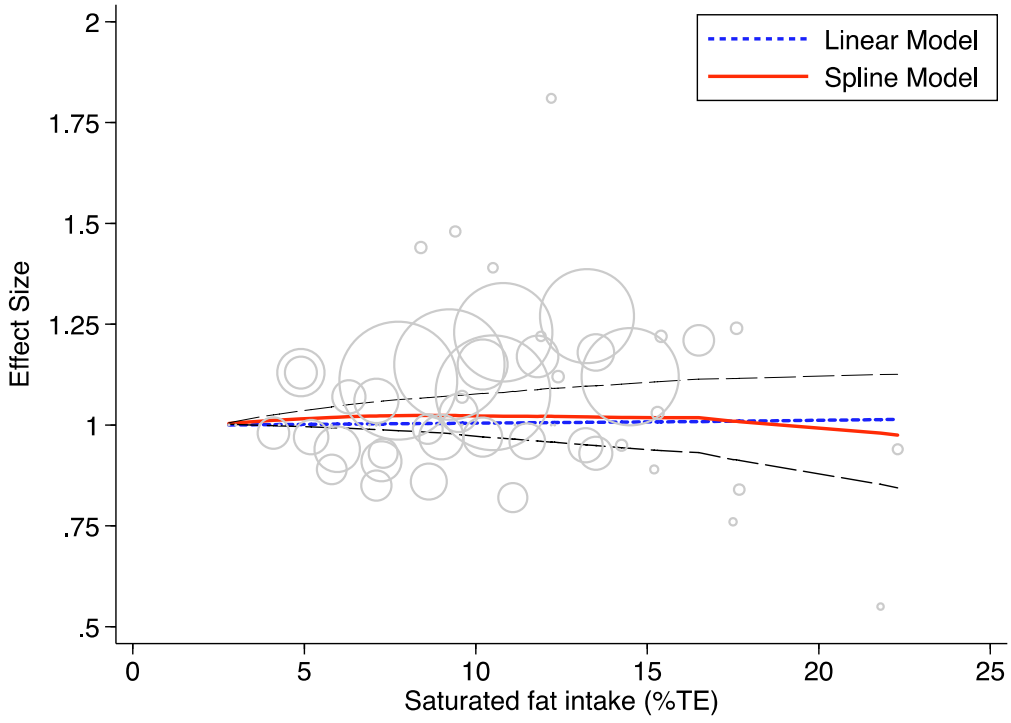
Initial heterogeneity was high (I^2 83%).



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

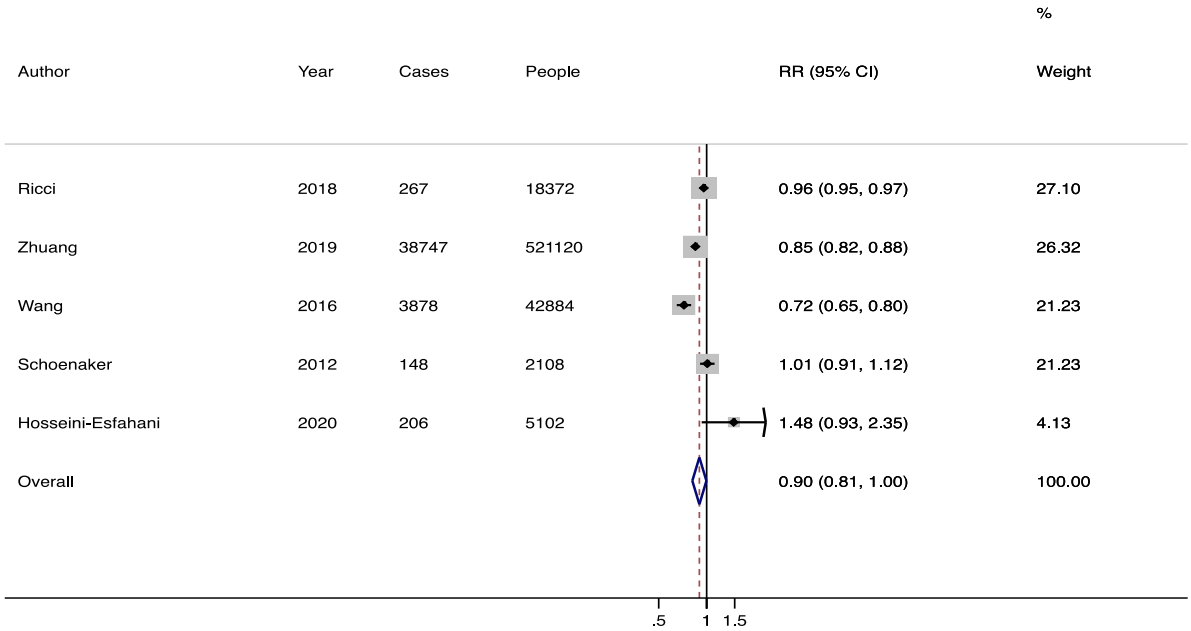
Fig. A5.3. Cubic spline dose response between self-reported total SFA intake (%TE) and CVD occurrence

Data were available from 16 cohorts of 60 629 cases during 16 227 781 PY. Assuming linearity, the relative risk of a 5% increase in SFA was 1.01 (95% CI: 0.94 to 1.08).



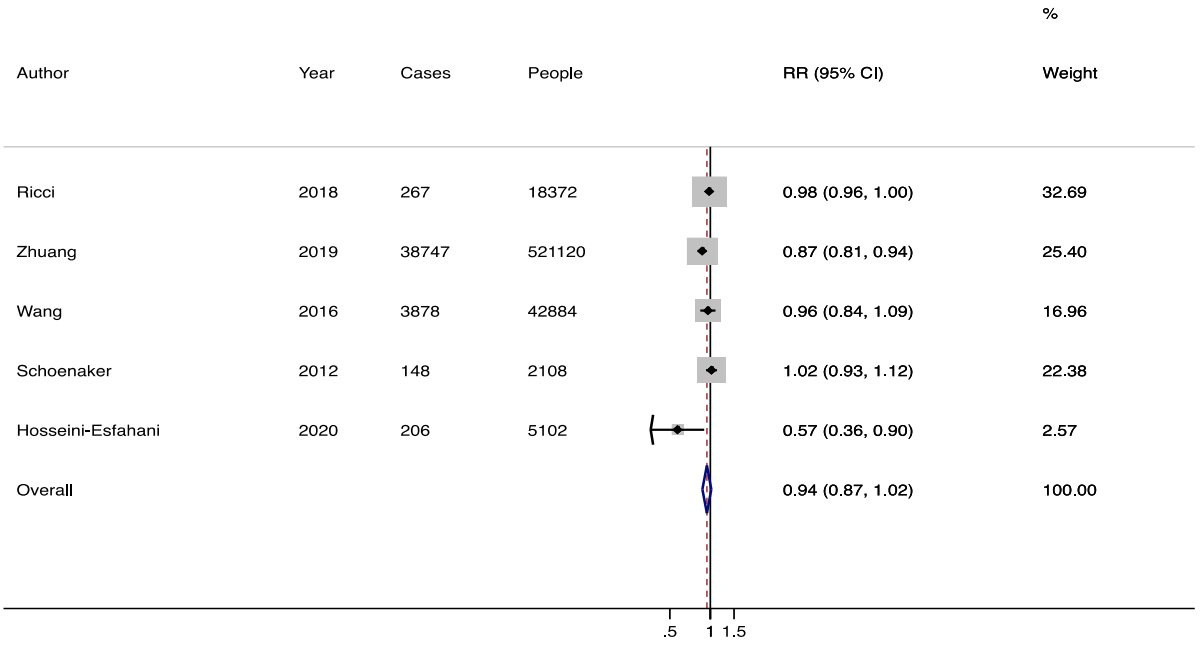
CI: confidence interval; CVD: cardiovascular disease; PY: person years; SFA: saturated fatty acids; TE: total energy.

Fig. A5.4a. Replacement of self-reported total SFA intakes with 5% PUFA and CVD occurrence



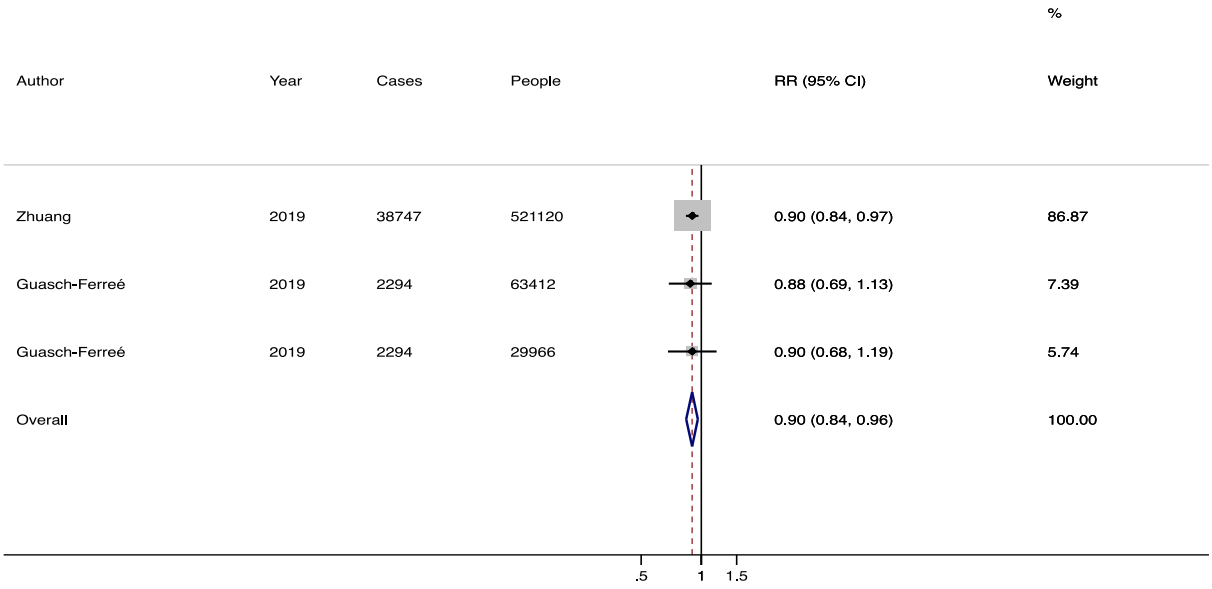
CI: confidence interval; CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.4b. Replacement of self-reported total SFA intakes with 5% MUFA and CVD occurrence



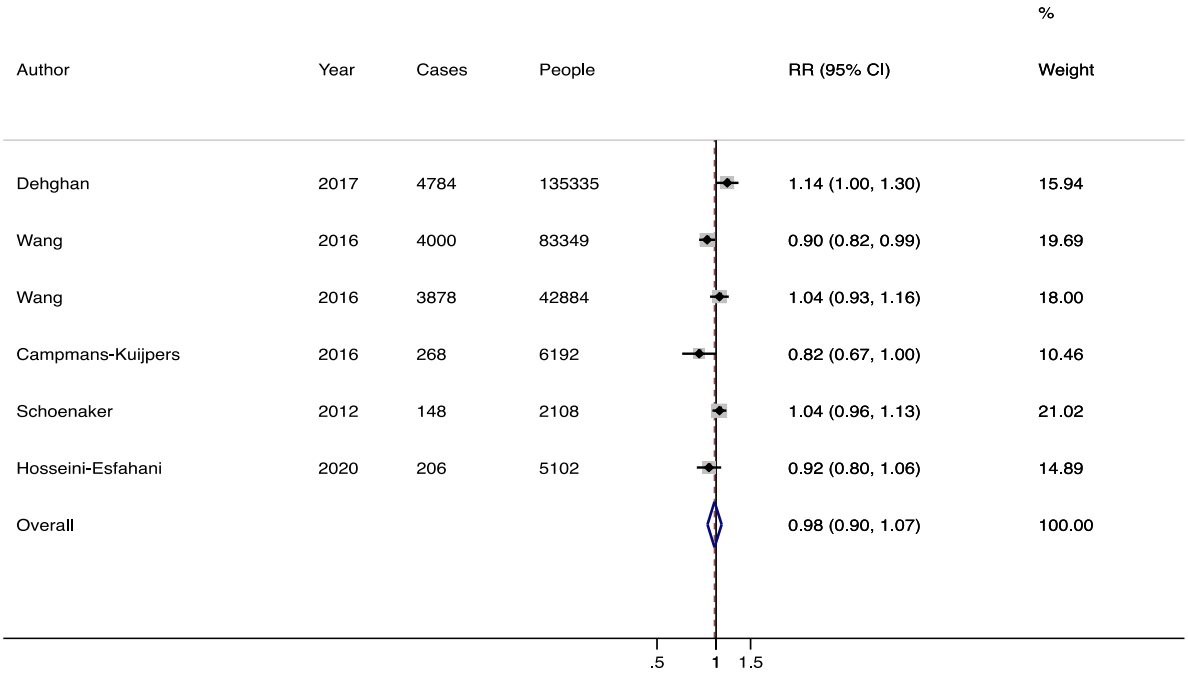
CI: confidence interval; CVD: cardiovascular disease; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.4c. Replacement of self-reported total SFA intakes with 5% plant MUFA and CVD occurrence



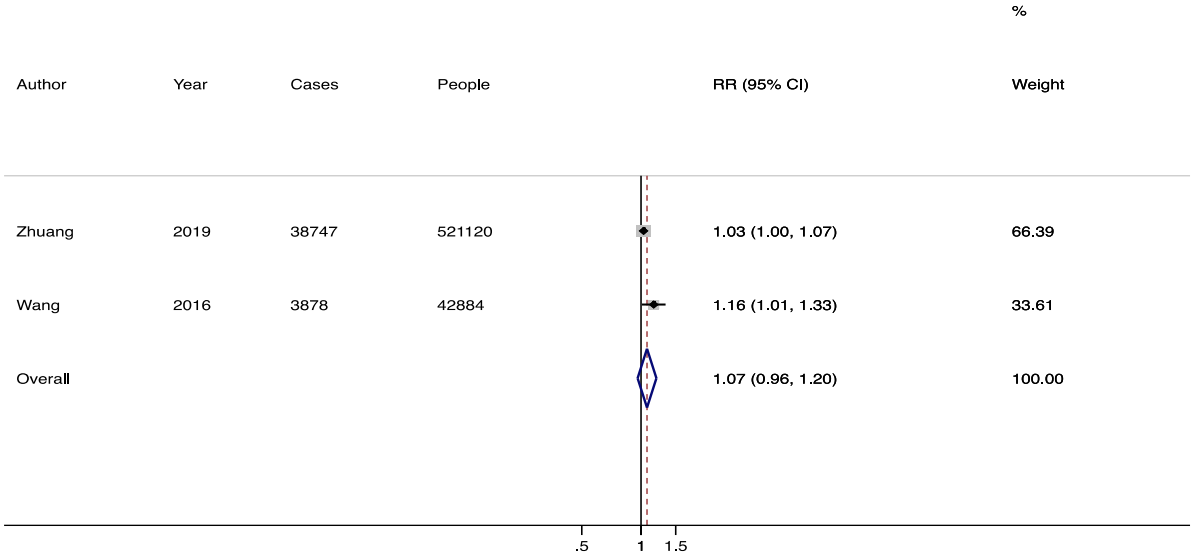
CI: confidence interval; CVD: cardiovascular disease; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.4d Replacement of self-reported total SFA intakes with 5% CHO and CVD occurrence



CI: confidence interval; CHO: carbohydrate; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

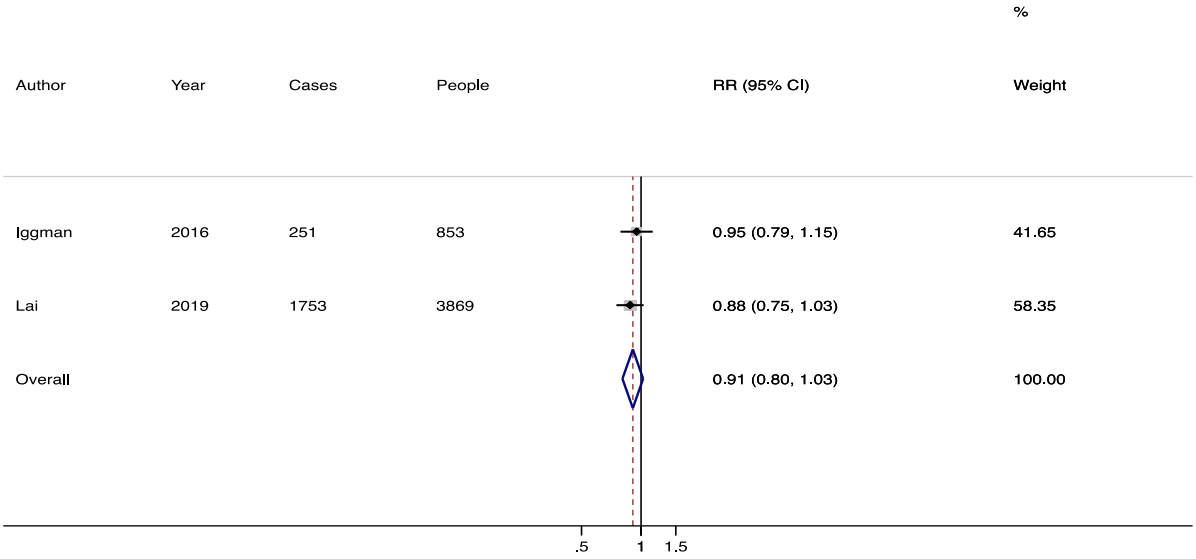
Fig. A5.4e. Replacement of self-reported total SFA intakes with 2% TFA and CVD occurrence



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids; TFA: trans-fatty acids.

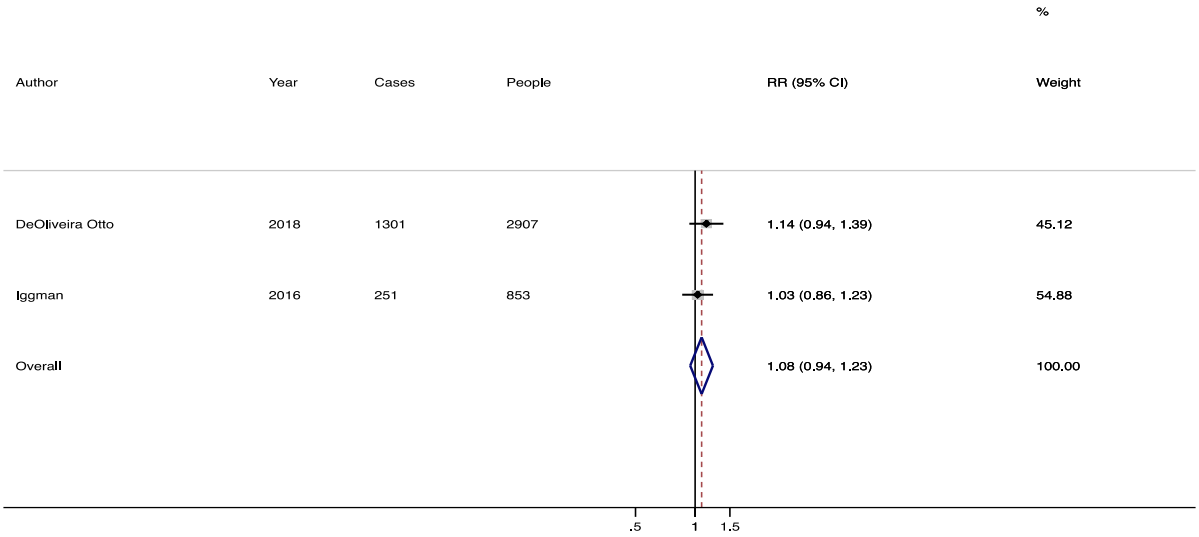
Tissue samples

Fig. A5.5a. SFA by chain length from tissue measurements of C14:0 and CVD occurrence



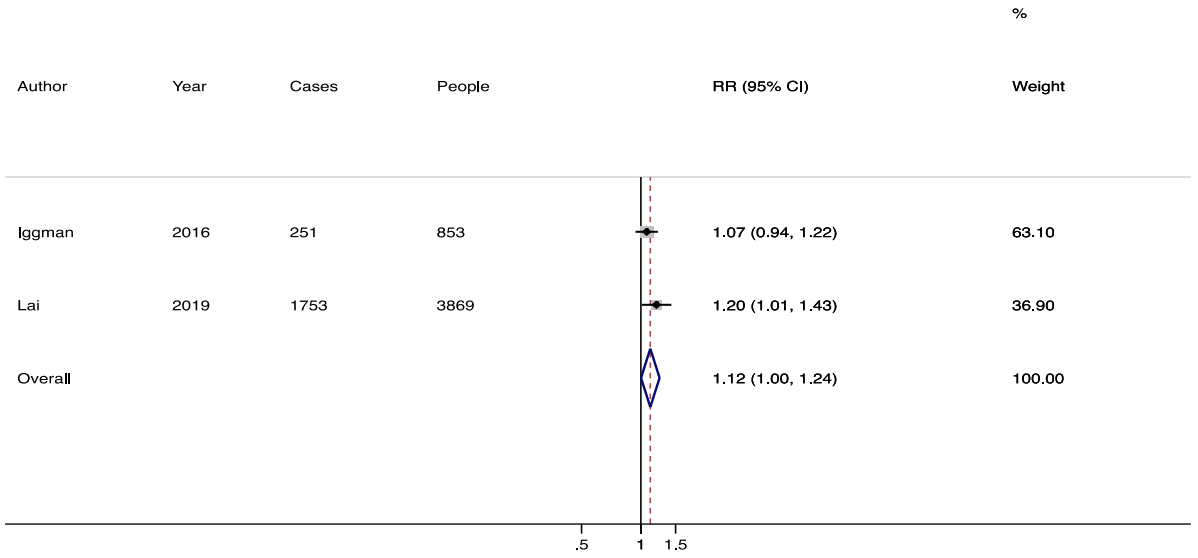
CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.5b. SFA by chain length from tissue measurements of C15:0 and CVD occurrence



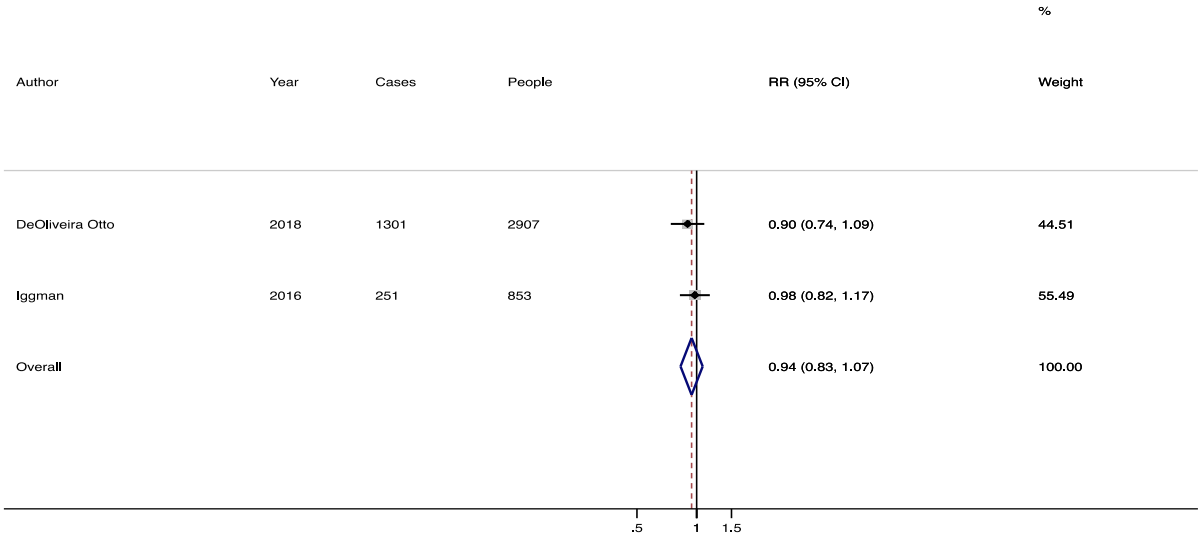
CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.5c. SFA by chain length from tissue measurements of C16:0 and CVD occurrence



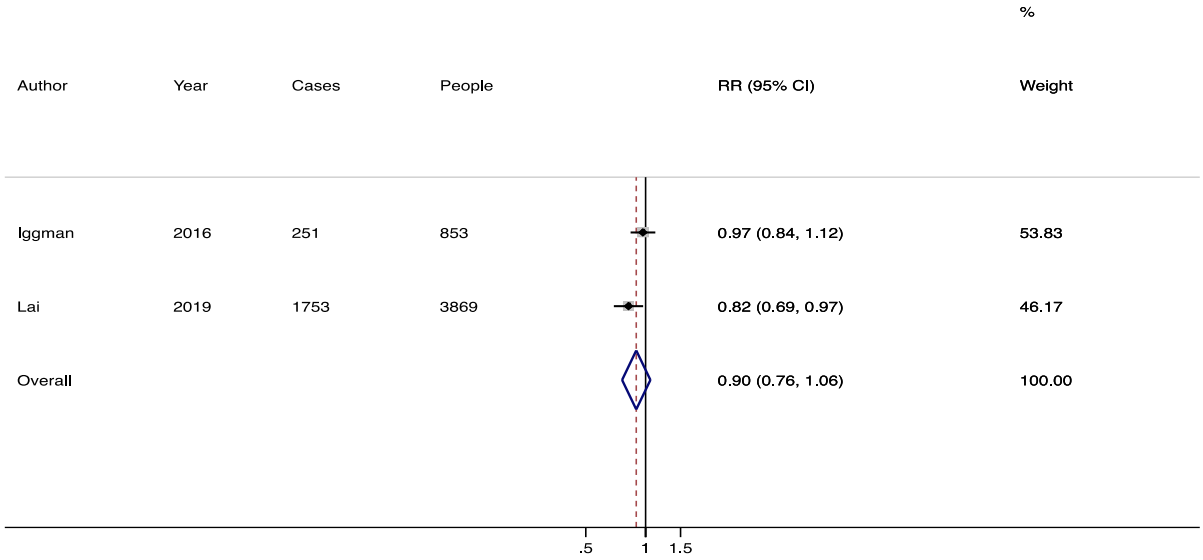
CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.5d. SFA by chain length from tissue measurements of C17:0 and CVD occurrence



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

Fig. A5.5e. SFA by chain length from tissue measurements of C18:0 and CVD occurrence



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

Reference for Annex 5

1 Zhuang P, Zhang Y, He W, Chen X, Chen J, He L et al. Dietary fats in relation to total and cause-specific mortality in a prospective cohort of 521,120 individuals with 16 years of follow-up. Circ Res. 2019;124(5):757–68.

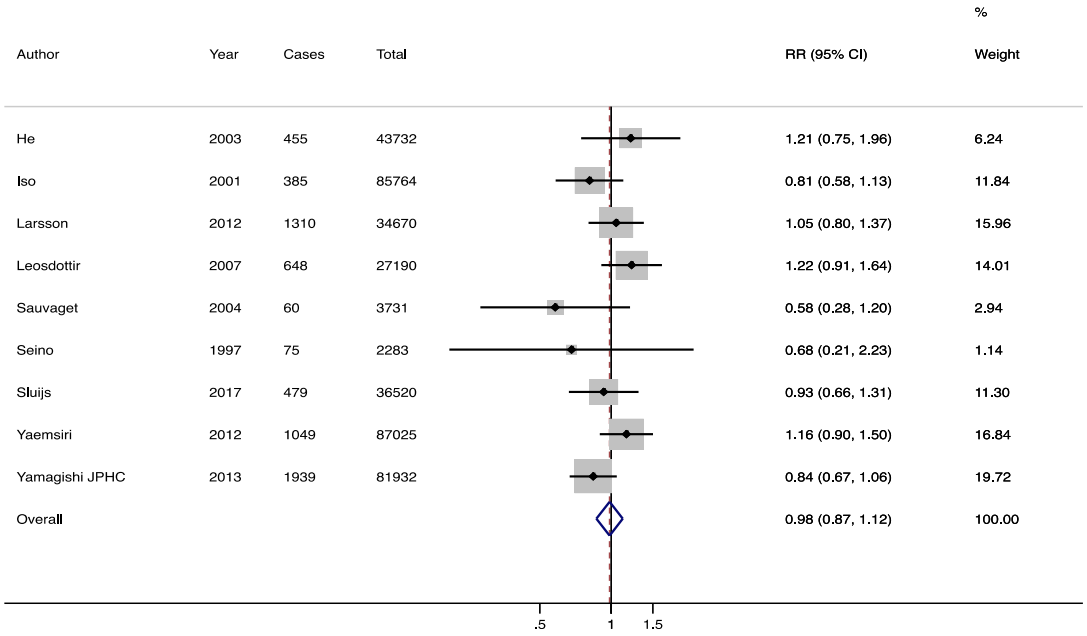
ANNEX 6.

SFA intakes and ischaemic stroke occurrence

Dietary intakes

Fig. A6.1. Self-reported intakes of total saturated fat and ischaemic stroke

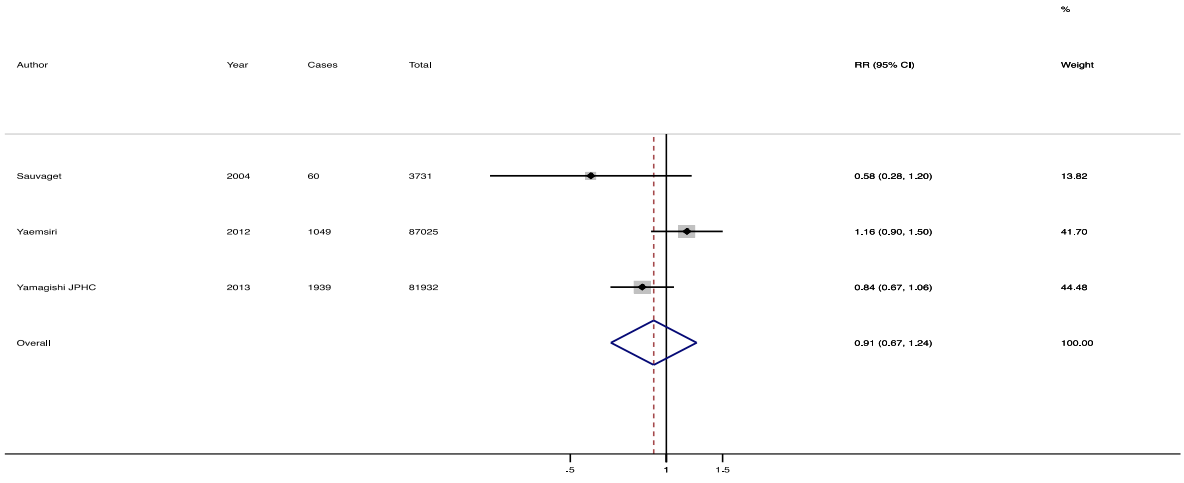
Initial heterogeneity was low (I^2 22%). No single study influenced the pooled estimate, and there was no evidence of a small study effect (Egger *P*=0.466). There were no different study types or cohorts of those with pre-existing conditions in this pool.



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A6.2. Self-reported intakes of <10% total SFA with >10% SFA and ischaemic stroke

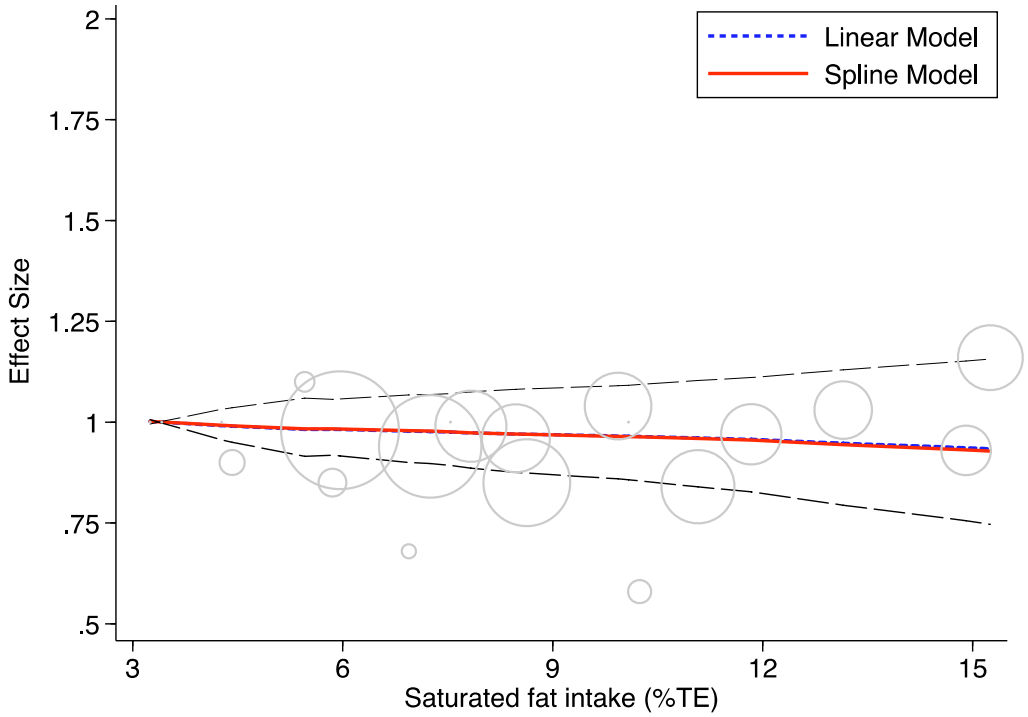
Initial heterogeneity was high (I^2 61%).



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A6.3. Cubic spline dose response between self-reported total SFA intake (%TE) and ischaemic stroke

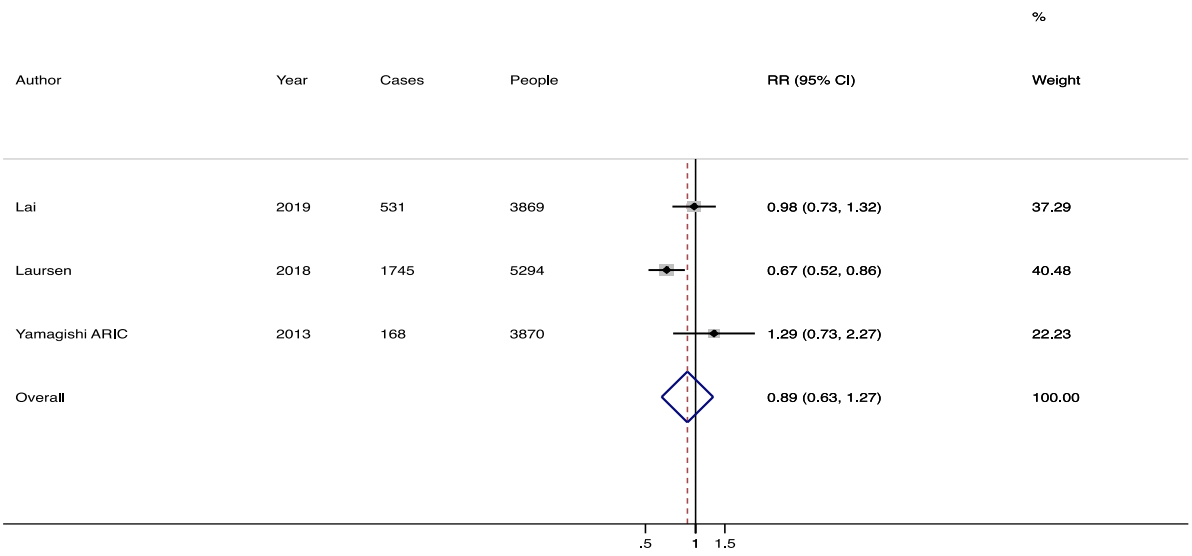
Data were available from five cohorts of 3601 cases over 2 198 066 PY. Assuming linearity, the increased risk of all-cause mortality per 5% increase in TE from total saturated fat was RR 0.94 (95% CI: 0.79 to 1.13).



CI: confidence interval; PY: person years; RR: relative risk; TE: total energy; SFA: saturated fatty acids.

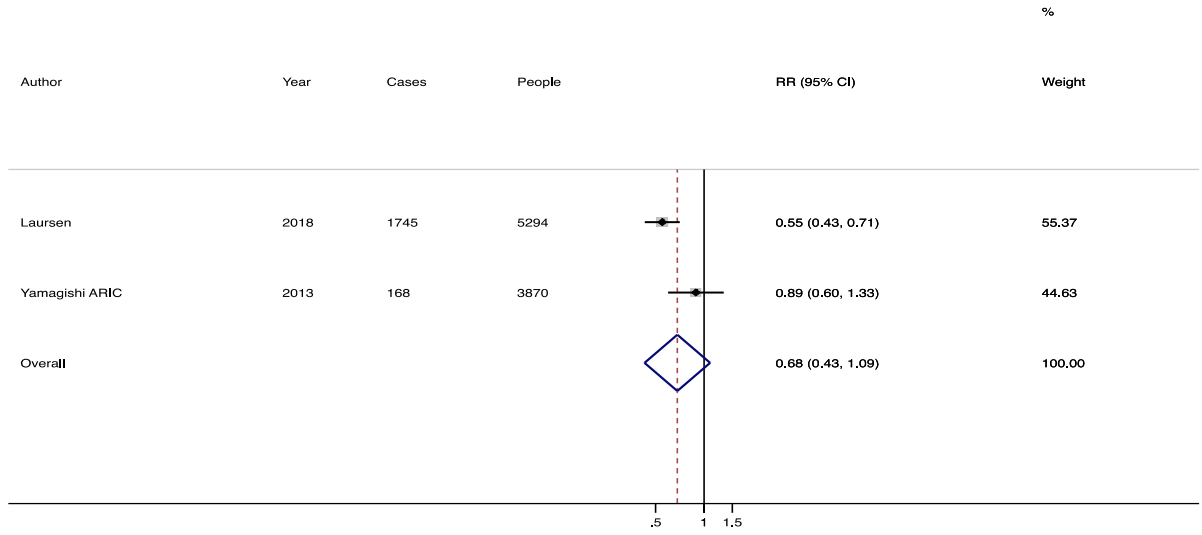
Tissue samples

Fig. A6.4a. SFA by chain length from tissue measurements of C14:0 and ischaemic stroke occurrence



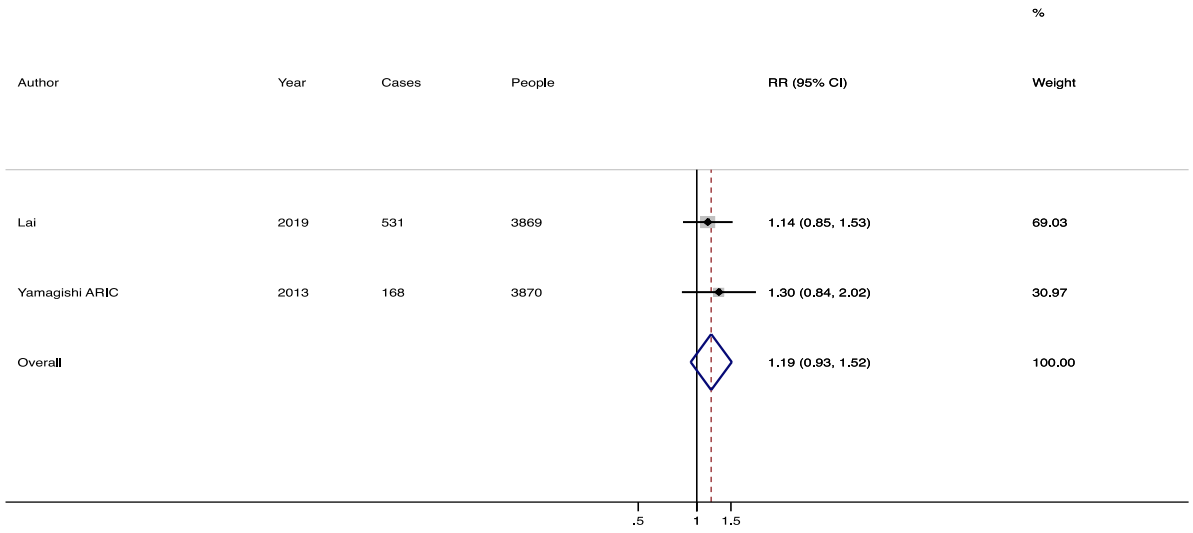
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A6.4b. SFA by chain length from tissue measurements of C15:0 and ischaemic stroke occurrence



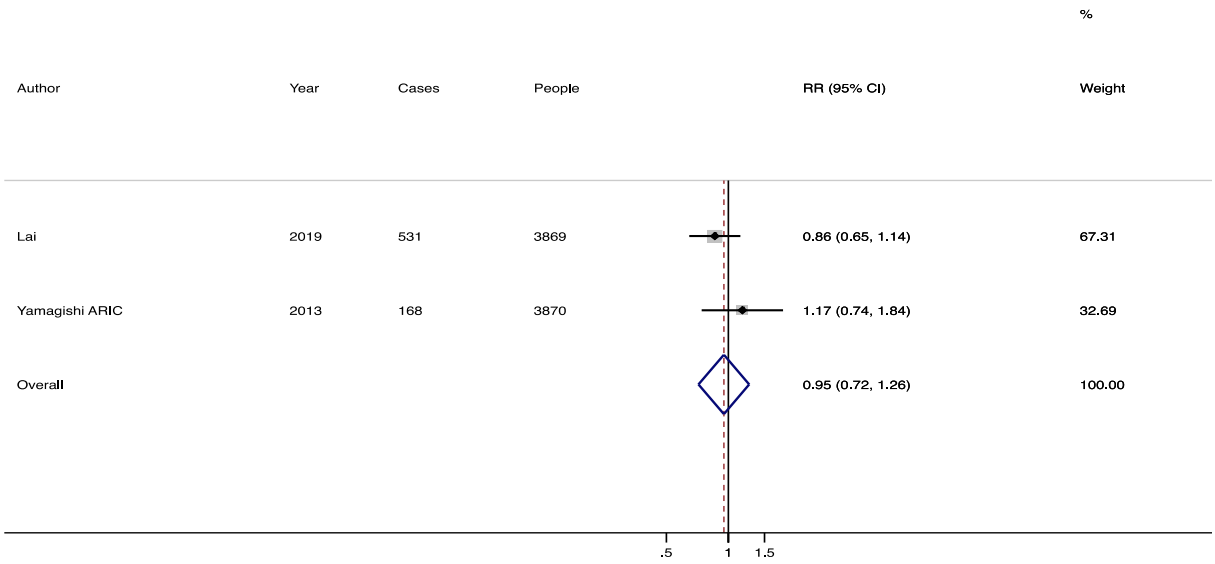
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A6.4c. SFA by chain length from tissue measurements of C16:0 and ischaemic stroke occurrence



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A6.4d. SFA by chain length from tissue measurements of C18:0 and ischaemic stroke occurrence



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

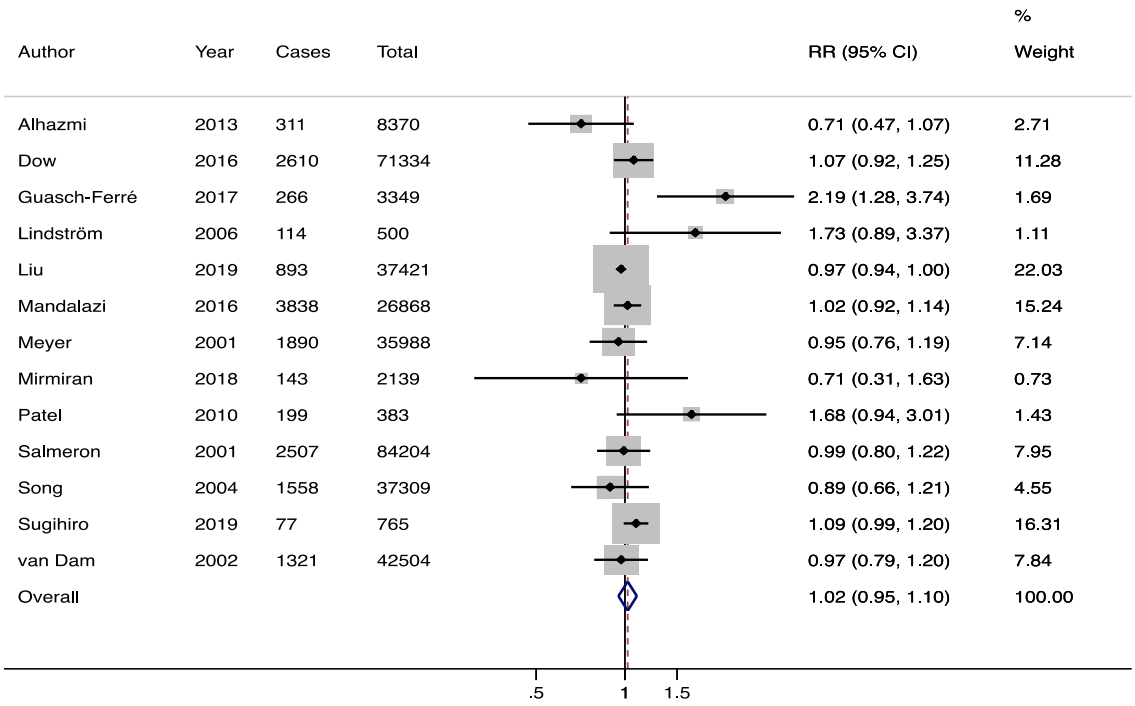
ANNEX 7.

SFA intakes and type 2 diabetes occurrence

Dietary intakes

Fig. A7.1. Self-reported intakes of total SFA and type 2 diabetes occurrence

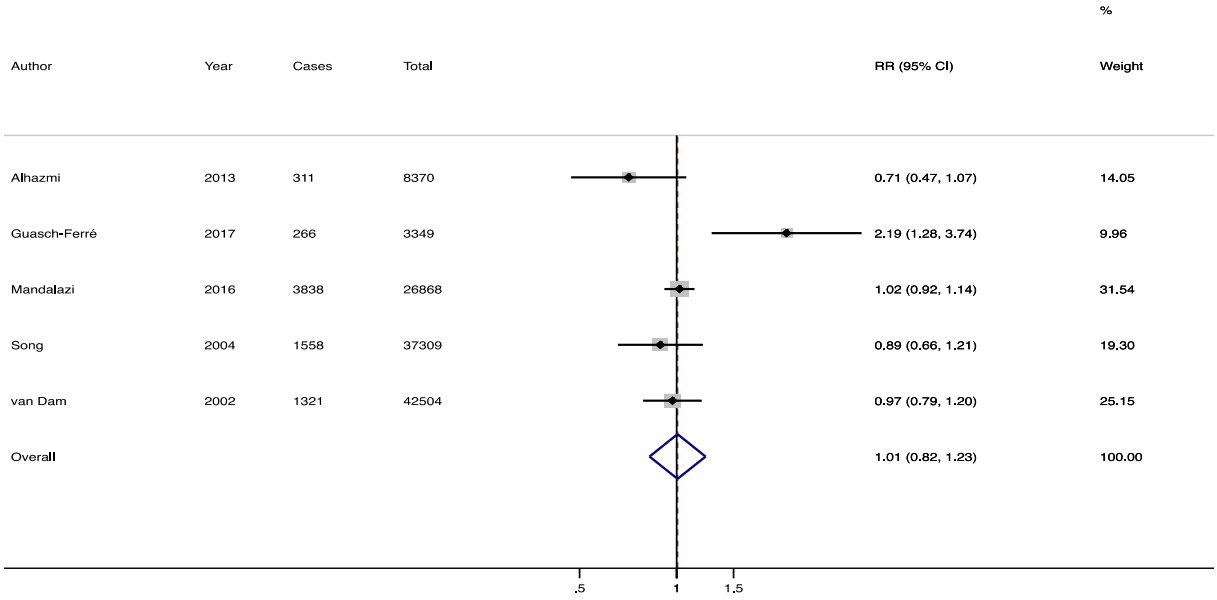
Initial heterogeneity was high (I^2 52%). In influence analysis, one study, Liu 2019 *(1)*, was found to unduly effect the pooled result. The pooled result without Liu 2019 was RR 1.04 (95% CI: 0.95 to 1.13) and heterogeneity was reduced (I^2 45%). There was no evidence of a small study effect (Egger *P*=0.185) and study type was not seen to influence the pooled results (*P*=0.075).



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.2. Self-reported intakes of <10% total energy from SFA with >10% and type 2 diabetes

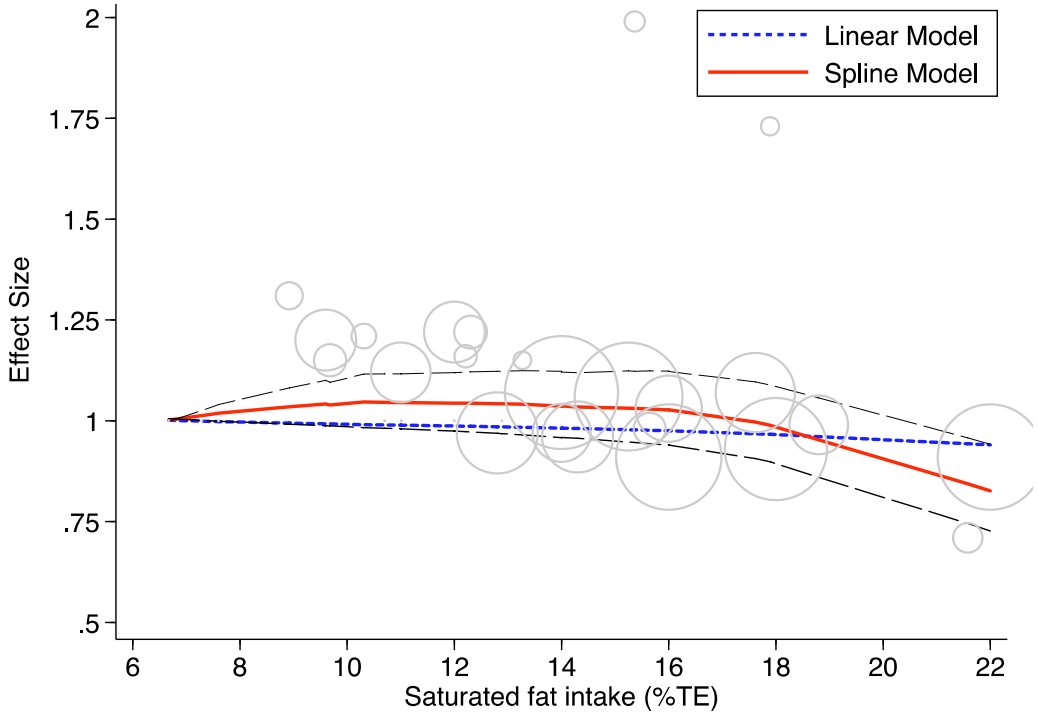
Initial heterogeneity was high (I^2 66%).



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

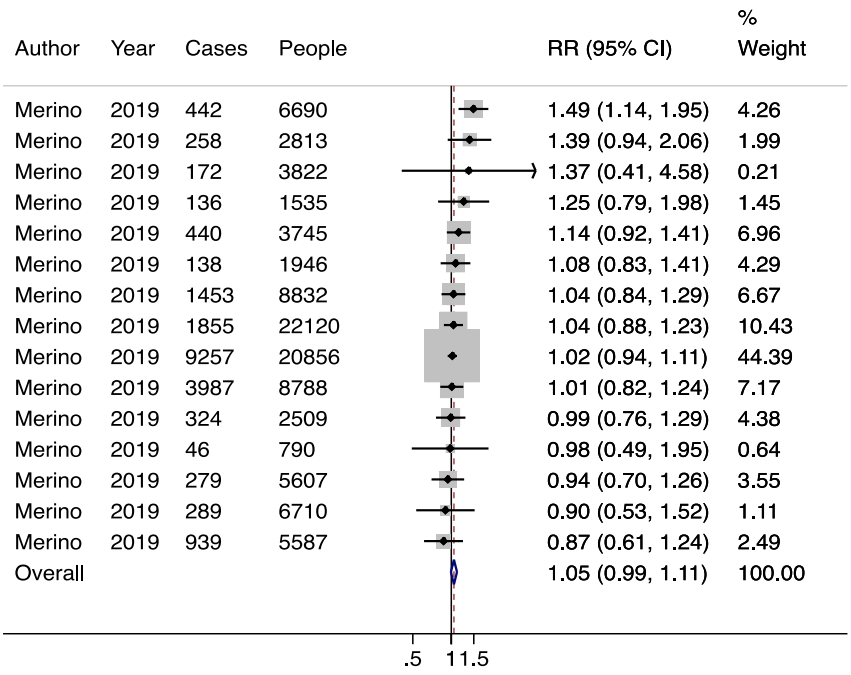
Fig. A7.3. Cubic spline dose response between self-reported total SFA intake (%TE) and type 2 diabetes occurrence

Data were available from seven cohorts of 9989 cases over 3 416 215 PY. Assuming linearity, the relative risk of a 5% increase in TE from SFA was 0.98 (95% CI: 0.91 to 1.05).



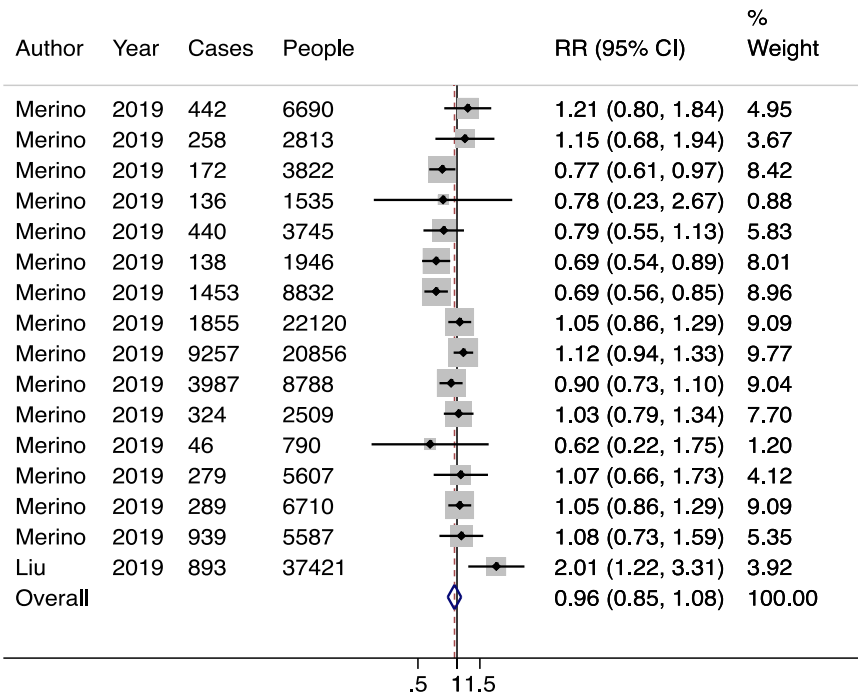
CI: confidence interval; PY: person years; TE: total energy; SFA: saturated fatty acids.

Fig. A7.4a. Replacement of self-reported total SFA intakes with 5% CHO and type 2 diabetes occurrence



CHO: carbohydrate; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.4b. Replacement of self-reported total SFA intakes with 5% PUFA and type 2 diabetes occurrence

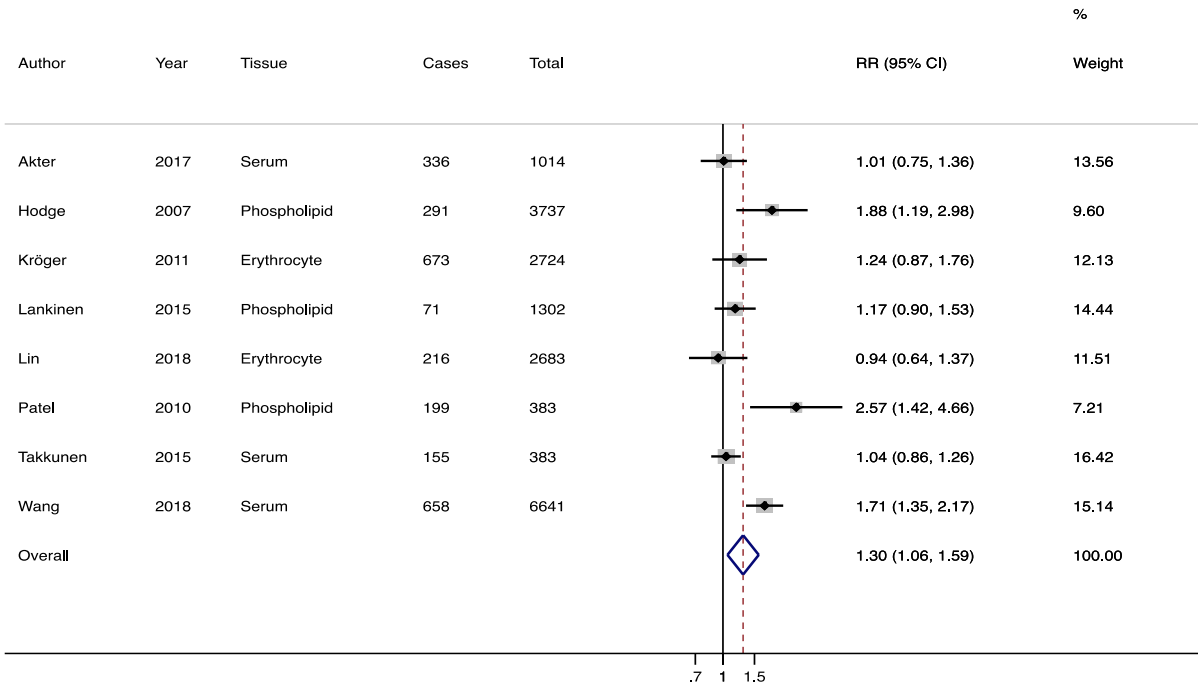


CI: confidence interval; PUFA: polyunsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Tissue samples

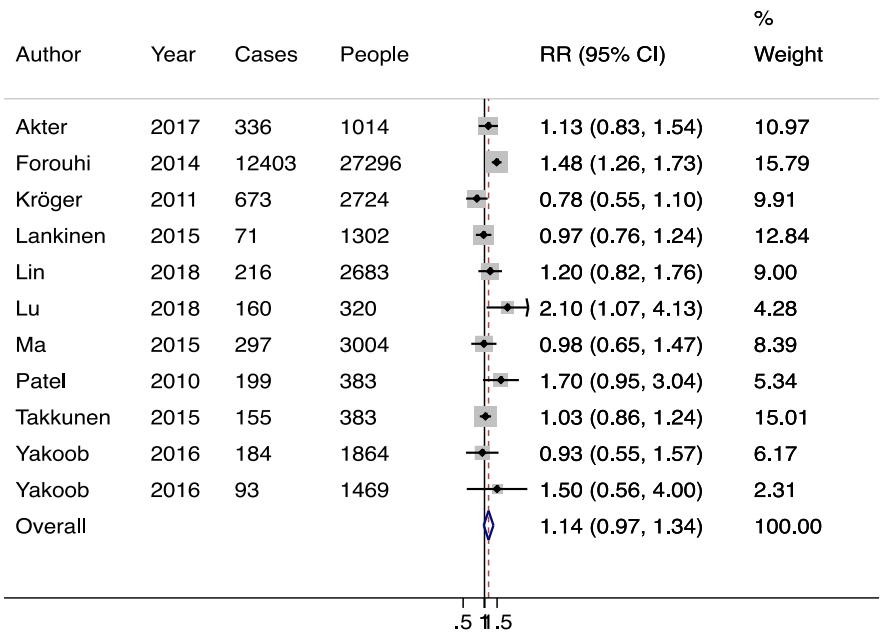
Fig. A7.5. Total SFA from tissue measurements and type 2 diabetes occurrence

Initial heterogeneity was high (I^2 70%). No single study unduly influenced the pooled results. There was no evidence of a small study effect (P=0.261). Study type (P=0.427) and tissue type (P>0.231) were not seen to influence the pooled result.



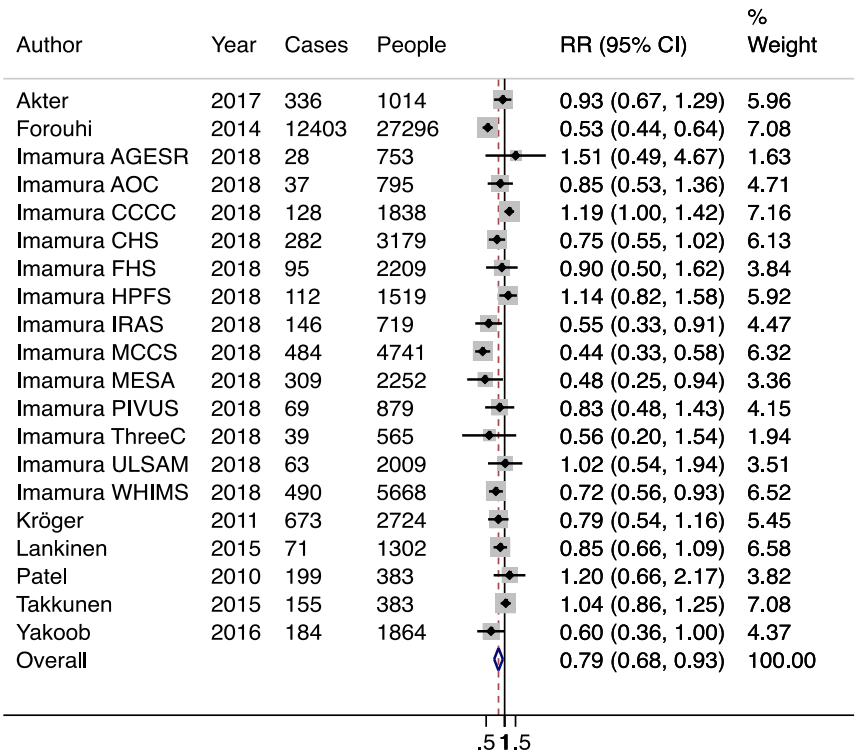
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7a. SFA chain lengths from tissue measurements of C14:0 and type 2 diabetes occurrence



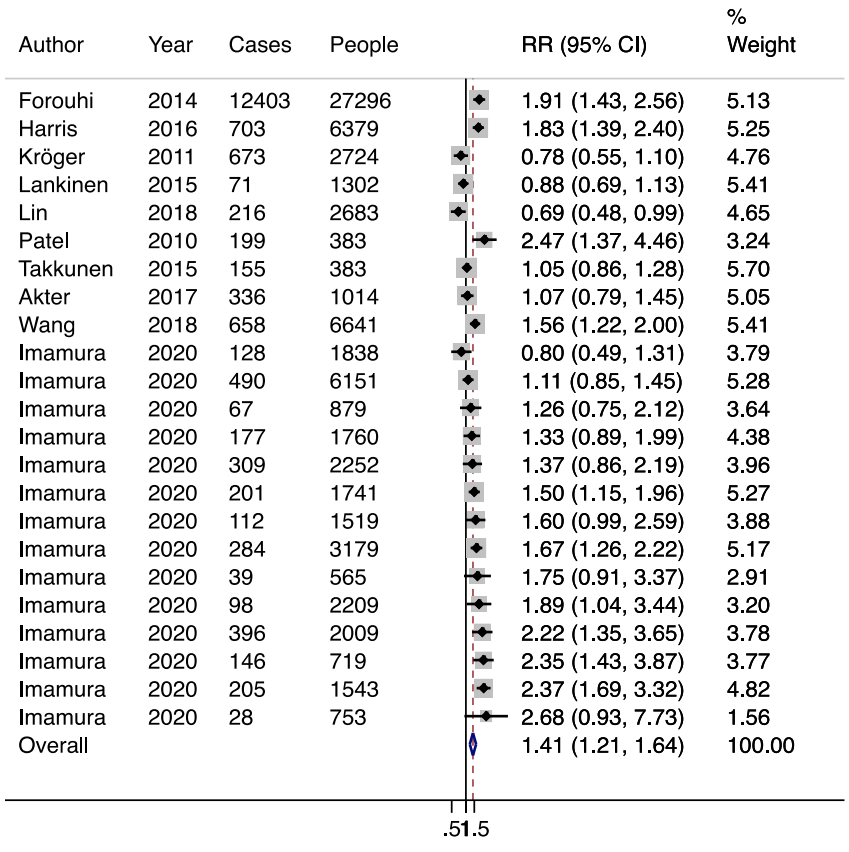
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7b. SFA chain lengths from tissue measurements of C15:0 and type 2 diabetes occurrence



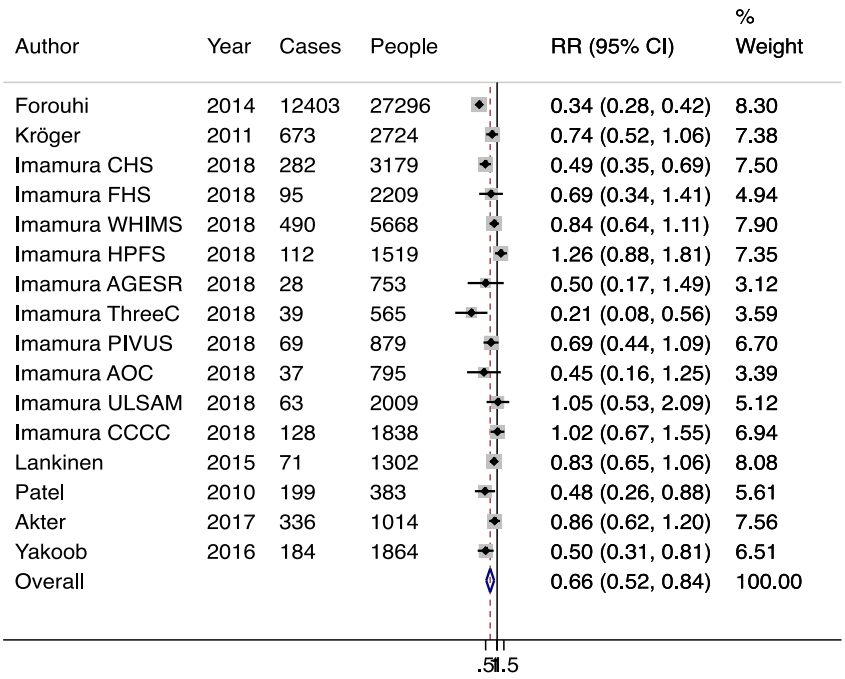
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7c. SFA chain lengths from tissue measurements of C16:0 and type 2 diabetes occurrence



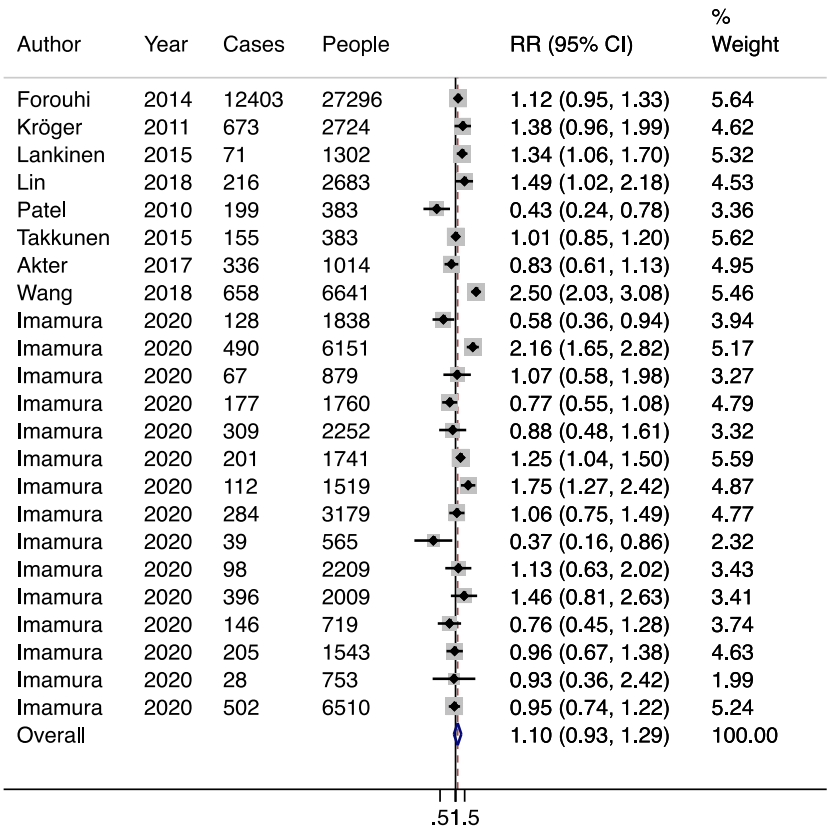
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7d. SFA chain lengths from tissue measurements of C17:0 and type 2 diabetes occurrence



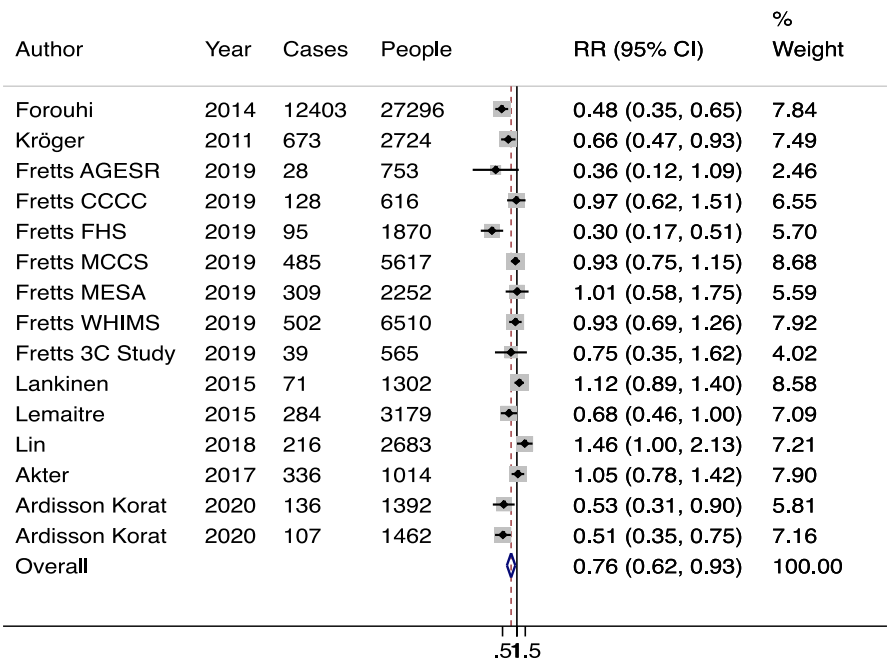
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7e. SFA chain lengths from tissue measurements of C18:0 and type 2 diabetes occurrence



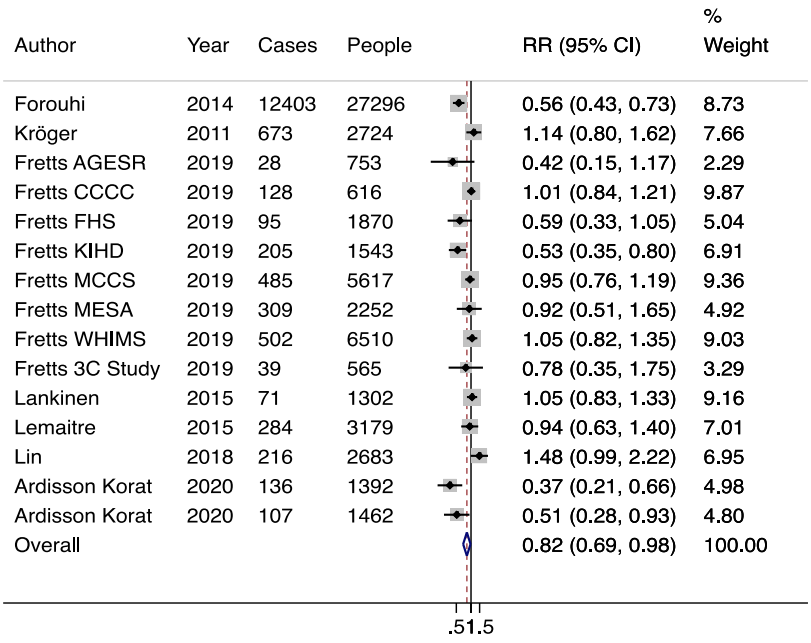
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7f. SFA chain lengths from tissue measurements of C20:0 and type 2 diabetes occurrence



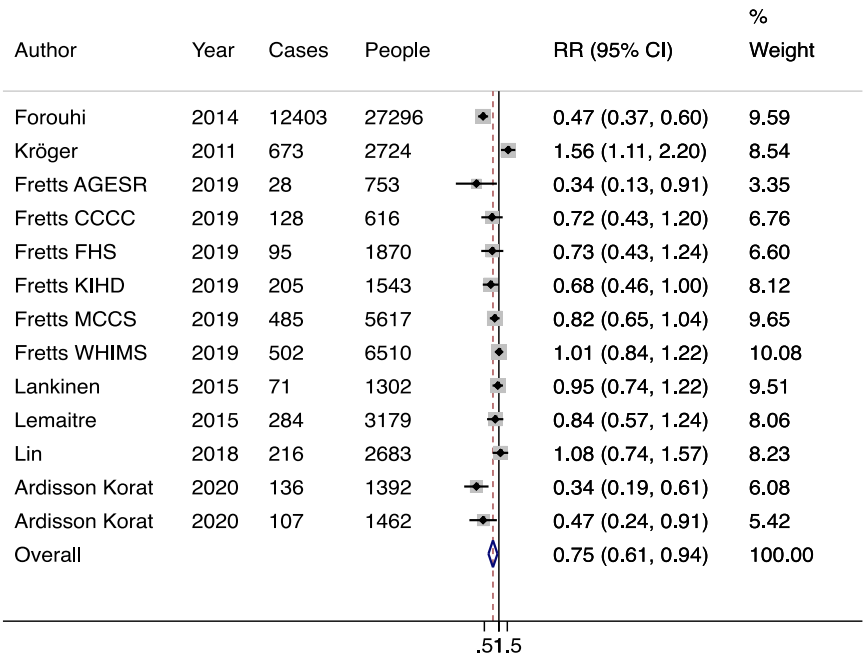
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7g. SFA chain lengths from tissue measurements of C22:0 and type 2 diabetes occurrence



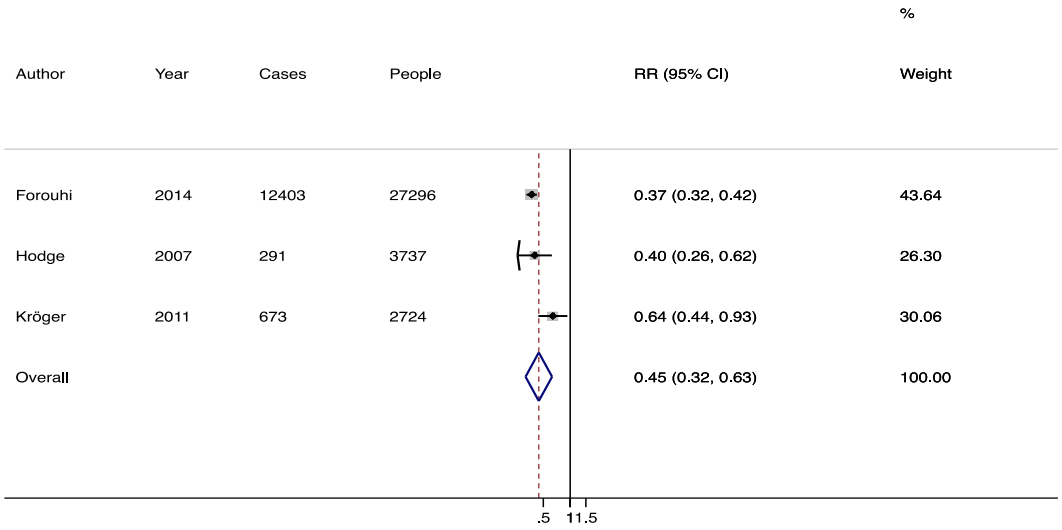
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7h. SFA chain lengths from tissue measurements of C24:0 and type 2 diabetes occurrence



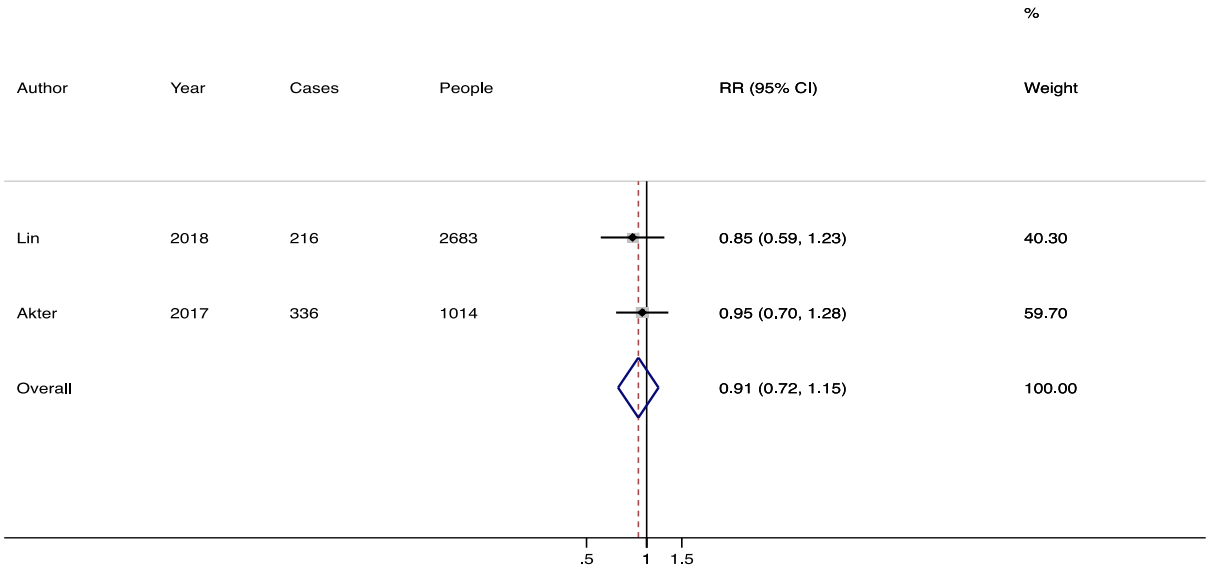
CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7i. SFA chain lengths from tissue measurements of C15:0 and C17:0 and type 2 diabetes occurrence



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A7.7j. SFA chain lengths from tissue measurements of even chain SFA and type 2 diabetes occurrence



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Reference for Annex 7

1 Liu S, van der Schouw YT, Soedamah-Muthu SS, Spijkerman AMW, Sluijs I. Intake of dietary saturated fatty acids and risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort: associations by types, sources of fatty acids and substitution by macronutrients. Eur J Nutr. 2019;58(3):1125–36.

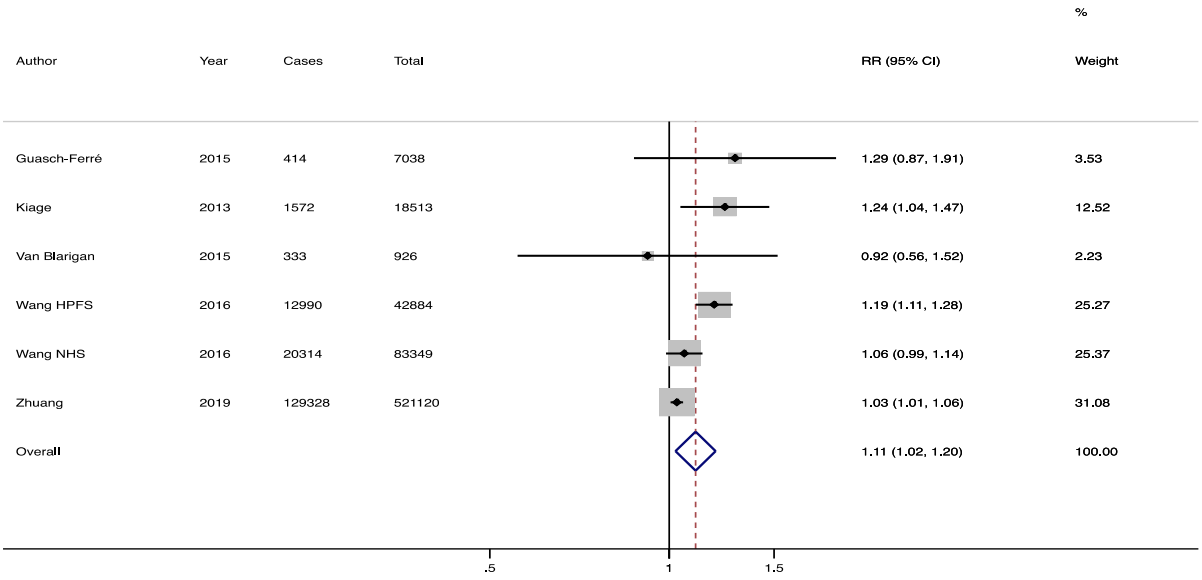
ANNEX 8.

TFA intakes and all-cause mortality

Dietary intakes

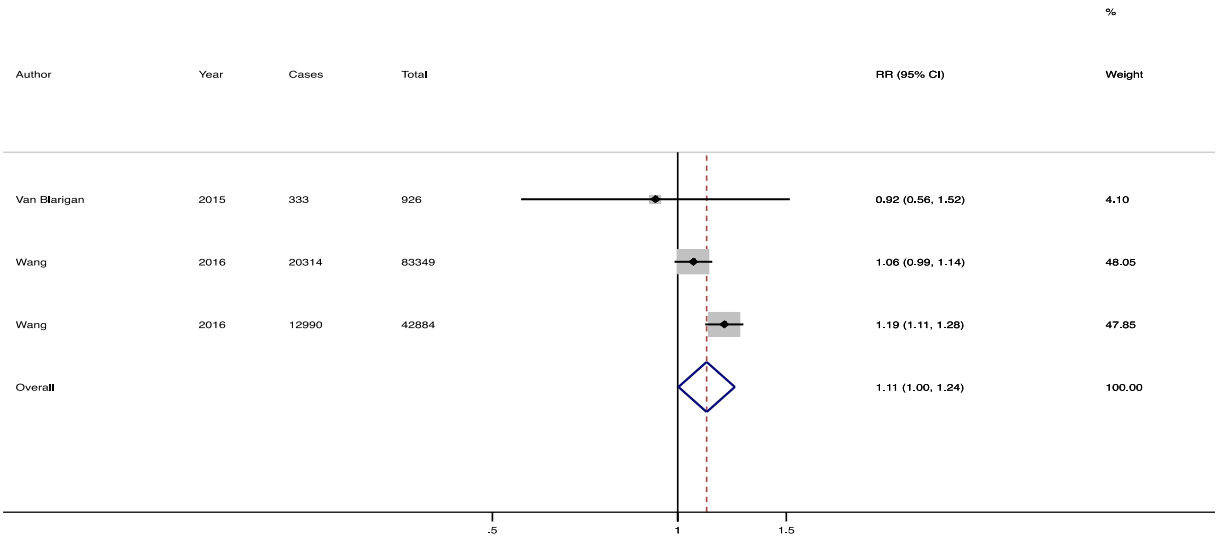
Fig. A8.1. Self-reported intakes of total TFA and all-cause mortality

Initial heterogeneity was high (I^2 74%). Influence analysis indicated one study (Zhuang 2019 *(1)*) pulled the pooled effect size towards the null. Analysis without Zhuang 2019 was RR 1.14 (95% CI: 1.05 to 1.24) and the heterogeneity was reduced (I^2 46%). The Egger test did not indicate a small study effect (*P*=0.214). Pre-existing conditions or study type were not identified as drivers of the pooled result.



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

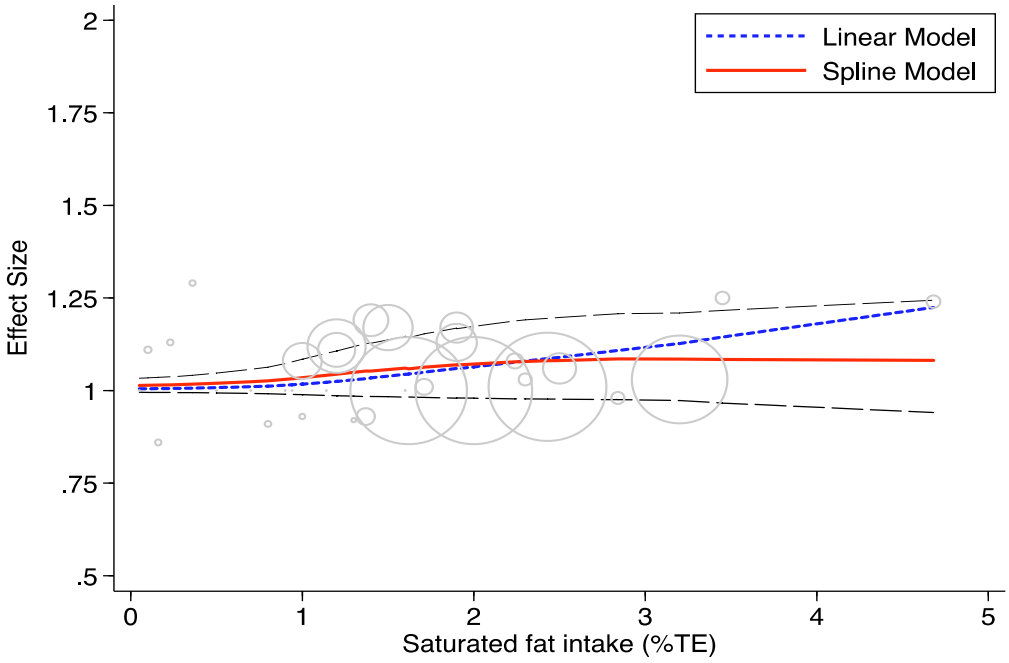
Fig. A8.2. Self-reported intakes of <1% total TFA with >1% TFA and all-cause mortality



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

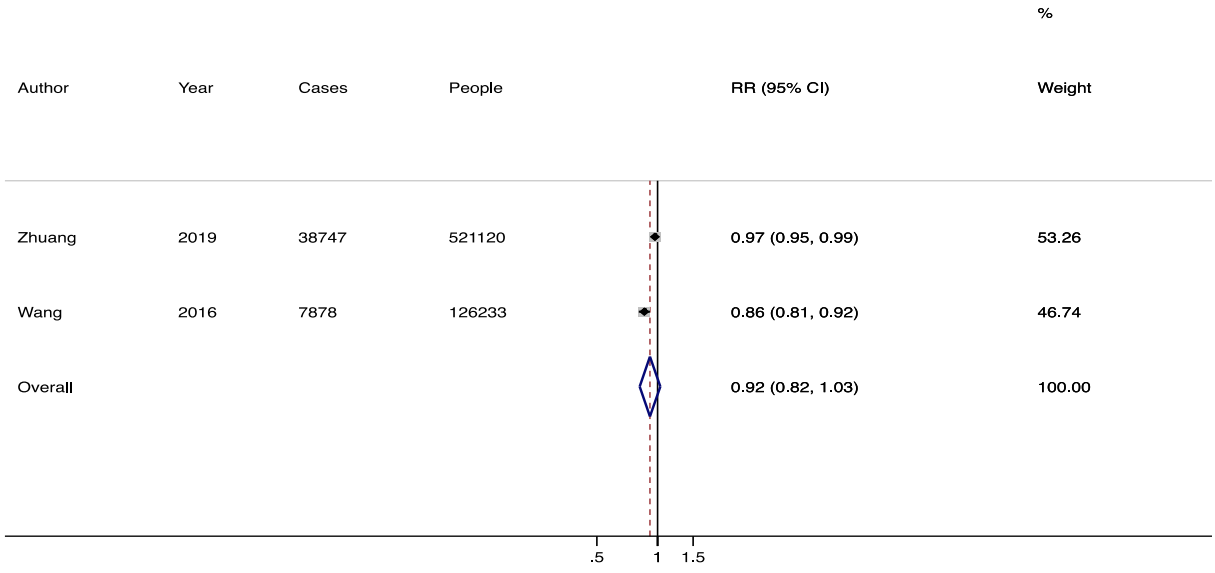
Fig. A8.3. Cubic spline dose response between self-reported total TFA intake (%TE) and all-cause mortality

Data were available from seven cohorts of 167 453 cases during 11 014 878 PY. Assuming linearity, the increased risk in all-cause mortality per 2% increase in TE from total TFA was RR 1.14 (95% CI: 1.04 to 1.26).



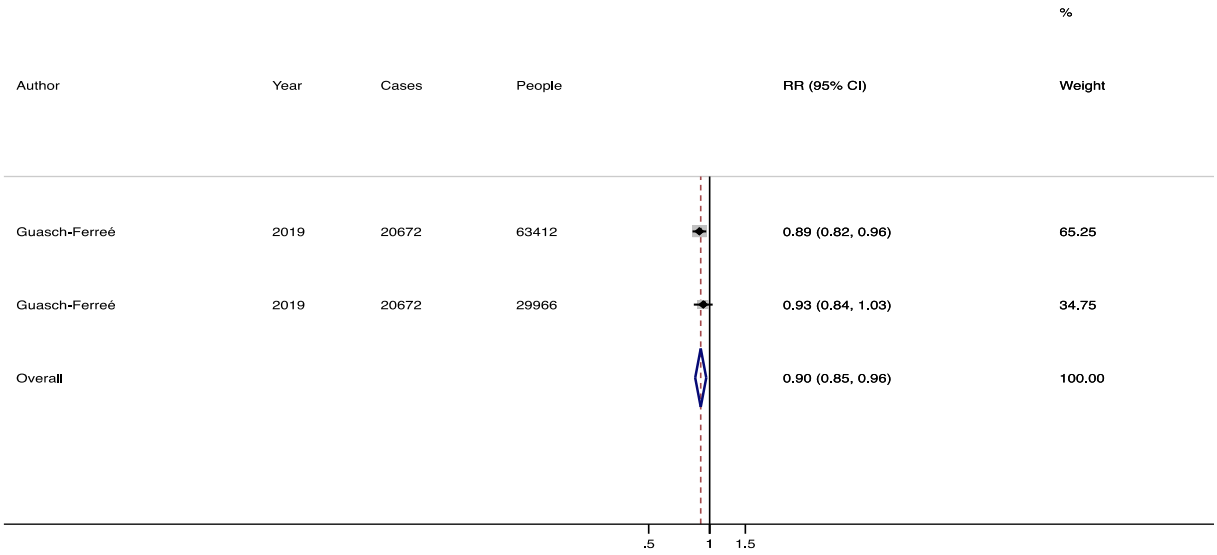
CI: confidence interval; PY: person years; RR: relative risk; TE: total energy; TFA: *trans*-fatty acids.

Fig. A8.4a. Replacement of self-reported total TFA intakes with 2% SFA and all-cause mortality



CI: confidence interval; RR: relative risk; SFA: saturated fatty acids; TFA: *trans*-fatty acids.

Fig. A8.4b. Replacement of self-reported total TFA intakes with 2% plant MUFA and all-cause mortality

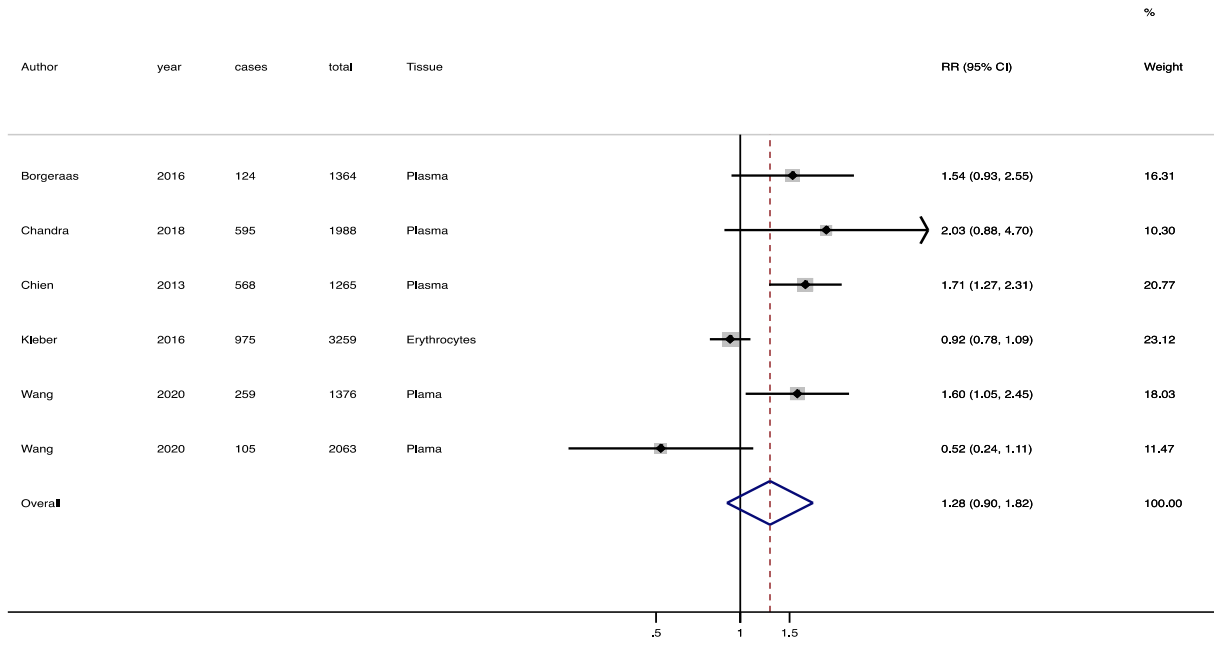


CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; TFA: *trans*-fatty acids.

Tissue samples

Fig. A8.5. Total TFA from tissue measurements and all-cause mortality

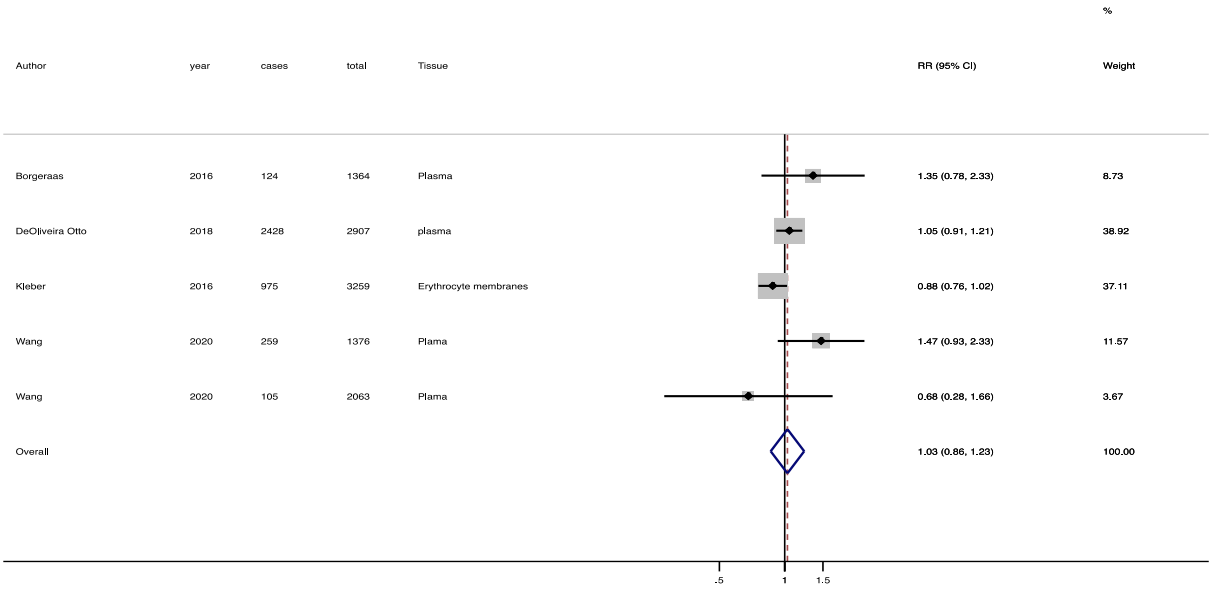
Initial heterogeneity was high (I^2 78%). Influence analysis indicated one study, Kleber 2016 *(2)* unduly influenced the pooled effect size. This was the only study reporting a measurement of total TFA in erythrocyte membranes. The pooled effect size without Kleber was RR 1.44 (95% CI: 1.02 to 2.01) and the heterogeneity was reduced (I^2 54%). Egger test did not indicate a small study effect (*P* 0.414) and presence of pre-existing conditions did not unduly influence the pooled result (*P* 0.914).



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A8.6a. 16:1n7 TFA from tissue measurements and all-cause mortality

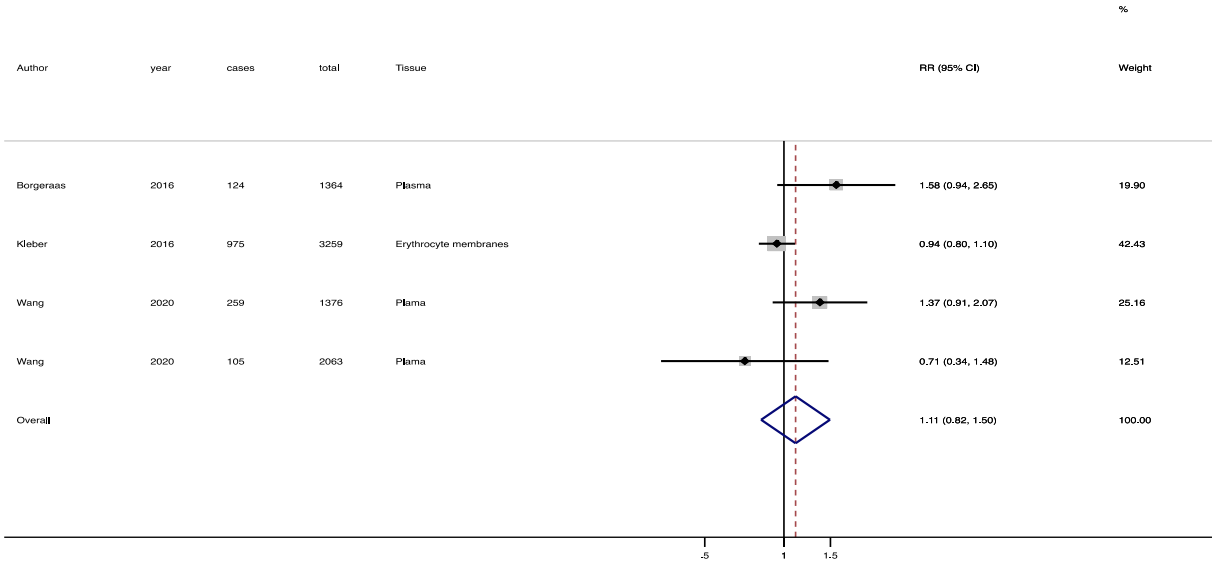
Initial heterogeneity I^2 48%.



CI: confidence interval; RR: relative risk; TFA: *trans*-unsaturated fatty acids.

Fig. A8.6b. *Trans* 18:1 TFA from tissue measurements and all-cause mortality

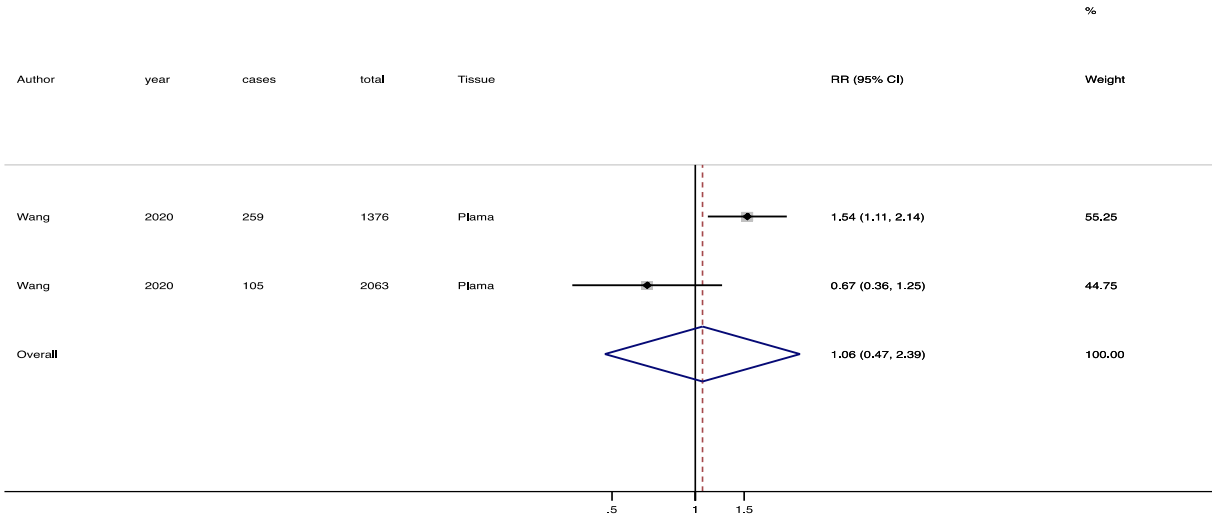
Initial heterogeneity I^2 55%.



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A8.6c. *Trans* 18:1n9 TFA from tissue measurements and all-cause mortality

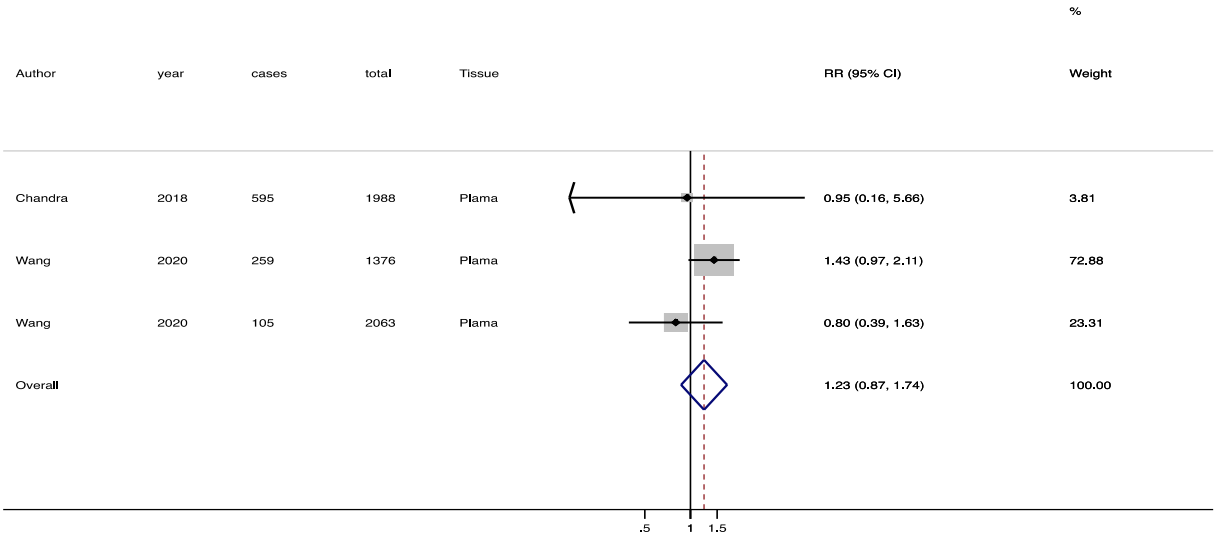
Initial heterogeneity I^2 81%.



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A8.7a. Ruminant-derived TFA from tissue measurements and all-cause mortality

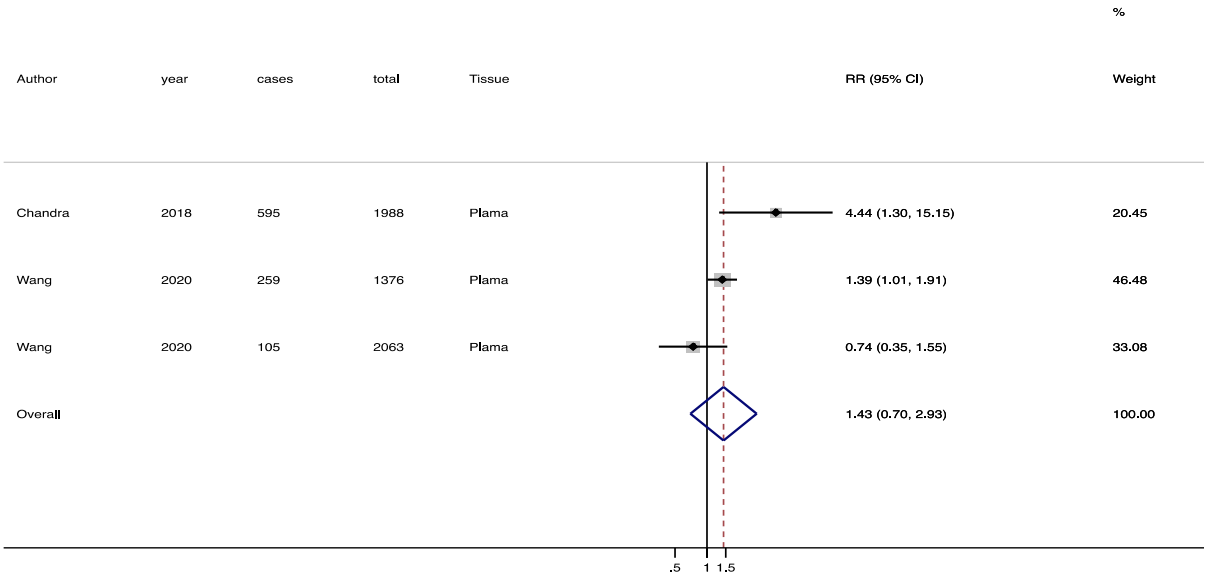
Initial heterogeneity I^2 3%.



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A8.7b. Industrially produced TFA from tissue measurements and all-cause mortality

Initial heterogeneity I^2 68%



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

References for Annex 8

1 Zhuang P, Zhang Y, He W, Chen X, Chen J, He L et al. Dietary fats in relation to total and cause-specific mortality in a prospective cohort of 521,120 individuals with 16 years of follow-up. Circ Res. 2019;124(5):757–68.

2 Kleber ME, Delgado GE, Lorkowski S, März W, von Schacky C. *Trans*-fatty acids and mortality in patients referred for coronary angiography: the Ludwigshafen Risk and Cardiovascular Health study. Eur Heart J. 2016;37(13):1072–8.

ANNEX 9.

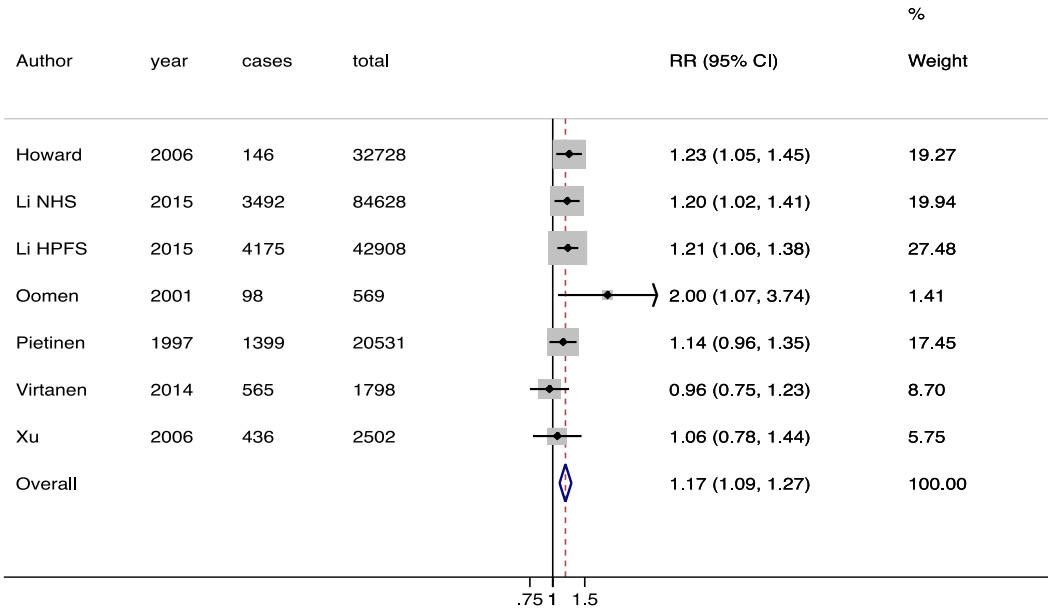
TFA intakes and CHD occurrence

Dietary intakes

Categorical meta-regression indicated no difference in effects sizes reported on fatal, non-fatal and total CHD incidence (*P*=>0.184), so data were run together without unit of measurement error by including the same participants more than once.

Fig. A9.1. Self-reported intakes of total TFA and CHD occurrence

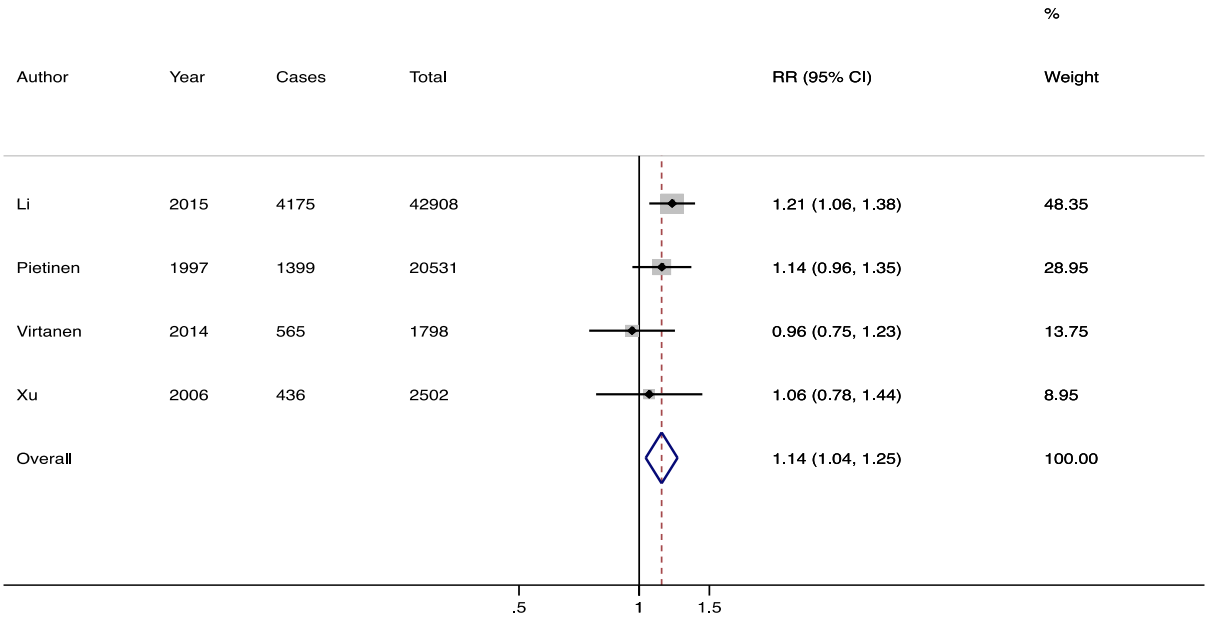
Initial heterogeneity was low (I^2 7%). The Egger test did not indicate small study effect (*P*=0.832) and influence analysis did not indicate that the pooled analysis was driven by one study more than any other. Study type was not identified as a driver of the pooled result, and there were no cohorts exclusively of participants with pre-existing conditions.



CHD: coronary heart disease; CI: confidence interval; RR: relative risk; TFA: *trans*-unsaturated fatty acids.

Fig. A9.2. Self-reported intakes of <1% total TFA with >1% TFA and CHD occurrence

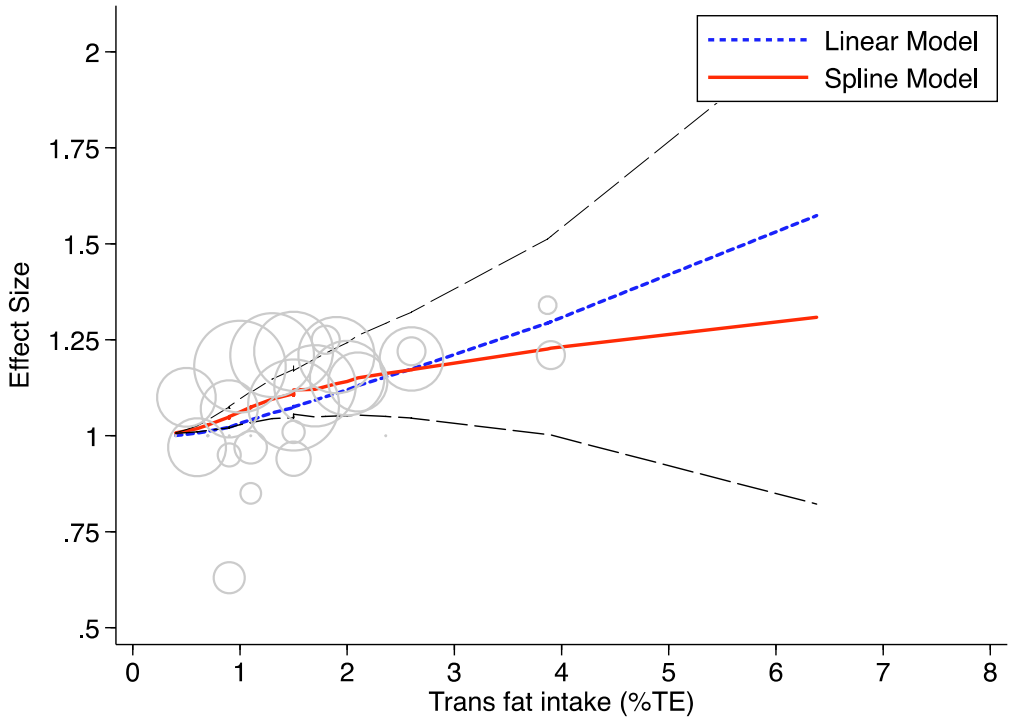
Initial heterogeneity was low (I^2 0%).



CHD: coronary heart disease; CI: confidence interval; RR: relative risk.

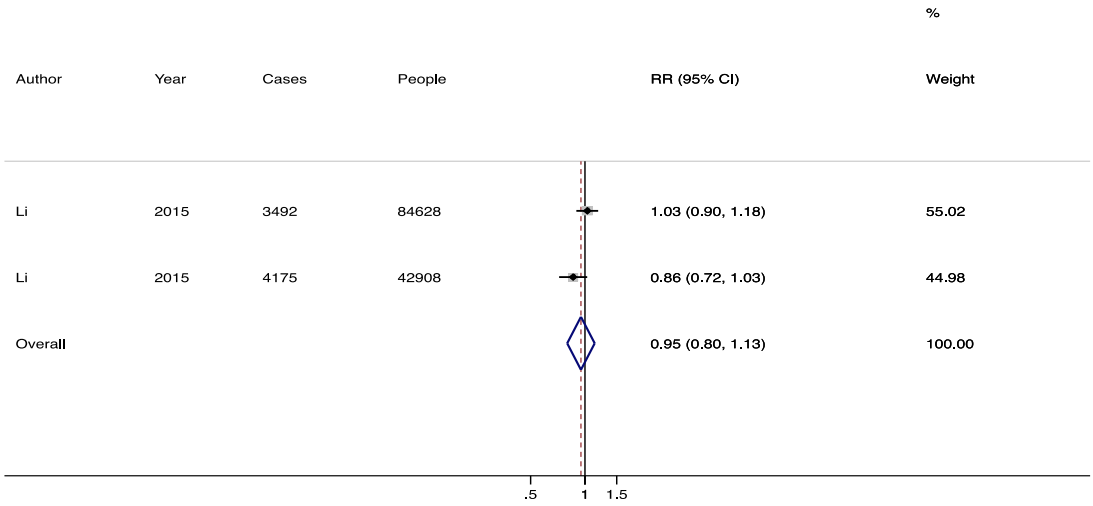
Fig. A9.3. Cubic spline dose response between self-reported total TFA intake (%TE) and CHD occurrence

Data were available from seven cohorts of 10 132 cases during 3 796 254 PY. Assuming linearity, the increase risk in CHD occurrence per 2% increase in TE from total TFA was RR 1.25 (95% CI: 1.15 to 1.36).



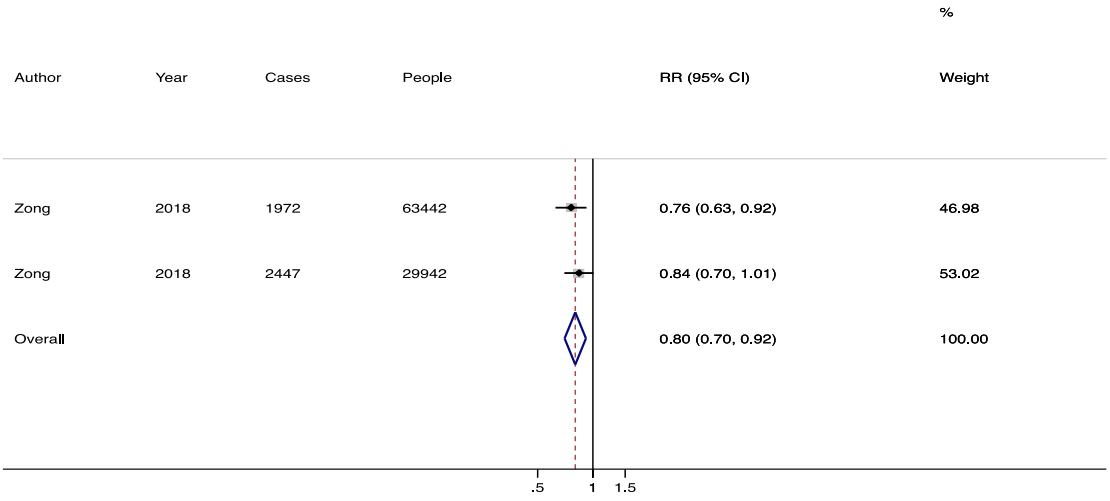
CHD: coronary heart disease; CI: confidence interval; PY: person years; RR: relative risk; TE: total energy; TFA: *trans*-fatty acids.

Fig. A9.4a. Replacement of self-reported total SFA level with 2% refined starches and sugars and CHD occurrence



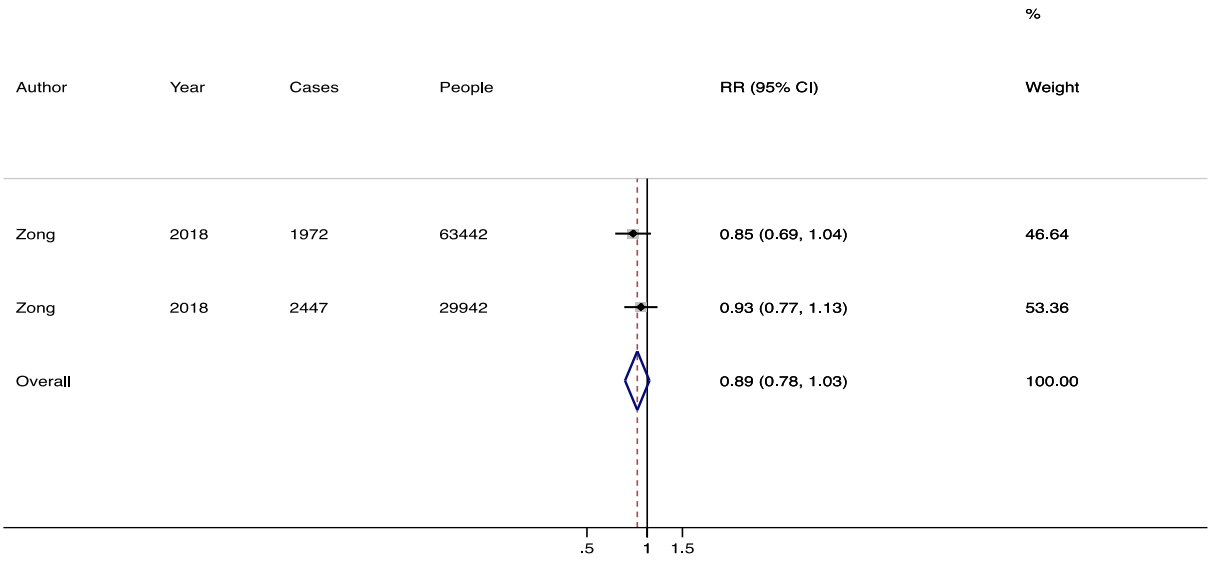
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A9.4b. Replacement of self-reported total SFA level with 2% plant MUFA and CHD occurrence



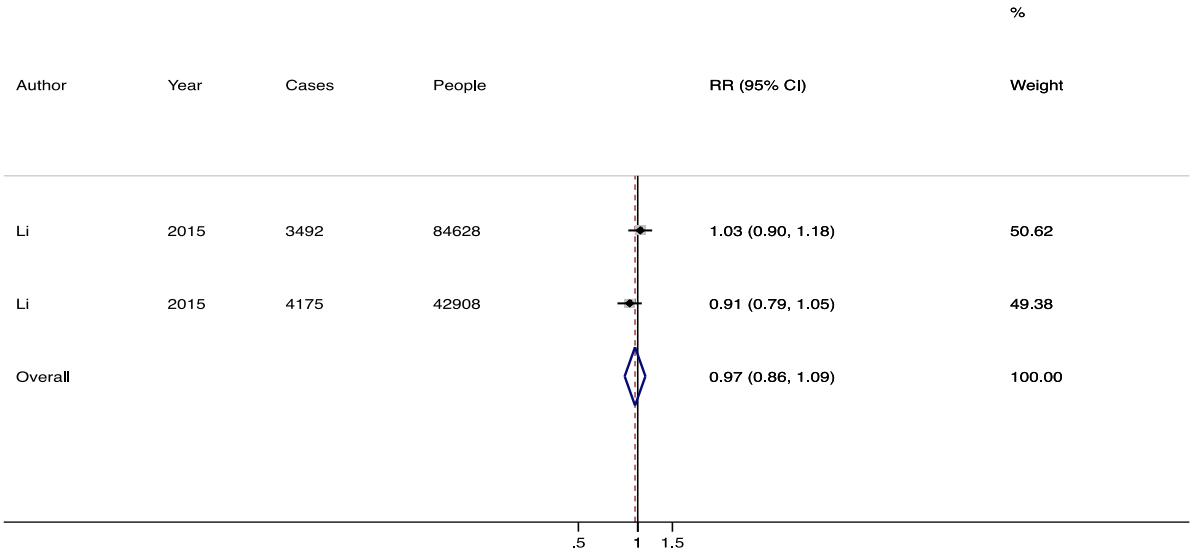
CHD: coronary heart disease; CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Fig. A9.4c. Replacement of self-reported total SFA level with 2% animal MUFA and CHD occurrence



CHD: coronary heart disease; CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

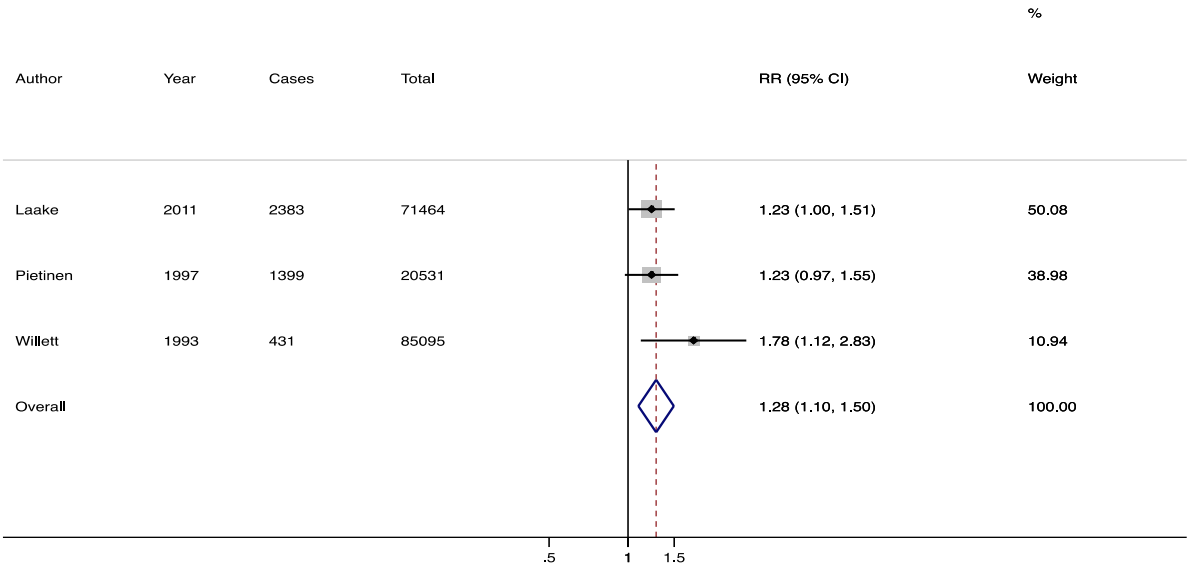
Fig. A9.4d. Replacement of self-reported total SFA level with 2% SFA and CHD occurrence



CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Fig. A9.5. Self-reported intakes of industrially produced TFA and CHD occurrence

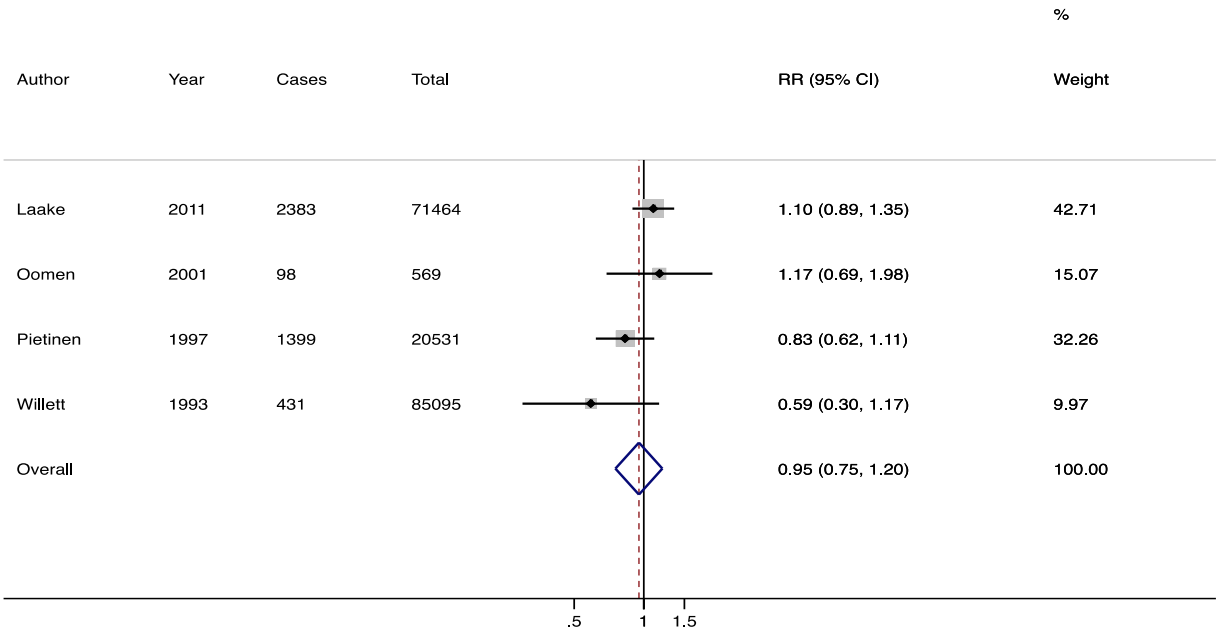
Initial heterogeneity was low (I^2 9%).



CHD: coronary heart disease; CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A9.6. Self-reported intakes of ruminant-derived TFA and CHD occurrence

Initial heterogeneity was low (I^2 40%).

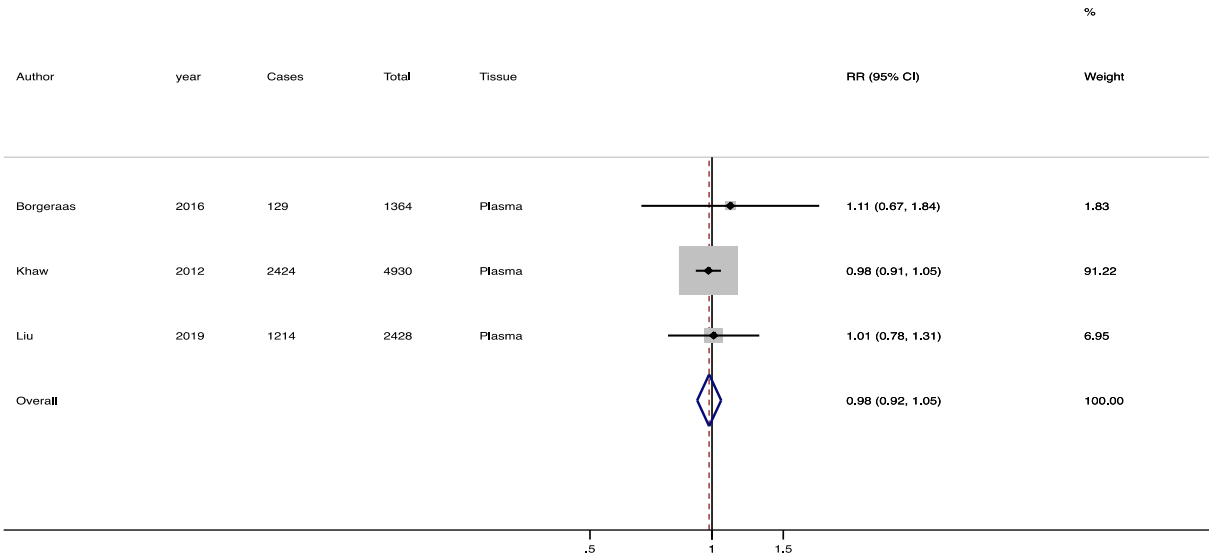


CHD: coronary heart disease; CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Tissue samples

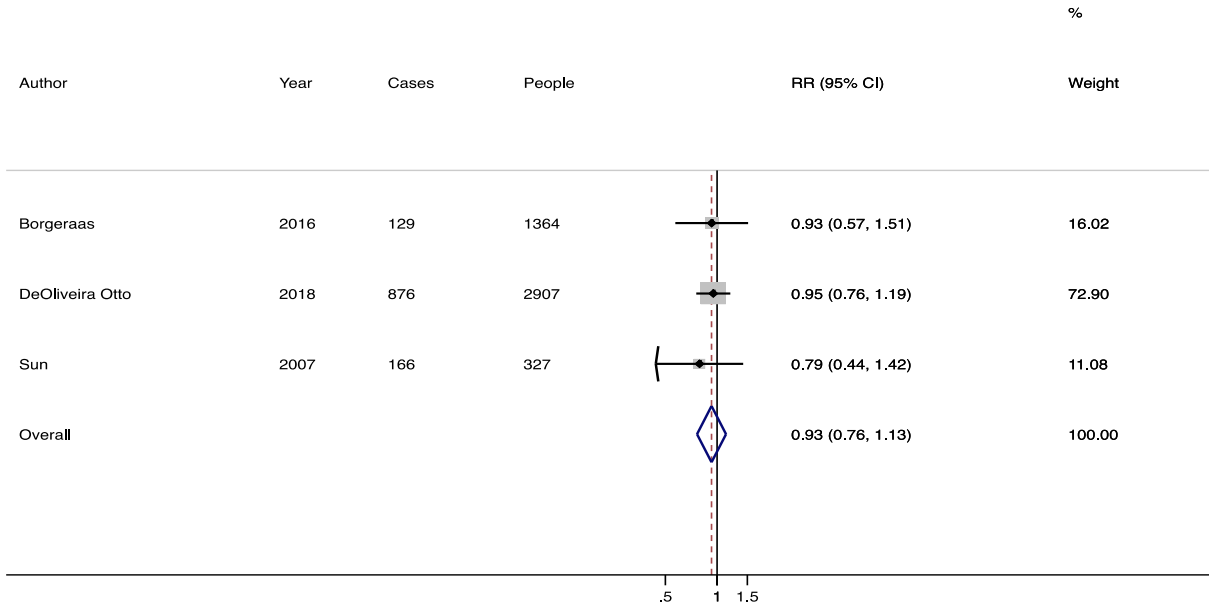
Fig. A9.7. Total TFA from tissue measurements and CHD occurrence

Initial heterogeneity was low (I^2 0%). Influence analysis did not indicate that one study influenced the pooled results unduly, and there was no evidence of a small study effect (Egger's *P*=0.169). Study type or presence of participants with pre-existing conditions did not appreciably influence the pooled result.



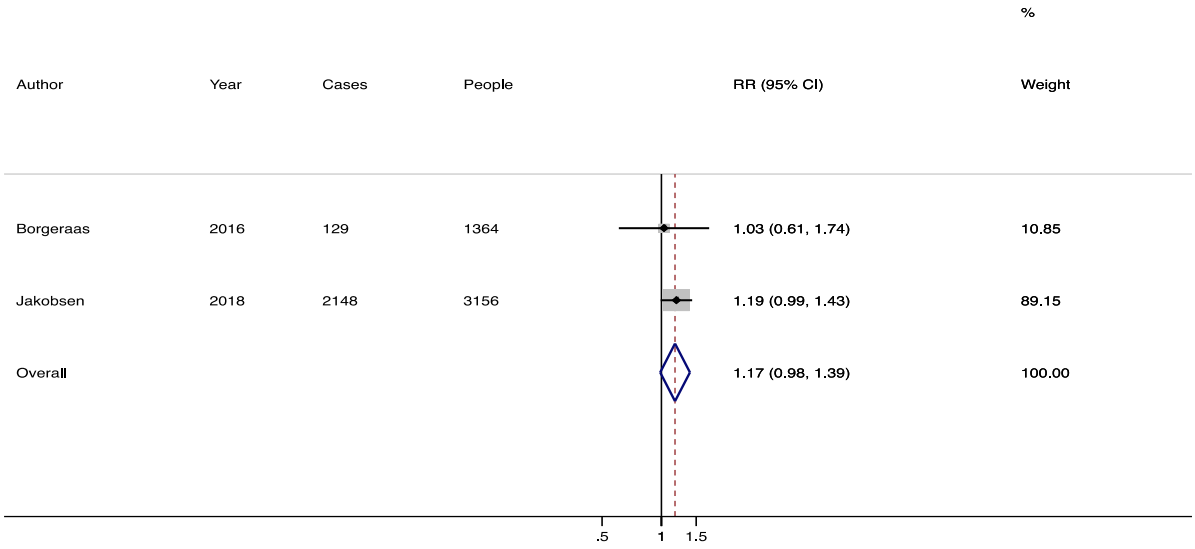
CHD: coronary heart disease; CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A9.8a. Tissue measures of T16:1n7 and CHD occurrence



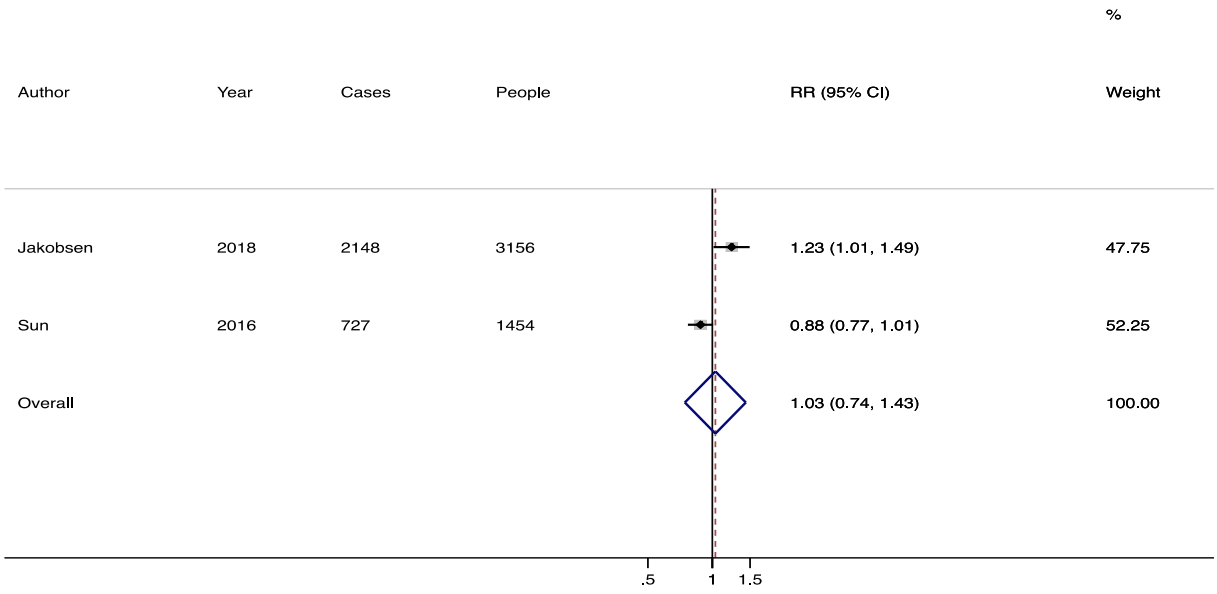
CHD: coronary heart disease; CI: confidence interval; RR: relative risk.

Fig. A9.8b. Tissue measures of T18:1 and CHD occurrence



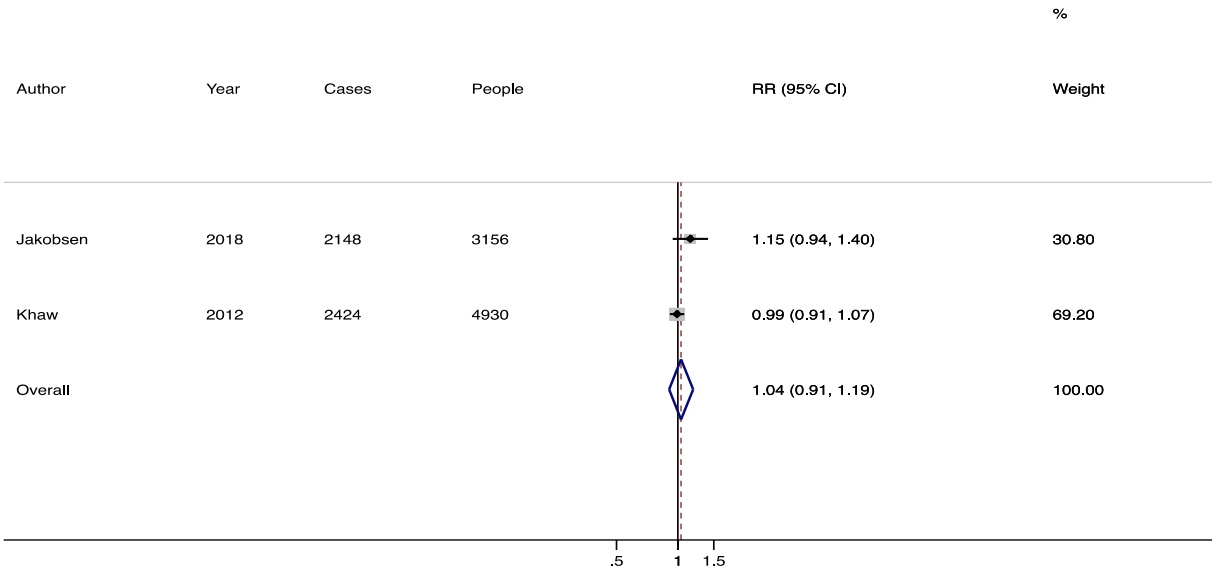
CHD: coronary heart disease; CI: confidence interval; RR: relative risk.

Fig. A9.8c. Tissue measures of T18:1 11t and CHD occurrence



CHD: coronary heart disease; CI: confidence interval; RR: relative risk.

Fig. A9.8d. Tissue measures of T18:1 6–10t and CHD occurrence



CHD: coronary heart disease; CI: confidence interval; RR: relative risk.

ANNEX 10.

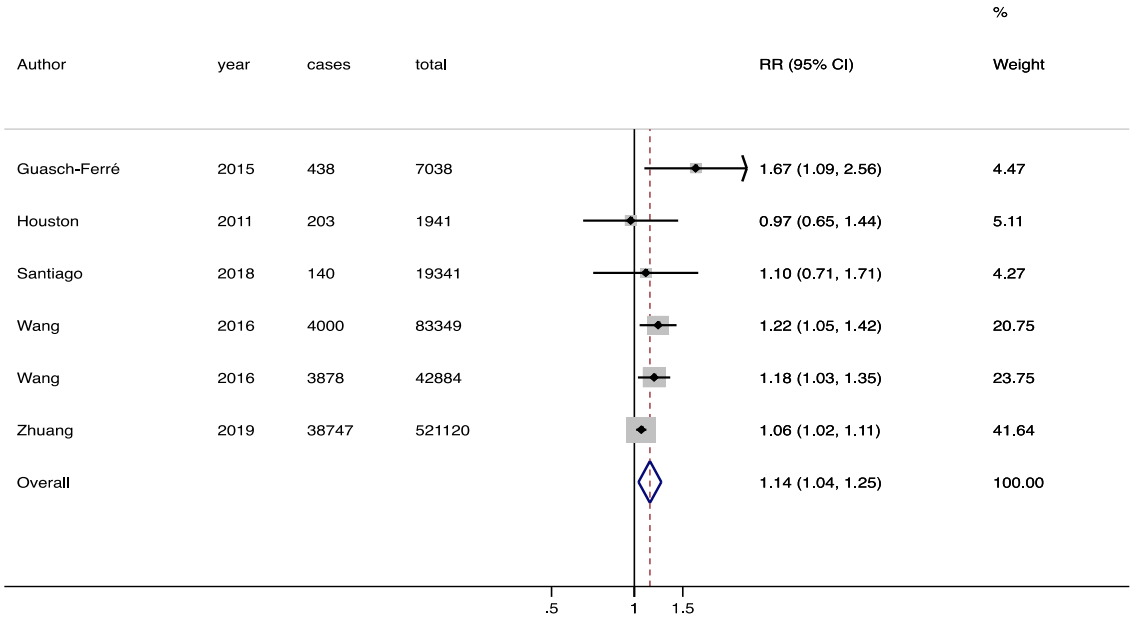
TFA intakes and CVD occurrence

Dietary intakes

Categorical meta-regression indicated no difference in effect sizes reported on fatal, non-fatal and total CVD incidence (*P*=>0.890), so data were run together without unit of measurement error by including the same participants more than once.

Fig. A10.1. Self-reported intakes of total TFA and CVD occurrence

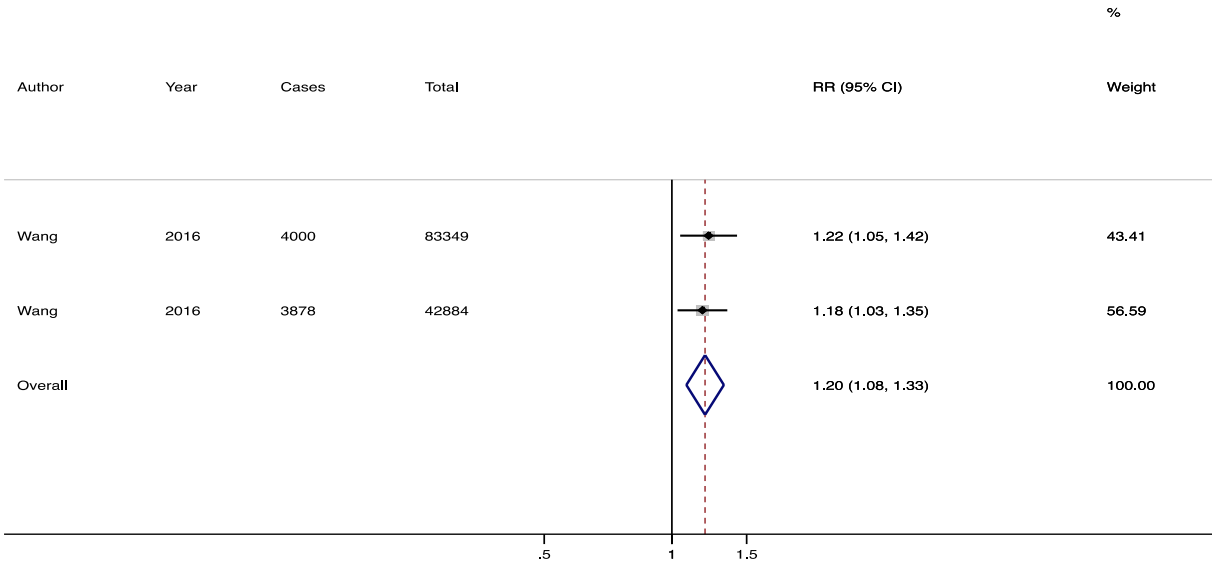
Initial heterogeneity was low (I^2 45%). Influence analysis indicated that one study (Zhuang 2019 *(1)*) pulled the pooled effect size towards the null. Analysis without Zhuang 2019 was RR 1.20 (95% CI: 1.09 to 1.32) and the heterogeneity was reduced (I^2 0%). The Egger test did not indicate a small study effect (*P*=0.174). There were no cohorts with pre-existing conditions or different study types in this analysis.



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A10.2. Self-reported intakes of <1% total TFA with >1% and CVD occurrence

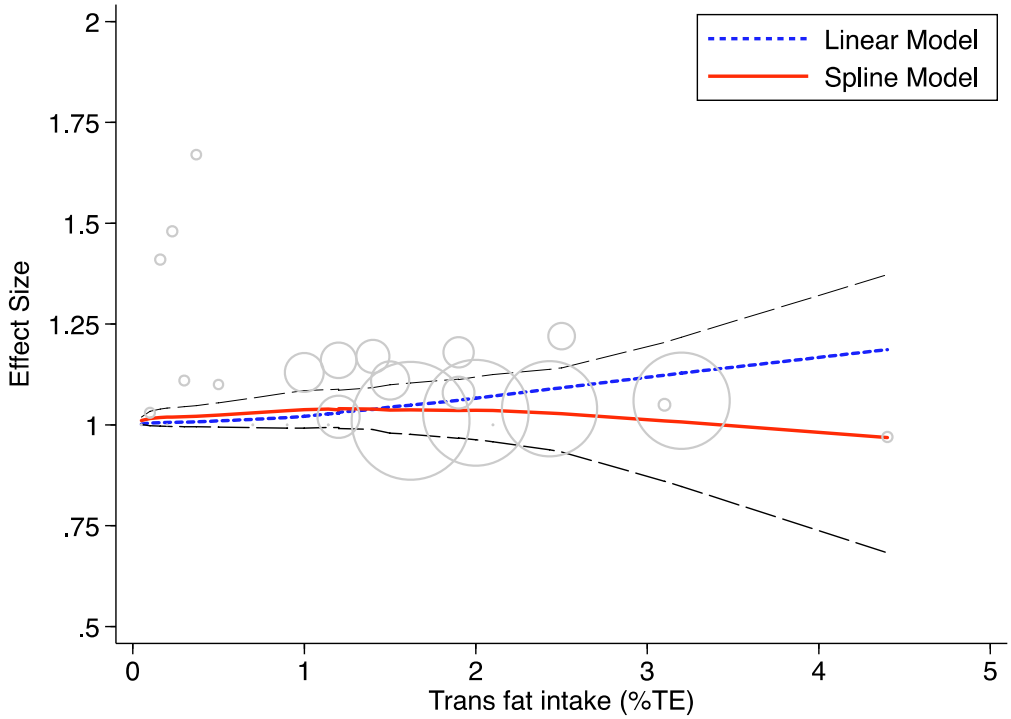
Initial heterogeneity was low (I^2 0%).



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk.

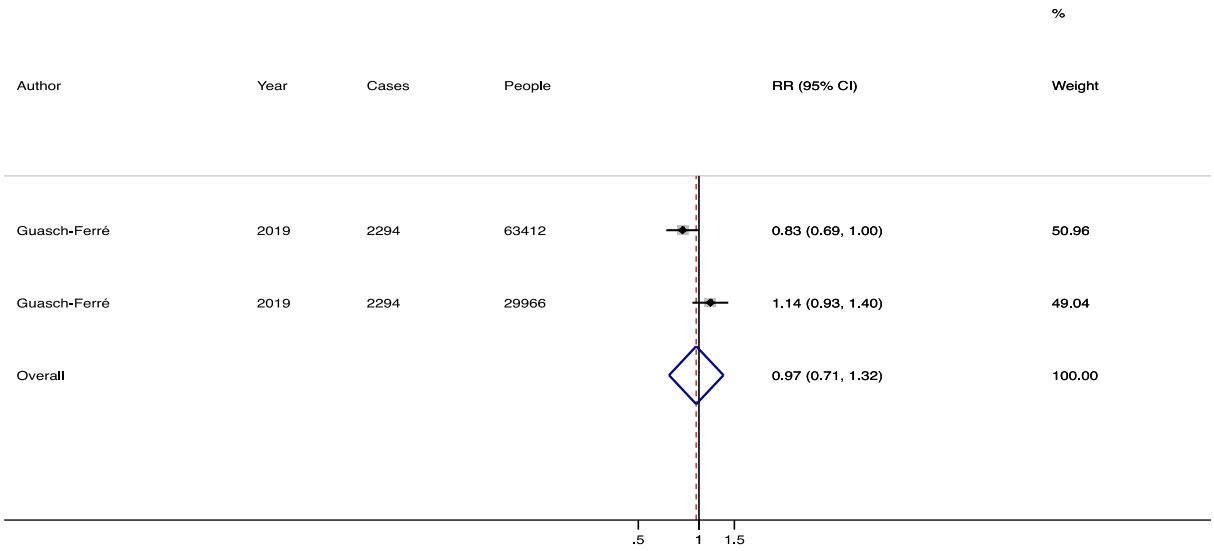
Fig. A10.3. Cubic spline dose response between self-reported total TFA intake (%TE) and CVD occurrence

Data were available from six cohorts of 47 244 cases during 11 997 720 PY. Assuming linearity, the relative risk in CVD occurrence per 2% increase in TE from total TFA was 1.16 (95% CI: 0.99 to 1.36).



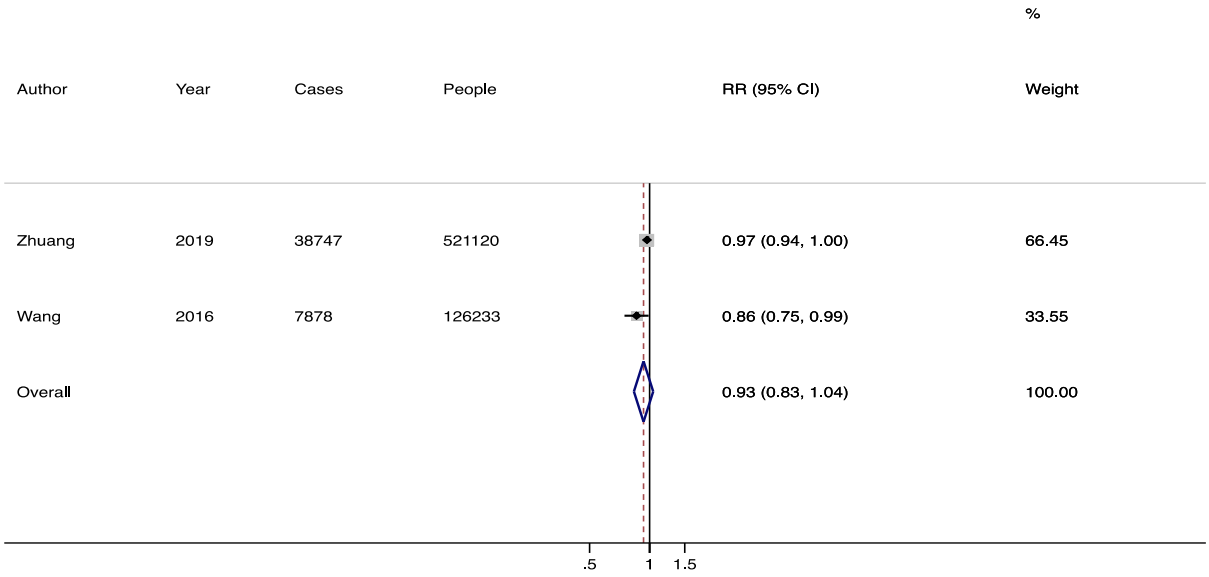
CI: confidence interval; CVD: cardiovascular disease; PY: person years; RR: relative risk; TE: total energy; TFA: *trans*-fatty acids.

Fig. A10.4a. Replacement of self-reported total TFA intakes with 2% plant MUFA and CVD occurrence



CI: confidence interval; CVD: cardiovascular disease; MUFA: monounsaturated fatty acids; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A10.4b. Replacement of self-reported total TFA intakes with 2% SFA and CVD occurrence

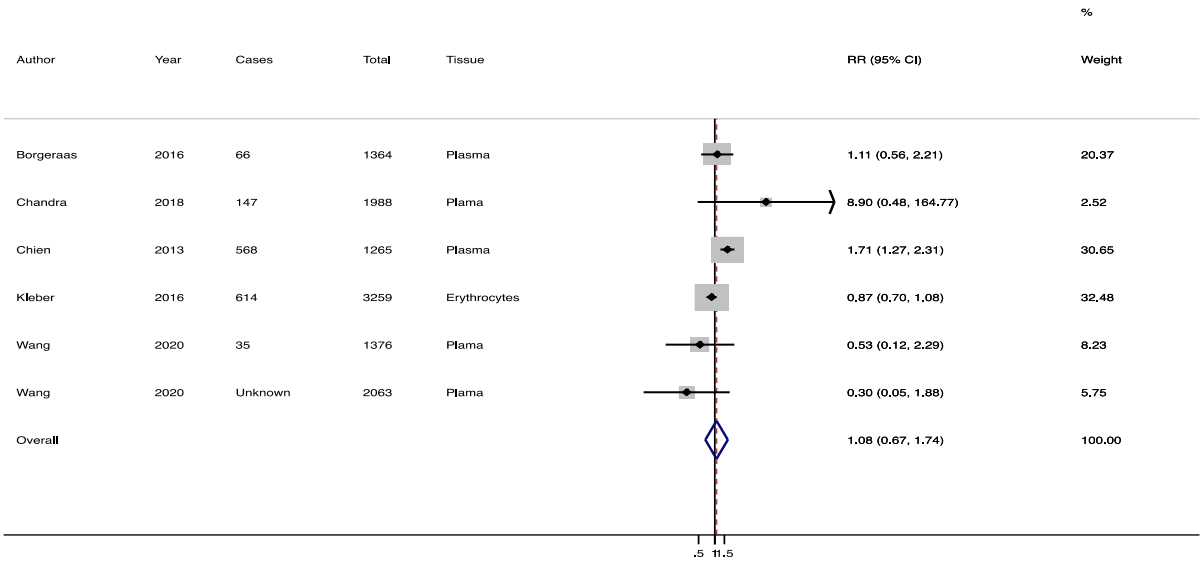


CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids; TFA: *trans*-fatty acids.

Tissue samples

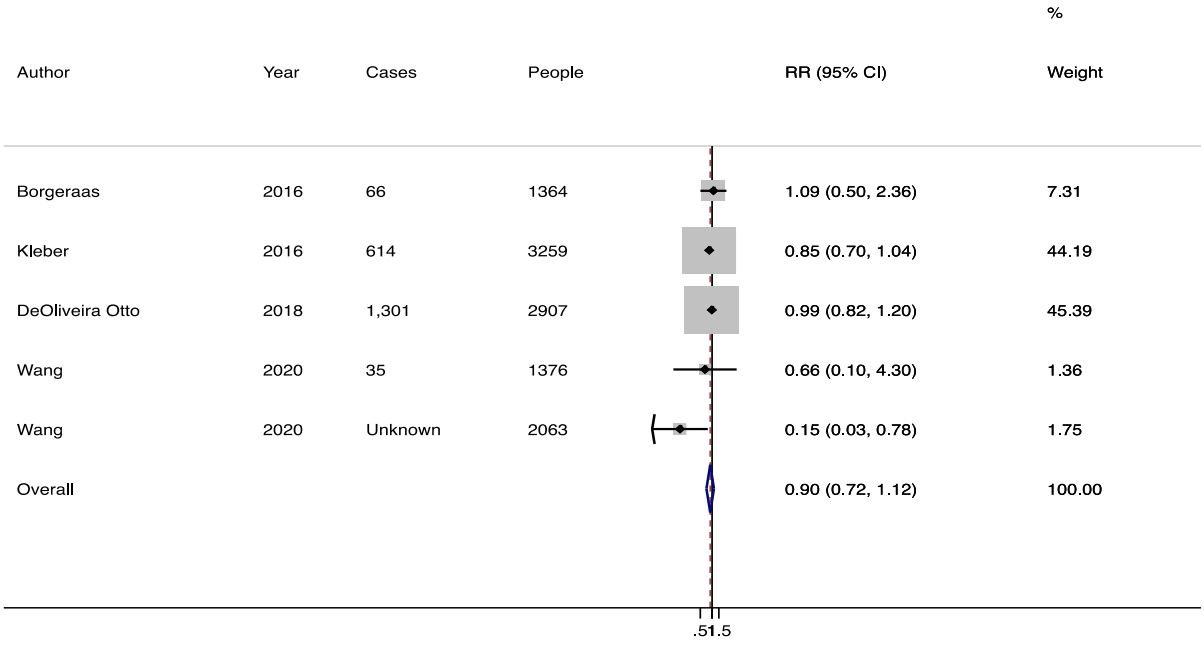
Fig. A10.5. Total TFA from tissue measurements and CVD occurrence

Initial heterogeneity was high (I^2 72%). Influence analysis indicated that Kleber 2016 *(2)* unduly influenced the pooled effect size. This was the only study reporting a measurement of total TFA in erythrocyte membranes. The pooled effect size without Kleber was RR 1.18 (95% CI: 0.64 to 2.17) and the heterogeneity was reduced (I^2 49%). The Egger test did not indicate a small study effect (*P*=0.966) and presence of pre-existing conditions did not unduly influence the pooled result (*P*=0.893).



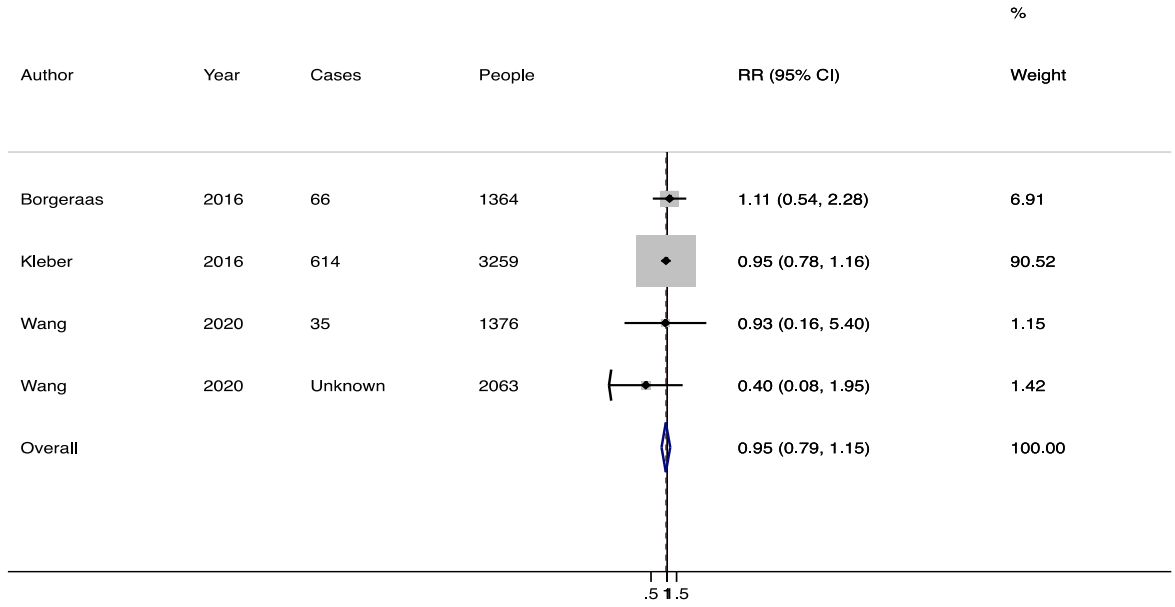
CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A10.6a. Tissue measurements of T16:1n7 and CVD occurrence



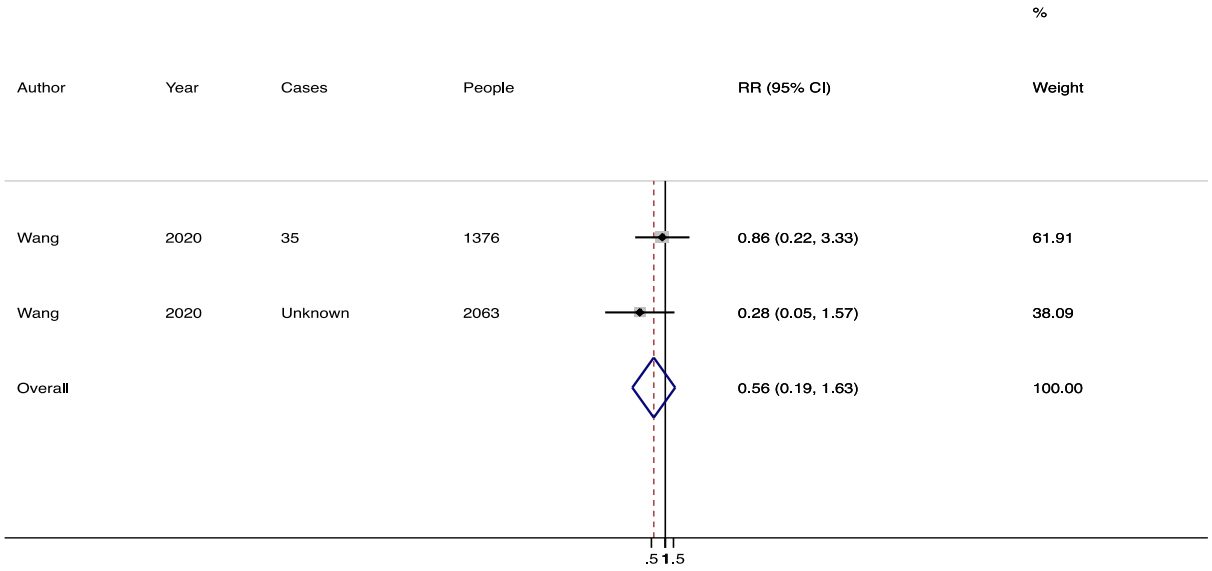
CI: confidence interval; CVD: cardiovascular disease; RR: relative risk.

Fig. A10.6b. Tissue measurements of T18:1 and CVD occurrence



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk.

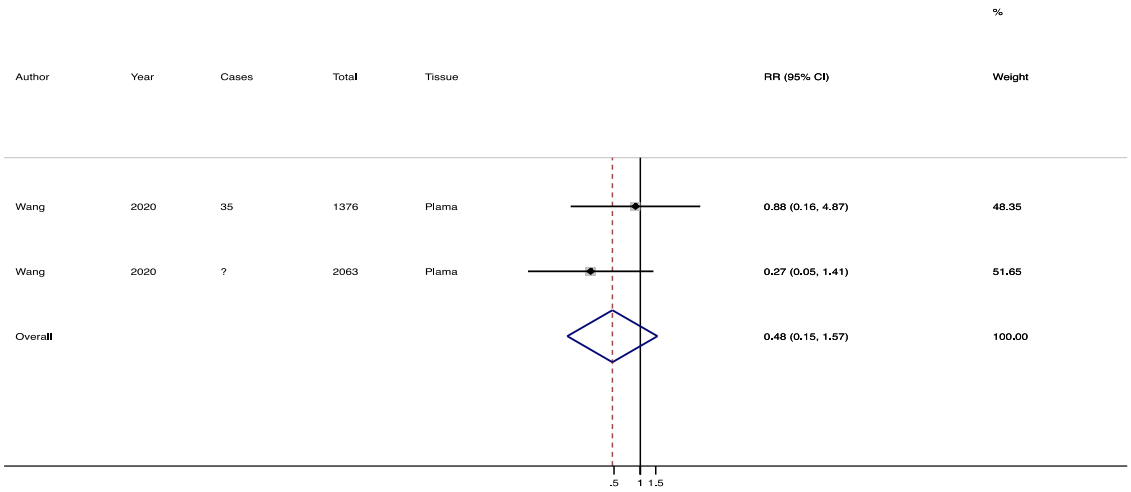
Fig. A10.6c. Tissue measurements of T18:1n9 and CVD occurrence



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk.

Fig. A10.7. Ruminant-derived TFA from tissue measurements and CVD occurrence

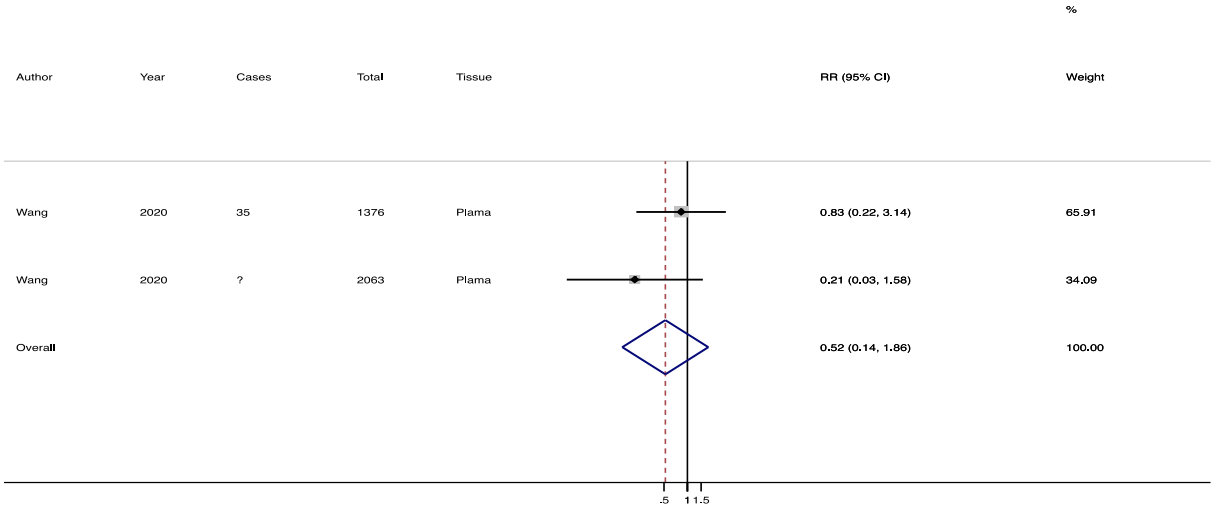
Initial heterogeneity was low (I^2 0%).



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; TFA: *trans*-fatty acids

Fig. A10.8. Industrially produced TFA from tissue measurements and CVD occurrence

Initial heterogeneity was low (I^2 20%).



CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; TFA: *trans*-unsaturated fatty acids

References for Annex 10

1 Zhuang P, Zhang Y, He W, Chen X, Chen J, He L et al. Dietary fats in relation to total and cause-specific mortality in a prospective cohort of 521,120 individuals with 16 years of follow-up. Circ Res. 2019;124(5):757–68.

2 Kleber ME, Delgado GE, Lorkowski S, März W, von Schacky C. *Trans*-fatty acids and mortality in patients referred for coronary angiography: the Ludwigshafen Risk and Cardiovascular Health study. Eur Heart J. 2016;37(13):1072–8.

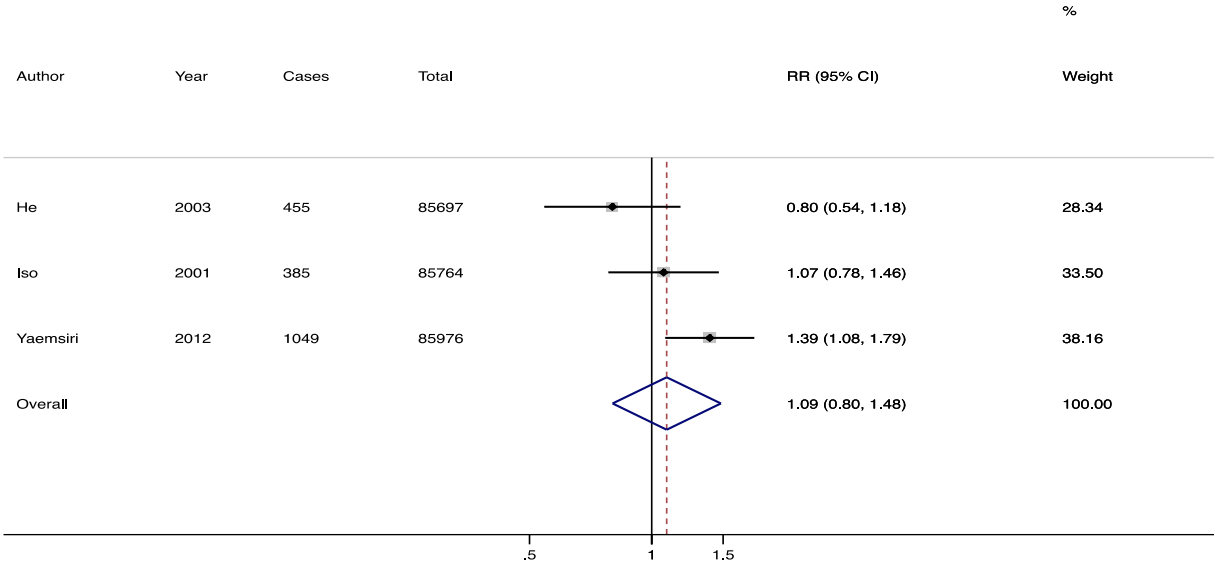
ANNEX 11.

TFA intakes and ischaemic stroke

Dietary intakes

Fig. A11.1. Self-reported intakes of total TFA and ischaemic stroke occurrence

Initial heterogeneity was high (I^2 65%). This is the same pool of studies that would have been analysed to consider self-reported intakes of <1% total TFA with >1% TFA and ischaemic stroke occurrence. There was only one study (Yaemsiri 2012 *(1)*) with the data available to calculate the cubic spline dose response. This one study indicated a relative risk of 1.17 (95% CI: 0.97 to 1.41) for each 2% (%TE) increase in TFA intake.



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids

Reference for Annex 11

1 Yaemsiri S, Sen S, Tinker L, Rosamond W, Wassertheil-Smoller S, He K. *Trans* fat, aspirin, and ischemic stroke in postmenopausal women. Ann Neurol. 2012;72(5):704–15.

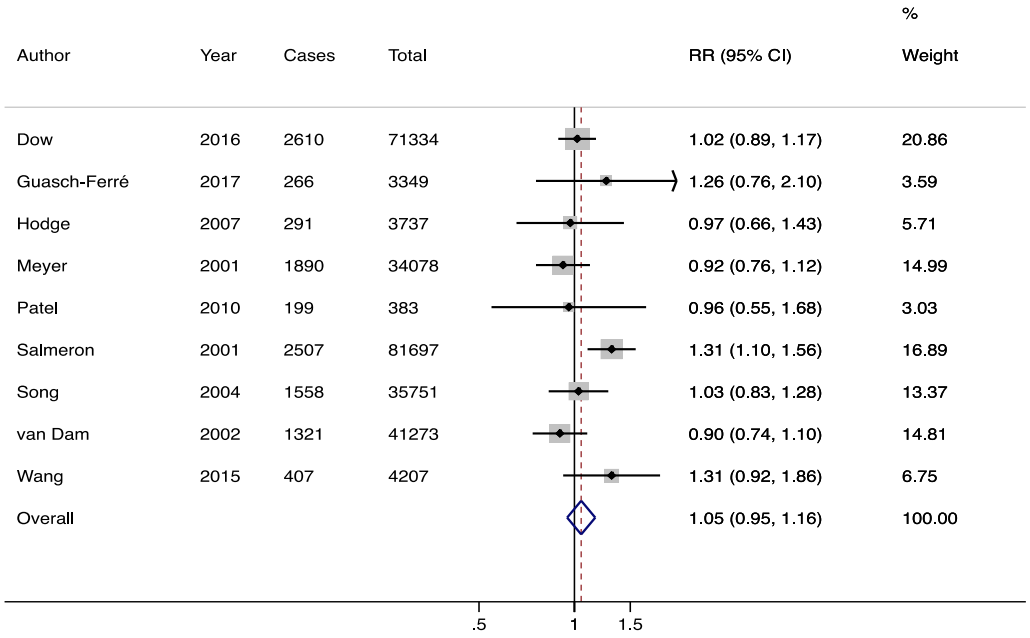
ANNEX 12.

TFA intakes and type 2 diabetes

Dietary intakes

Fig. A12.1. Self-reported intakes of total TFA and type 2 diabetes occurrence

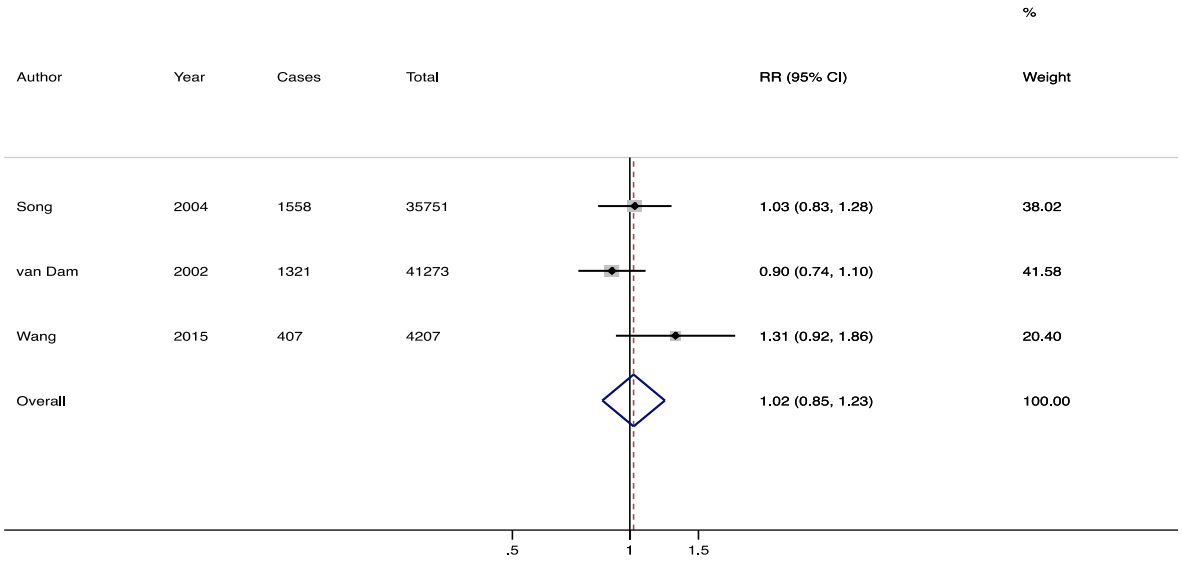
Initial heterogeneity was low (I^2 37%). There was no evidence of undue influence within the pool of studies, nor of a small study effect (Egger's *P*=0.799). Study type was not a determinant of the pooled results (*P*=0.641) and there were no cohorts of pre-existing conditions.



CI: confidence interval; RR: relative risk; T2DM: type 2 diabetes; TFA: *trans*-fatty acids

Fig. A12.2. Self-reported intakes of <1% total TFA with >1% TFA and type 2 diabetes occurrence

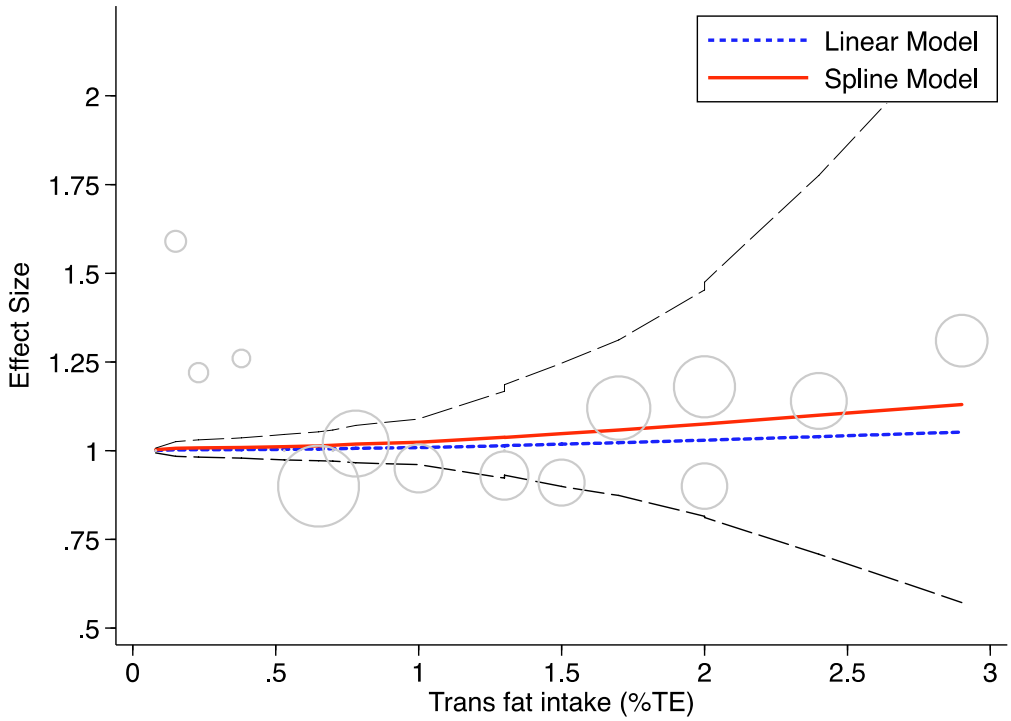
Initial heterogeneity was low (I^2 42%).



CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids

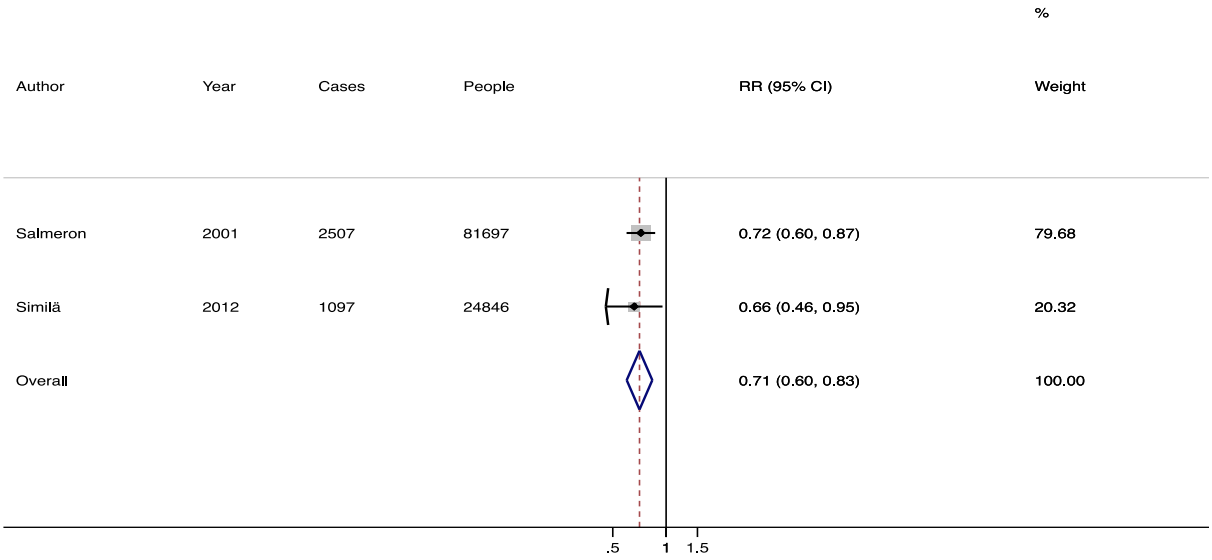
Fig. A12.3. Cubic spline dose response between self-reported total TFA intake (%TE) and type 2 diabetes occurrence

Data were available from 6704 cases during 2 936 838 PY. Assuming linearity, the relative risk of a 2%TE increase in TFA was 1.07 (95% CI: 0.77 to 1.48).



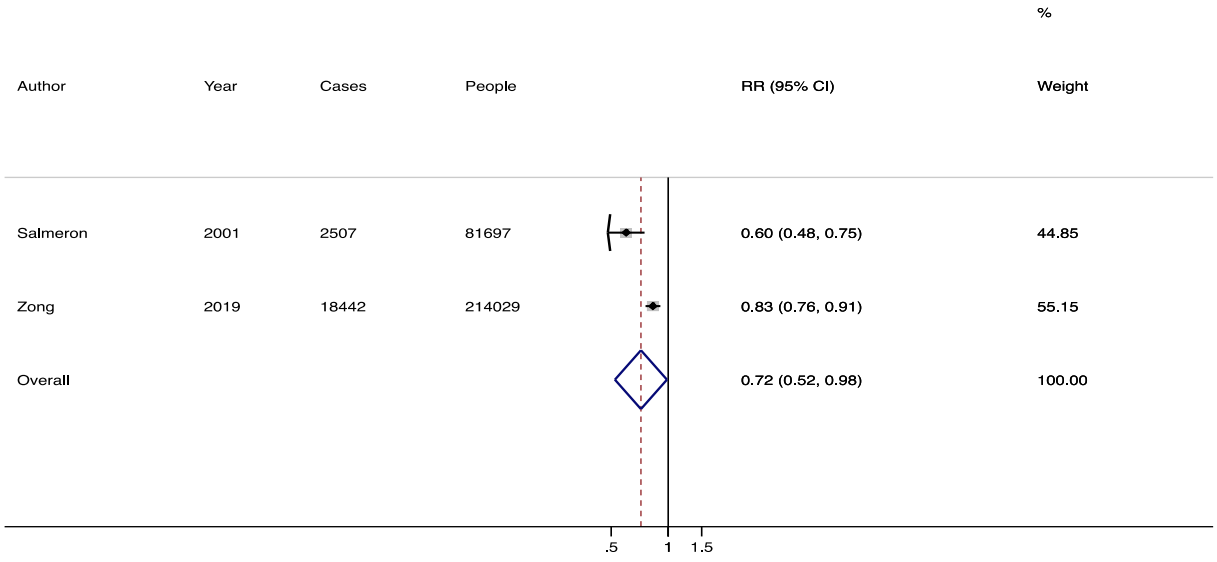
CI: confidence interval; PY: person years; RR: relative risk; TE: total energy; TFA: *trans*-fatty acids.

Fig. A12.4a. Replacement of self-reported total TFA intakes with 2% CHO and type 2 diabetes occurrence



CHO: carbohydrate; CI: confidence interval; RR: relative risk; TFA: *trans*-unsaturated fatty acids.

Fig. A12.4b. Replacement of self-reported total TFA intakes with 2% PUFA and type 2 diabetes occurrence

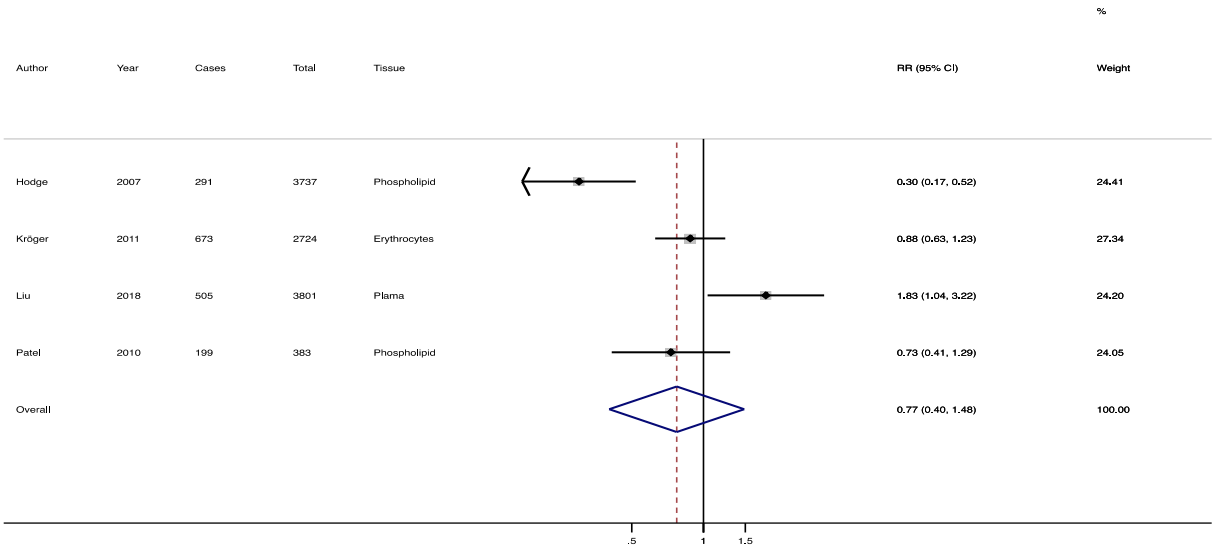


CI: confidence interval; PUFA: polyunsaturated fatty acids; RR: relative risk; TFA: *trans*-fatty acids.

Tissue samples

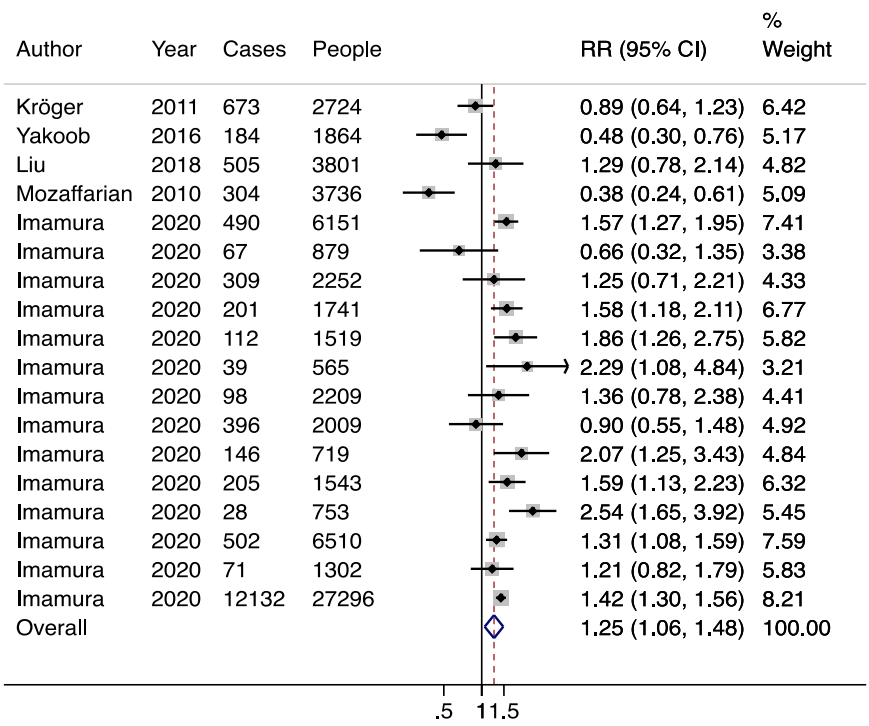
Fig. A12.5. Total TFA from tissue measurements and type 2 diabetes occurrence

Initial heterogeneity was high (I^2 86%). No single study unduly influenced the pooled result, and there was no evidence of a small study effect (Eggers *P*=0.862). Neither the type of study (*P*=0.236) nor the tissue considered (*P*=0.877) were identified as appreciably influencing the pooled results.



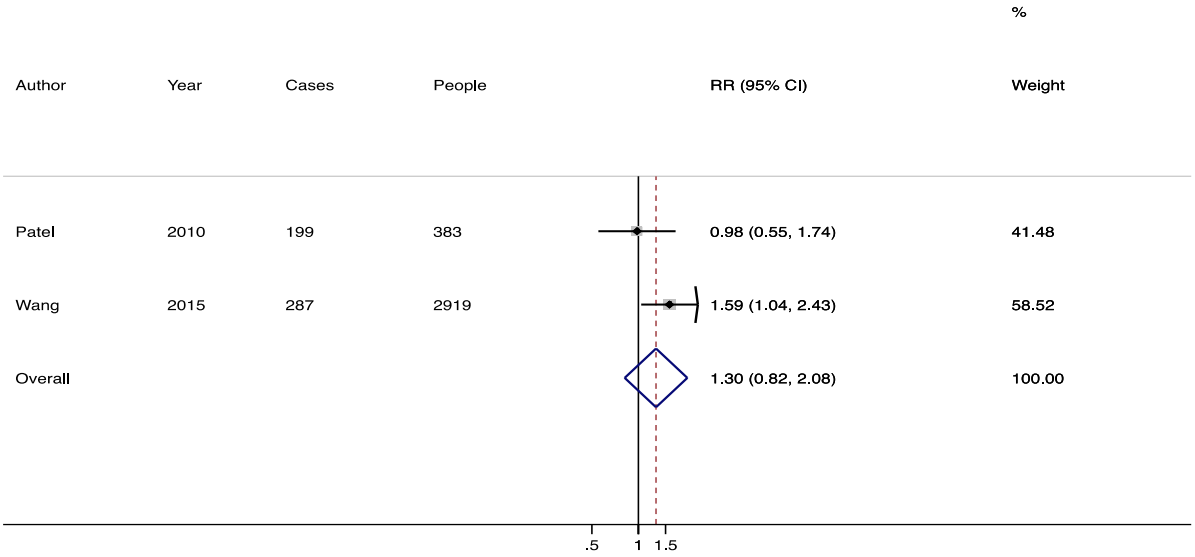
CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Fig. A12.6a. Tissue measurements of T16:1n7 and type 2 diabetes occurrence



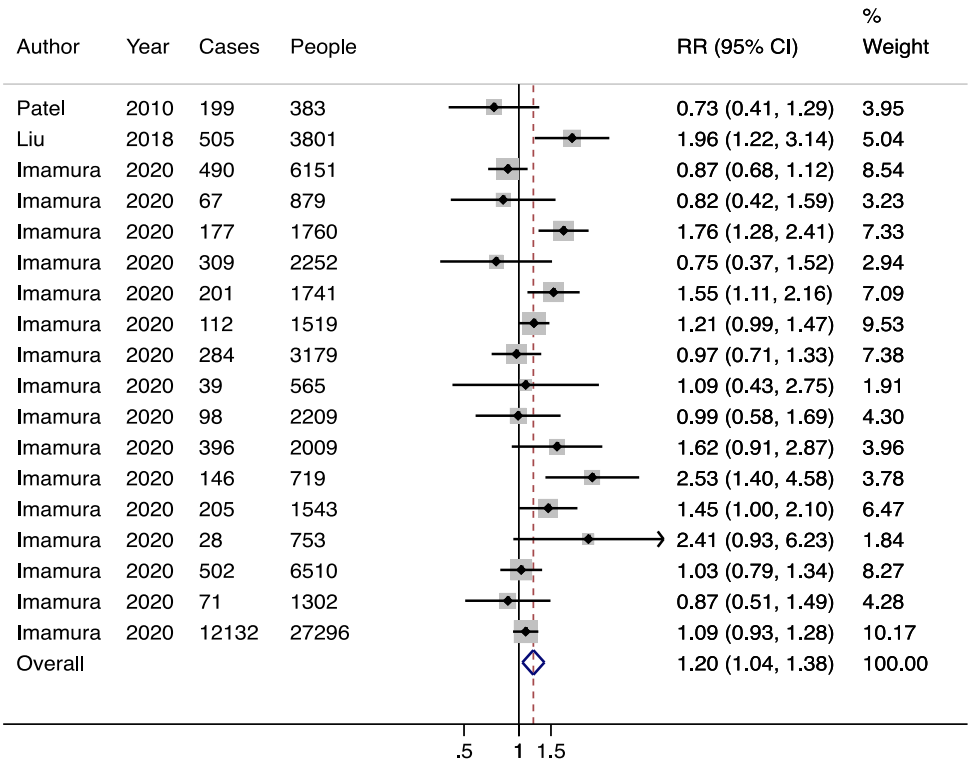
CI: confidence interval; RR: relative risk.

Fig. A12.6b. Tissue measurements of T16:1n9 and type 2 diabetes occurrence



CI: confidence interval; RR: relative risk.

Fig. A12.6c. Tissue measurements of T18:1n9 and type 2 diabetes occurrence



CI: confidence interval; RR: relative risk.

ANNEX 13. GRADE tables

SFA and all-cause mortality data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY FROM SELF-REPORTED DIETARY INTAKES OF TOTAL SATURATED FAT										
21	observational studies	not serious [a]	serious [b]	not serious	not serious	none [c]	213 579/1 211 729 (17.6%)	RR 1.08 (1.00 to 1.17)	14 more per 1000 (from 0 fewer to 30 more)	⨁ VERY LOW
ALL-CAUSE MORTALITY FROM SELF-REPORTED INTAKES OF SFA ABOVE 10%TE COMPARED WITH INTAKES BELOW 10%TE										
13	observational studies	not serious	not serious	not serious	not serious	none	194 456/1 095 528 (17.7%)	RR 1.09 (1.01 to 1.18)	16 more per 1000 (from 2 more to 32 more)	⨁⨁ LOW
ALL-CAUSE MORTALITY FROM SELF-REPORTED INTAKES OF ANIMAL SFA										
2	observational studies	serious [d]	not serious	not serious	serious [e]	none [f]	724/17 530 (4.1%)	RR 1.05 (0.82 to 1.35)	2 more per 1000 (from 7 fewer to 14 more)	⨁ VERY LOW
ALL-CAUSE MORTALITY FROM SELF-REPORTED INTAKES OF DAIRY SFA										
2	observational studies	not serious [g]	serious [h]	not serious	serious [e]	none [f]	6982/137 739 (5.1%)	RR 1.05 (0.64 to 1.71)	3 more per 1000 (from 18 fewer to 36 more)	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF C14:0										
2	observational studies	serious [d]	[f]	not serious	not serious	[f]	–	RR 0.95 (0.87 to 1.04)	–	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF C15:0										
2	observational studies	serious [d]	[f]	not serious	not serious	[f]	–	RR 0.99 (0.90 to 1.09)	–	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF C16:0										
2	observational studies	serious [d]	[f]	not serious	serious [e]	[f]	–	RR 1.18 (0.91 to 1.52)	–	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF C17:0										
2	observational studies	serious [d]	[f]	not serious	not serious	[f]	–	RR 0.97 (0.81 to 1.16)	–	⨁ VERY LOW

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF C18:0										
2	observational studies	serious [d]	[f]	not serious	serious [e]	[f]	–	RR 0.84 (0.70 to 1.02)	–	⨁ VERY LOW

CI: confidence interval; RR: risk ratio; SFA: saturated fatty acids; TE: total energy.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. One study (Zhuang 2019 *(1)*) was considered to unduly influence the pooled result in influence analysis. Removal of this study from the pool indicated an RR of 1.02 (95% CI: 0.95 to 1.09).
b. Initial heterogeneity high (I^2 90%) and unexplained by sensitivity analysis.
c. The restricted cubic spline dose response analysis for self-reported total saturated fat intakes based on 15.8 million person years from 19 cohorts was non-significant (per 5%TE increase RR 1.03 (95% CI: 0.98 to 1.09)).
d. Data from only one or two studies is not considered sufficiently generalizable to other countries and peoples.
e. CIs are wide including both a null and strong effect.
f. Not assessed.
g. Although data were obtained from only two studies, one was a large multinational cohort.
h. Initial heterogeneity was high (I^2 63%) with insufficient studies to consider with sensitivity analyses.

SFA and CHD incidence (non-fatal and fatal) data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE AND SELF-REPORTED DIETARY INTAKES OF TOTAL SATURATED FAT										
18	observational studies	not serious	serious [a]	not serious	not serious	none [b]	19 263/570 326 (3.4%)	RR 1.04 (0.98 to 1.12)	1 more per 1000 (from 1 fewer to 4 more)	⨁ VERY LOW
CHD INCIDENCE AND SELF-REPORTED INTAKES OF SFA ABOVE 10%TE COMPARED WITH INTAKES BELOW 10%TE										
5	observational studies	not serious	not serious	not serious	not serious	none	10 538/268 221 (3.9%)	RR 1.00 (0.87 to 1.14)	0 fewer per 1000 (from 5 fewer to 6 more)	⨁⨁ LOW
CHD INCIDENCE AND SELF-REPORTED INTAKES OF ANIMAL SOURCE SFA										
3	observational studies	not serious [c]	serious [d]	not serious	not serious	none [e]	3509/85 917 (4.1%)	RR 1.06 (0.96 to 1.17)	2 more per 1000 (from 2 fewer to 7 more)	⨁ VERY LOW
CHD INCIDENCE AND SELF-REPORTED INTAKES OF DAIRY SFA										
2	observational studies	serious [f]	not serious	not serious	not serious	none [e]	3464/75 425 (4.6%)	RR 1.00 (0.98 to 1.02)	0 fewer per 1000 (from 1 fewer to 1 more)	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF TOTAL SFA										
4	observational studies	not serious [g]	not serious [h]	not serious	not serious	none [e]	3916/24 108 (16.2%)	RR 1.46 (1.09 to 1.94)	75 more per 1000 (from 15 more to 153 more)	⨁⨁ LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C12:0										
2	observational studies	serious [f]	[e]	not serious	serious [i]	[e]	–	RR 0.92 (0.76 to 1.11)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C14:0										
3	observational studies	not serious	[e]	not serious	serious [i]	[e]	–	RR 0.90 (0.76 to 1.07)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C15:0										
3	observational studies	not serious	[e]	not serious	serious [i]	[e]	–	RR 1.23 (0.79 to 1.91)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C16:0										
3	observational studies	not serious	[e]	not serious	serious [i]	[e]	–	RR 1.06 (0.92 to 1.23)	–	⨁ VERY LOW

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C17:0										
2	observational studies	serious [f]	[e]	not serious	serious [i]	[e]	–	RR 0.92 (0.61 to 1.38)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C18:0										
3	observational studies	not serious	[e]	not serious	serious [i]	[e]	–	RR 0.86 (0.62 to 1.18)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C20:0										
3	observational studies	not serious	[e]	not serious	serious [i]	[e]	–	RR 0.69 (0.46 to 1.04)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C22:0										
4	observational studies	not serious	[e]	not serious	serious [i]	[e]	–	RR 0.81 (0.53 to 1.23)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF C24:0										
4	observational studies	not serious	[e]	not serious	serious [i]	[e]	–	RR 0.74 (0.50 to 1.09)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF >C19:0										
2	observational studies	serious [f]	[e]	not serious	not serious	[e]	–	RR 0.48 (0.32 to 0.73)	–	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids; TE: total energy.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. Initial heterogeneity was high (I^2 54%).
b. The restricted cubic spline dose response analysis for self-reported saturated fat intakes and CHD risk based on 5.2 million person years from 9 cohorts was non-significant (per 5%TE increase RR 0.99 (95% CI: 0.94 to 1.03)).
c. Influence analysis indicated one study (Praagman 2016 *(2)*) disproportionately influenced the pooled result. Without this study, the observed association did not change in direction or significance (RR 1.54 95% CI: 0.58 to 4.09).
d. Initial heterogeneity was high (I^2 79%) and not explained by sensitivity analysis.
e. Not assessed.
f. This effect size estimate relies on data from only 1–2 studies, which is not viewed as generalizable to all countries.
g. Influence analysis indicated one study (Matthan 2014) disproportionately influenced the pooled result. Without this study, the observed association did not change in direction or significance (RR 1.74 95% CI: 1.14 to 2.68).
h. Initial inconsistency was high (I^2 83%). Removal of the influential study reduced the heterogeneity (I^2 45%). A meta-regression assessing the tissue type assessed for SFA did not indicate this was a contributing factor.
i. CIs are wide containing a potential null or strong effect.

SFA and CVD incidence (non-fatal and fatal) data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CVD INCIDENCE AND SELF-REPORTED DIETARY INTAKES OF TOTAL SFA										
16	observational studies	not serious [a]	serious [b]	not serious	not serious	none [c]	68 232/1 088 501 (6.3%)	RR 1.07 (0.99 to 1.17)	4 more per 1000 (from 1 fewer to 11 more)	⊕ VERY LOW
CVD INCIDENCE AND SELF-REPORTED INTAKES OF SFA ABOVE 10%TE COMPARED WITH INTAKES BELOW 10%TE										
11	observational studies	not serious	serious [b]	not serious	not serious	none	61 329/969 859 (6.3%)	RR 1.10 (0.99 to 1.22)	6 more per 1000 (from 1 fewer to 14 more)	⊕ VERY LOW
CVD INCIDENCE AND SELF-REPORTED DIETARY INTAKES OF SFA FROM DAIRY										
2	observational studies	not serious [d]	not serious	not serious	serious [e]	none [f]	6103/137 739 (4.4%)	RR 0.92 (0.75 to 1.12)	4 fewer per 1000 (from 11 fewer to 5 more)	⊕ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF C14:0										
2	observational studies	serious [g]	[f]	not serious	not serious	[f]	–	RR 0.91 (0.80 to 1.03)	–	⊕ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF C15:0										
2	observational studies	serious [g]	[f]	not serious	serious [e]	[f]	–	RR 1.08 (0.94 to 1.23)	–	⊕ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF C16:0										
2	observational studies	serious [g]	[f]	not serious	not serious	[f]	–	RR 1.12 (1.00 to 1.24)	–	⊕ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF C17:0										
2	observational studies	serious [g]	[f]	not serious	not serious	[f]	–	RR 0.94 (0.83 to 1.07)	–	⊕ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF C18:0										
2	observational studies	serious [g]	[f]	not serious	serious [e]	[f]	–	RR 0.90 (0.76 to 1.06)	–	⊕ VERY LOW

CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids; TE: total energy.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. Influence analysis indicated one study (Zhuang 2019 *(1)*) unduly influenced the pooled result. Removal of Zhuang 2019 did not change the direction or significance of the pooled effect size RR 1.05 (95% CI: 0.94 to 1.14).
b. Initial heterogeneity high (I^2 77%) and not explained by sensitivity analysis.
c. The restricted cubic spline dose response analysis for self-reported saturated fat intakes and CVD risk based on 16.2 million person years from 16 cohorts was non-significant (per 5%TE increase RR 1.01 (95% CI: 0.94 to 1.08)).
d. One cohort is multinational.
e. CIs contain both a null effect and a strong effect.
f. Not assessed.
g. Data from only one or two cohorts is not considered generalizable to other countries and regions.

SFA and ischaemic stroke incidence (non-fatal and fatal) data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ISCHAEMIC STROKE INCIDENCE AND SELF-REPORTED DIETARY INTAKES OF TOTAL SFA										
9	observational studies	not serious	not serious	not serious	not serious	none [a]	6400/402 847 (1.6%)	RR 0.98 (0.87 to 1.12)	0 fewer per 1000 (from 2 fewer to 2 more)	⊕⊕ LOW
ISCHAEMIC STROKE INCIDENCE FROM SELF-REPORTED INTAKES OF SFA ABOVE 10%TE COMPARED WITH INTAKES BELOW 10%TE										
3	observational studies	not serious	serious [b]	not serious	serious [c]	none	3048/172 688 (1.8%)	RR 0.91 (0.67 to 1.24)	2 fewer per 1000 (from 6 fewer to 4 more)	⊕ VERY LOW
ISCHAEMIC STROKE INCIDENCE AND TISSUE MEASUREMENTS OF C14:0										
3	observational studies	not serious	[d]	not serious	serious [c]	[d]	–	RR 0.89 (0.63 to 1.27)	–	⊕ VERY LOW
ISCHAEMIC STROKE INCIDENCE AND TISSUE MEASUREMENTS OF C15:0										
2	observational studies	serious [e]	[d]	not serious	serious [c]	[d]	–	RR 0.68 (0.43 to 1.09)	–	⊕ VERY LOW
ISCHAEMIC STROKE INCIDENCE AND TISSUE MEASUREMENTS OF C16:0										
2	observational studies	serious [e]	[d]	not serious	serious [c]	[d]	–	RR 1.19 (0.93 to 1.52)	–	⊕ VERY LOW
ISCHAEMIC STROKE INCIDENCE AND TISSUE MEASUREMENTS OF C18:0										
2	observational studies	serious [e]	[d]	not serious	serious [c]	[d]	–	RR 0.95 (0.72 to 1.26)	–	⊕ VERY LOW

CI: confidence interval; PY: person years; RR: relative risk; SFA: saturated fatty acids; TE: total energy.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. The restricted cubic spline dose response analysis for self-reported saturated fat intakes based on five cohorts of 3601 cases over 2 198 066 PY did not indicate a dose response relationship. Assuming linearity, the increased risk of all-cause mortality per 5% increase in TE from total SFA was RR 0.94 (95% CI: 0.79 to 1.13).

b. Initial heterogeneity was high (I^2 61%).

c. The CIs contain both a null and strong effect.

d. Not assessed.

e. Data from only one or two studies is not considered generalizable into other countries or regions.

SFA and type 2 diabetes incidence data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
TYPE 2 DIABETES INCIDENCE AND SELF-REPORTED INTAKES OF TOTAL SFA										
13	observational studies	not serious [a]	not serious [b]	not serious	not serious	none [c]	15 727/351 134 (4.5%)	RR 1.02 (0.95 to 1.10)	1 more per 1000 (from 2 fewer to 4 more)	⊕⊕ LOW
TYPE 2 DIABETES INCIDENCE AND SELF-REPORTED INTAKES OF SFA ABOVE 10%TE COMPARED WITH INTAKES BELOW 10%TE										
5	observational studies	not serious	serious [d]	not serious	serious [e]	none	7294/118 400 (6.2%)	RR 1.01 (0.82 to 1.23)	1 more per 1000 (from 11 fewer to 14 more)	⊕ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF TOTAL SFA										
8	observational studies	not serious	serious [f]	not serious	not serious	none [g,h]	2599/18 867 (13.8%)	RR 1.30 (1.06 to 1.59)	41 more per 1000 (from 8 more to 81 more)	⊕ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C14:0										
11	observational studies	not serious	serious [i]	not serious	serious e	none	–	RR 1.14 (0.97 to 1.34)	–	⊕ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C15:0										
20	observational studies	not serious	serious [j]	not serious	not serious	none	–	RR 0.79 (0.68 to 0.93)	–	⊕ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C16:0										
23	observational studies	not serious	serious [j]	not serious	not serious	none	–	RR 1.41 (1.21 to 1.64)	–	⊕ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C17:0										
16	observational studies	not serious	serious [k]	not serious	not serious	none	–	RR 0.66 (0.52 to 0.84)	–	⊕ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C18:0										
23	observational studies	not serious	serious [l]	not serious	serious [e]	none	–	RR 1.10 (0.93 to 1.29)	–	⊕ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C20:0										
15	observational studies	not serious	serious [m]	not serious	not serious	none	–	RR 0.76 (0.62 to 0.93)	–	⊕ VERY LOW

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C22:0										
15	observational studies	not serious	serious [n]	not serious	not serious	none	–	RR 0.82 (0.69 to 0.98)	–	⨁ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C24:0										
13	observational studies	not serious	serious [o]	not serious	not serious	none	–	RR 0.75 (0.61 to 0.94)	–	⨁ VERY LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF C15:0 AND C17:0										
3	observational studies	not serious	serious [p]	not serious	not serious	strong association	–	RR 0.45 (0.32 to 0.63)	–	⨁⨁ LOW
TYPE 2 DIABETES AND TISSUE MEASUREMENTS OF EVEN CHAIN SFA										
2	observational studies	serious [q]	[r]	not serious	serious [e]	[r]	552/3697 (14.9%)	RR 0.91 (0.72 to 1.15)	13 fewer per 1000 (from 42 fewer to 22 more)	⨁ VERY LOW

CI: confidence interval; PY: person years; RR: relative risk; SFA: saturated fatty acids; TE: total energy.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. Influence analysis identified one study (Liu 2019 *(3)*) that disproportionately influenced the pooled results. Without this study, the pooled effect size was 1.03 (0.94 to 1.12).
b. Initially heterogeneity (I^2 49%).
c. The restricted cubic spline dose response analysis for self-reported SFA intakes based on seven cohorts of 9989 cases over 3 416 215 PY. Assuming linearity, the relative risk of a 5% increase in TE from SFA was 0.98 (95% CI: 0.91 to 1.05).
d. Initial heterogeneity was high (I^2 66%).
e. CIs contain both a null and strong effect.
f. Meta-regression analyses did not identify influencing variables in the reported results, unexplained heterogeneity was high (I^2 74%).
g. Associations between individual chain length fatty acids and incidence of type 2 diabetes appears to differ. C14:0 and C16:0 intakes increased the risk of type 2 diabetes, whereas C15:0, C17:0 and C24:0 intakes appear to be protective.
h. Dose–response gradient not assessed.
i. Initial heterogeneity was high (I^2 58%).
j. Initial heterogeneity was high (I^2 76%).
k. Initial heterogeneity was high (I^2 81%).
l. Initial heterogeneity was high (I^2 83%).
m. Initial heterogeneity was high (I^2 77%).
n. Initial heterogeneity was high (I^2 71%).
o. Initial heterogeneity was high (I^2 79%).
p. Initial heterogeneity was high (I^2 73%).
q. This effect size estimate relies on data from only 1–2 studies, which is not viewed as generalizable to all countries.
r. Not assessed.

TFA and all-cause mortality data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY AND SELF-REPORTED DIETARY INTAKES OF TOTAL TFA										
6	observational studies	not serious [a]	not serious	not serious	not serious	dose response gradient [b]	164 951/673 830 (24.5%)	RR 1.11 (1.02 to 1.20)	27 more per 1000 (from 5 more to 49 more)	⨁⨁⨁ MODERATE
ALL-CAUSE MORTALITY AND SELF-REPORTED INTAKES OF TFA ABOVE 1%TE COMPARED WITH INTAKES BELOW 1%TE										
3	observational studies	not serious	serious [c]	not serious	not serious	none [d]	33 637/127 159 (26.5%)	RR 1.11 (1.00 to 1.24)	29 more per 1000 (from 0 fewer to 63 more)	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF TOTAL TFA										
6	observational studies	not serious [e]	not serious [f]	not serious	serious [g]	none [d]	2626/11 315 (23.2%)	RR 1.28 (0.90 to 1.82)	65 more per 1000 (from 23 fewer to 190 more)	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF RUMINANT-DERIVED TFA										
3	observational studies	not serious	not serious	not serious	serious [g]	none [d]	959/5427 (17.7%)	RR 1.23 (0.87 to 1.74)	41 more per 1000 (from 23 fewer to 131 more)	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF INDUSTRIALLY PRODUCED TFA										
3	observational studies	not serious	serious [h]	not serious	serious [g]	none [d]	959/5427 (17.7%)	RR 1.43 (0.70 to 2.93)	76 more per 1000 (from 53 fewer to 341 more)	⨁ VERY LOW
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF T16:1N7										
5	observational studies	not serious	not serious	not serious	serious [g]	[d]	–	RR 1.03 (0.86 to 1.23)	–	–
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF T18:1										
4	observational studies	not serious	serious [i]	not serious	serious [g]	[d]	–	RR 1.11 (0.82 to 1.50)	–	–
ALL-CAUSE MORTALITY AND TISSUE MEASUREMENTS OF T18:1N9										
2	observational studies	serious [j]	serious [k]	not serious	serious [g]	[d]	–	RR 1.06 (0.47 to 2.39)	–	–

CI: confidence interval; RR: relative risk; TE: total energy; TFA: trans-fatty acids.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. Influence analysis identified one study (Zhuang 2019 *(1)*) unduly influenced the pooled result. Without this study, the pooled effect size was RR 1.14 (95% CI: 1.03 to 1.27).
b. The restricted cubic spline dose response analysis for self-reported total TFA intakes based on 167 456 cases in 11.0 million person years from seven cohorts was significant (per 2%TE increase RR 1.14 (95% CI: 1.04 to 1.26)). Because of the visible dose response, the evidence was upgraded once.
c. Initial heterogeneity was high (I^2 65%).
d. Not assessed.
e. Influence analysis identified that one study (Kleber 2016 (4)) unduly influenced the pooled result. Without this study, the pooled effect size was RR 1.70 (95% CI: 1.32 to 2.18) and heterogeneity was low (I^2 0%).
f. Initial heterogeneity was high (I^2 81%) but was entirely explained by the inclusion of one study (Kleber 2016 (4)). Removal of this study reduced the I2 to 0%. This study assessed erythrocyte membranes whereas the others assessed plasma.
g. The CIs contain both a null and strong effect.
h. Initial heterogeneity was high (I^2 68%).
i. Initial heterogeneity was high (I^2 55%).
j. Data from only 1 or 2 cohorts is unlikely to be generalizable to other people and countries.
k. Initial heterogeneity was high (I^2 81%).

TFA and CHD incidence (non-fatal and fatal) data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE AND SELF-REPORTED DIETARY INTAKES OF TOTAL TFA										
7	observational studies	not serious	not serious	not serious	not serious	dose response gradient [a]	0/0 10 311/185 664 (5.6%)	RR 1.17 (1.09 to 1.27)	9 more per 1000 (from 5 more to 15 more)	⊕⊕⊕ MODERATE
CHD INCIDENCE AND SELF-REPORTED INTAKES OF TFA ABOVE 1%TE COMPARED WITH INTAKES BELOW 1%TE										
4	observational studies	not serious	not serious	not serious	not serious	none [b]	6575/67 739 (9.7%)	RR 1.14 (1.04 to 1.25)	14 more per 1000 (from 4 more to 24 more)	⊕⊕ LOW
CHD INCIDENCE AND DIETARY INTAKES OF RUMINANT-DERIVED TFA										
4	observational studies	not serious	not serious	not serious	serious [c]	none [b]	4311/177 659 (2.4%)	RR 0.93 (0.75 to 1.15)	2 fewer per 1000 (from 6 fewer to 4 more)	⊕ VERY LOW
CHD INCIDENCE AND DIETARY INTAKES OF INDUSTRIALLY PRODUCED TFA										
3	observational studies	not serious	not serious	not serious	not serious	none [b]	4213/177 090 (2.4%)	RR 1.28 (1.10 to 1.50)	7 more per 1000 (from 2 more to 12 more)	⊕⊕ LOW

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE AND TISSUE MEASUREMENTS OF TOTAL TFA										
3	observational studies	not serious	not serious	not serious	not serious	none [b]	–	RR 0.98 (0.92 to 1.05)	–	⨁⨁ LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF T16:1N7										
3	observational studies	not serious	[b]	not serious	serious c	[b]	–	RR 0.93 (0.76 to 1.13)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF T18:1										
2	observational studies	serious [d]	[b]	not serious	serious c	[b]	–	RR 1.17 (0.98 to 1.39)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF T18:1N11										
2	observational studies	serious [d]	[b]	not serious	serious c	[b]	–	RR 1.03 (0.74 to 1.43)	–	⨁ VERY LOW
CHD INCIDENCE AND TISSUE MEASUREMENTS OF T18:1N6–10										
2	observational studies	serious [d]	[b]	not serious	not serious	[b]	–	RR 1.04 (0.91 to 1.19)	–	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; RR: relative risk; TE: total energy; TFA: *trans*-fatty acids.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. The restricted cubic spline dose response analysis for self-reported total *trans* fat intakes based on 10 132 cases in 3.8 million person years from 7 cohorts was significant (per 2%TE increase RR 1.25 (95% CI: 1.15 to 1.36)). Because of the visible dose response, the evidence was upgraded once.

b. Not assessed.

c. The CIs contain both a null and strong effect.

d. Data from only 1 or 2 cohorts is unlikely to be generalizable to other people and countries.

TFA and CVD incidence (non-fatal and fatal) data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CVD INCIDENCE AND SELF-REPORTED DIETARY INTAKES OF TOTAL TFA										
6	observational studies	not serious	not serious	not serious	serious [a]	none [b]	47 406/675 673 (7.0%)	RR 1.14 (1.04 to 1.25)	10 more per 1000 (from 3 more to 18 more)	⨁ VERY LOW
CVD INCIDENCE AND SELF-REPORTED INTAKES OF TFA ABOVE 1%TE COMPARED WITH INTAKES BELOW 1%TE										
2	observational studies	serious [c]	not serious	not serious	not serious	none [d]	7878/126 233 (6.2%)	RR 1.20 (1.08 to 1.33)	12 more per 1000 (from 5 more to 21 more)	⨁ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF TOTAL TFA										
6	observational studies	not serious	not serious	not serious	serious [a]	none [d]	–	RR 1.08 (0.67 to 1.74)	–	⨁ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF RUMINANT-DERIVED TFA										
2	observational studies	serious [c]	[d]	not serious	serious [a]	[d]	35/3439 (1.0%)	RR 0.48 (0.15 to 1.57)	5 fewer per 1000 (from 9 fewer to 6 more)	⨁ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF INDUSTRIALLY PRODUCED TFA										
2	observational studies	serious [c]	[d]	not serious	serious [a]	[d]	35/3439 (1.0%)	RR 0.52 (0.14 to 1.86)	5 fewer per 1000 (from 9 fewer to 9 more)	⨁ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF T16:1N7										
5	observational studies	not serious	not serious	not serious	serious [a]	none [d]	–	RR 0.90 (0.72 to 1.12)	–	⨁ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF T18:1										
4	observational studies	not serious	not serious	not serious	serious [a]	none [d]	–	RR 0.95 (0.79 to 1.15)	–	⨁ VERY LOW
CVD INCIDENCE AND TISSUE MEASUREMENTS OF T18:1N9										
2	observational studies	serious [c]	[d]	not serious	serious c	[d]	–	RR 0.56 (0.19 to 1.63)	–	⨁ VERY LOW

CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; TE: total energy; TFA: *trans*-fatty acids.

Absolute values and participant numbers are not provided where most included studies are nested case control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. The CIs contain both a null and strong effect.
b. The restricted cubic spline dose response analysis for self-reported total *trans* fat intakes based on 47 244 cases in 12.0 million person years from 6 cohorts was non-significant (per 2%TE increase RR 1.16 (95% CI: 0.99 to 1.36)).
c. Data from only 1 or 2 cohorts is unlikely to be generalizable to other people or countries.
d. Not assessed.

TFA and ischaemic stroke incidence (non-fatal and fatal) data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ISCHAEMIC STROKE AND SELF-REPORTED DIETARY INTAKES OF TOTAL TFA										
3	observational studies	serious [a]	serious [b]	not serious	serious [c]	none [d]	1889/257 437 (0.7%)	RR 1.09 (0.80 to 1.48)	1 more per 1000 (from 1 fewer to 4 more)	⨁ VERY LOW

CI: confidence interval; RR: relative risk; TFA: trans-fatty acids.

Absolute values and participant numbers are not provided where most included studies are nested case–control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. Data from only one or two studies is not considered reflective of the general population.
b. Heterogeneity is high (I^2 82%).
c. CIs contain both a null and strong effect.
d. There was insufficient data to consider dose response.

TFA and type 2 diabetes incidence data from prospective observational studies

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
TYPE 2 DIABETES INCIDENCE AND SELF-REPORTED DIETARY INTAKES OF TOTAL TFA										
9	observational studies	not serious	not serious	not serious	not serious	none [a]	11 049/275 402 (4.0%)	RR 1.05 (0.95 to 1.16)	2 more per 1000 (from 2 fewer to 6 more)	⨁⨁ LOW
TYPE 2 DIABETES INCIDENCE AND SELF-REPORTED INTAKES OF TFA ABOVE 1%TE COMPARED WITH INTAKES BELOW 1%TE										
3	observational studies	not serious	not serious	not serious	serious [b]	none [c]	3286/81 231 (4.0%)	RR 1.02 (0.85 to 1.23)	1 more per 1000 (from 6 fewer to 9 more)	⨁ VERY LOW
TYPE 2 DIABETES INCIDENCE AND TISSUE MEASUREMENTS OF TOTAL TFA										
4	observational studies	not serious	serious [d]	not serious	serious [b]	none [c]	–	RR 0.77 (0.40 to 1.48)	–	⨁ VERY LOW
TYPE 2 DIABETES INCIDENCE AND TISSUE MEASUREMENTS OF T16:1N7										
18	observational studies	not serious	serious [e]	not serious	not serious	none [c]	–	RR 1.25 (1.06 to 1.48)	–	⨁ VERY LOW
TYPE 2 DIABETES INCIDENCE AND TISSUE MEASUREMENTS OF T16:1N9										
2	observational studies	serious [f]	[c]	not serious	serious [b]	none [c]	–	RR 1.30 (0.82 to 2.08)	–	⨁ VERY LOW
TYPE 2 DIABETES INCIDENCE AND TISSUE MEASUREMENTS OF T18:1N9										
18	observational studies	not serious	serious [g]	not serious	not serious	none [c]	–	RR 1.20 (1.04 to 1.38)	–	⨁ VERY LOW

CI: confidence interval; RR: relative risk; TE: total energy; TFA: trans-fatty acids.

Absolute values and participant numbers are not provided where most included studies are nested case–control studies, because they provide inflated values for potential benefit or harm. For meta-analyses of only two studies, full assessment was not necessary because the certainty of evidence from these comparisons was very low, and was unable to be upgraded.

Explanations

a. The restricted cubic spline dose response analysis for self-reported total trans fat intakes based on 6704 cases in 2.9 million person years from 4 cohorts was non-significant (per 2%TE increase RR 1.07 (95% CI: 0.77 to 1.48)).
b. CIs contain both a null and strong effect.
c. Not assessed.
d. Heterogeneity high (I^2 86%) unexplained by sensitivity analyses.
e. Initial heterogeneity was high (I^2 79%).
f. Data from only 1 or 2 cohorts is unlikely to be generalizable to other peoples and countries.
g. Initial heterogeneity was high (I^2 58%).

References for Annex 13

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What is the effect of replacing 5% SFA in the diet of adults with PUFA?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
5	observational studies	not serious	serious [a]	not serious	not serious	dose response gradient	165 011/606 552 (27.2%)	RR 0.85 (0.75 to 0.97)	41 fewer per 1000 (from 68 fewer to 8 fewer)	⨁⨁ LOW
CHD INCIDENCE										
17	observational studies	not serious	serious [a]	not serious	not serious	dose response gradient	22 320/448 921 (5.0%)	RR 0.89 (0.81 to 0.98)	5 fewer per 1000 (from 9 fewer to 1 fewer)	⨁⨁ LOW
CVD INCIDENCE										
5	observational studies	not serious	serious [a]	not serious	not serious	dose response gradient	43 892/600 850 (7.3%)	RR 0.90 (0.81 to 1.00)	7 fewer per 1000 (from 14 fewer to 0 fewer)	⨁⨁ LOW
TYPE 2 DIABETES										
16	observational studies	not serious	serious [a]	not serious	not serious	none	20 908/139 771 (15.0%)	RR 0.96 (0.85 to 1.08)	6 fewer per 1000 (from 22 fewer to 12 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; PUFA: polyunsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Initial heterogeneity was high.

What is the effect of replacing 5% SFA in the diet of adults with MUF?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
5	observational studies	not serious	serious [a]	not serious	not serious	dose response gradient	165 011/606 552 (27.2%)	RR 0.84 (0.75 to 0.95)	44 fewer per 1000 (from 68 fewer to 14 fewer)	⨁⨁ LOW
CHD INCIDENCE										
4	observational studies	not serious	serious [a]	not serious	serious [b]	none	10 133/167 855 (6.0%)	RR 1.00 (0.82 to 1.21)	0 fewer per 1000 (from 11 fewer to 13 more)	⨁ VERY LOW
CVD INCIDENCE										
5	observational studies	not serious	serious [a]	not serious	not serious	none	43 892/600 850 (7.3%)	RR 0.94 (0.87 to 1.02)	4 fewer per 1000 (from 9 fewer to 1 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Initial heterogeneity was high.
b. CIs contain both a null and strong effect.

What is the effect of replacing 5% SFA in the diet of adults with CHO?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
5	observational studies	not serious	serious [a]	not serious	not serious	dose response gradient	40 141/277 553 (14.5%)	RR 0.92 (0.86 to 0.99)	12 fewer per 1000 (from 20 fewer to 1 fewer)	⨁⨁ LOW
CHD INCIDENCE										
6	observational studies	not serious	serious [a]	not serious	not serious	none	10 458/313 066 (3.3%)	RR 0.98 (0.88 to 1.09)	1 fewer per 1000 (from 4 fewer to 3 more)	⨁ VERY LOW
CVD INCIDENCE										
6	observational studies	not serious	serious [a]	not serious	not serious	none	13 284/274 970 (4.8%)	RR 0.98 (0.90 to 1.07)	1 fewer per 1000 (from 5 fewer to 3 more)	⨁ VERY LOW
TYPE 2 DIABETES										
15	observational studies	not serious	not serious	not serious	not serious	none	20 015/102 350 (19.6%)	RR 1.05 (0.99 to 1.11)	10 more per 1000 (from 2 fewer to 22 more)	⨁⨁ LOW

CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids.

Explanations

[a] Initial heterogeneity was high.

What is the effect of replacing 5% SFA in the diet of adults with TFA?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
2	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	130 334/535 425 (24.3%)	RR 1.09 (0.97 to 1.22)	22 more per 1000 (from 7 fewer to 54 more)	⨁ VERY LOW
CHD INCIDENCE										
2	observational studies	serious [a]	serious [b]	not serious	serious [c]	none	7667/127 536 (6.0%)	RR 1.06 (0.89 to 1.26)	4 more per 1000 (from 7 fewer to 16 more)	⨁ VERY LOW
CVD INCIDENCE										
2	observational studies	serious [a]	serious [b]	not serious	not serious	none	42 625/564 004 (7.6%)	RR 1.07 (0.96 to 1.20)	5 more per 1000 (from 3 fewer to 15 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids; TFA: *trans*-fatty acids.

Explanations

a. Data from only one or two cohorts is unlikely to be generalizable to other people or countries.
b. Initial heterogeneity was high.
c. CIs contain both a null and strong effect.

What is the effect of replacing 5% SFA in the diet of adults with protein?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	2466/40 319 (6.1%)	RR 1.26 (1.06 to 1.50)	16 more per 1000 (from 4 more to 31 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Data from only one or two cohorts are unlikely to be generalizable to other people or countries.
b. CIs contain both a null and strong effect.

What is the effect of replacing 5% SFA in the diet of adults with MUFA from plants?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
4	observational studies	not serious	not serious	not serious	not serious	dose response gradient	151 006/628 803 (24.0%)	RR 0.85 (0.82 to 0.88)	36 fewer per 1000 (from 43 fewer to 29 fewer)	⨁⨁⨁ MODERATE
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	not serious	dose response gradient	4419/93 384 (4.7%)	RR 0.83 (0.69 to 1.00)	8 fewer per 1000 (from 15 fewer to 0 fewer)	⨁⨁ LOW
CVD INCIDENCE										
3	observational studies	not serious	not serious	not serious	not serious	dose response gradient	43 335/614 498 (7.1%)	RR 0.90 (0.84 to 0.96)	7 fewer per 1000 (from 11 fewer to 3 fewer)	⨁⨁⨁ MODERATE

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Data from only one or two cohorts are unlikely to be generalizable to other peoples or countries.

What is the effect of replacing 5% SFA in the diet of adults with MUFA from animals?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
2	observational studies	serious [a]	serious [b]	not serious	not serious	none	130 334/535 425 (24.3%)	RR 1.00 (0.83 to 1.20)	0 fewer per 1000 (from 41 fewer to 49 more)	⨁ VERY LOW
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	serious [c]	none	4419/93 385 (4.7%)	RR 1.06 (0.80 to 1.41)	3 more per 1000 (from 9 fewer to 19 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Data from only one or two cohorts are unlikely to be generalizable to other people or countries.
b. Initial heterogeneity are high.
c. CIs contain both a null and strong effect.

What is the effect of replacing 5% SFA in the diet of adults with sugars or high glycaemic index CHO?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
7	observational studies	not serious	serious [a]	not serious	not serious	none	12 641/225 278 (5.6%)	RR 1.08 (0.99 to 1.17)	4 more per 1000 (from 1 fewer to 10 more)	⨁ VERY LOW

CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Initial heterogeneity was high.

What is the effect of replacing 5% SFA in the diet of adults with moderate glycaemic index CHO?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
3	observational studies	not serious	serious [a]	not serious	serious [b]	dose response gradient	4409/93 963 (4.7%)	RR 1.03 (0.79 to 1.33)	1 more per 1000 (from 10 fewer to 15 more)	⊕ VERY LOW

CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Initial heterogeneity was high.
b. CIs contain both a null and strong effect.

What is the effect of replacing 5% SFA in the diet of adults with protein from animals?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	not serious	dose response gradient	2466/40 319 (6.1%)	RR 1.31 (1.14 to 1.50)	19 more per 1000 (from 9 more to 31 more)	⊕⊕ LOW

CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Data from only one or two studies are unlikely to be generalizable to other peoples or countries.

What is the effect of replacing 5% SFA in the diet of adults with protein from plants?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	2466/40 319 (6.1%)	RR 0.83 (0.61 to 1.12)	10 fewer per 1000 (from 24 fewer to 7 more)	⊕ VERY LOW

CHD: coronary heart disease; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

Explanations

a. Data from only one or two studies are unlikely to be generalizable to other peoples or countries.
b. CIs contain both a null and strong effect.

What is the effect of replacing 5% SFA in the diet of adults with wholegrains or low glycaemic index CHO?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
7	observational studies	not serious	not serious	not serious	not serious	dose response gradient	12 641/225 278 (5.6%)	RR 0.94 (0.89 to 0.99)	3 fewer per 1000 (from 6 fewer to 1 fewer)	⊕⊕⊕ MODERATE

CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; RR: relative risk; SFA: saturated fatty acids.

What is the effect of replacing 2% TFA in the diet of adults with PUFA?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
TYPE 2 DIABETES										
2	observational studies	serious [a]	serious [b]	not serious	not serious	dose response gradient	20 949/295 726 (7.1%)	RR 0.72 (0.52 to 0.99)	20 fewer per 1000 (from 34 fewer to 1 fewer)	⨁ VERY LOW

CI: confidence interval; PUFA: polyunsaturated fatty acids; RR: relative risk; TFA: *trans*-fatty acids.

Explanations

a. Data from only one or two cohorts are unlikely to be generalizable to other people or cohorts.
b. Initial heterogeneity was high.

What is the effect of replacing 2% TFA in the diet of adults with CHO?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
TYPE 2 DIABETES										
2	observational studies	serious [a]	not serious	not serious	not serious	dose response gradient	3604/106 543 (3.4%)	RR 0.71 (0.60 to 0.84)	10 fewer per 1000 (from 14 fewer to 5 fewer)	⨁⨁ LOW

CHO: carbohydrates; CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Explanations

a. Data from only one or two cohorts are unlikely to be generalizable to other people or countries.

What is the effect of replacing 2% TFA in the diet of adults with SFA?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
2	observational studies	serious [a]	serious [b]	not serious	not serious	none	46 625/647 353 (7.2%)	RR 0.92 (0.82 to 1.03)	6 fewer per 1000 (from 13 fewer to 2 more)	⨁ VERY LOW
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	not serious	none	7667/127 536 (6.0%)	RR 0.97 (0.86 to 1.09)	2 fewer per 1000 (from 8 fewer to 5 more)	⨁ VERY LOW
CVD INCIDENCE										
2	observational studies	serious [a]	serious [b]	not serious	not serious	none	46 625/64 7353 (7.2%)	RR 0.93 (0.83 to 1.04)	5 fewer per 1000 (from 12 fewer to 3 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; SFA: saturated fatty acids; TFA: *trans*-fatty acids.

Explanations

a. Data from only one or two cohorts are unlikely to be generalizable to other people or countries.
b. Initial heterogeneity was high.

What is the effect of replacing 2% TFA in the diet of adults with MUFA from animals?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	serious [b]	none	4419/93 384 (4.7%)	RR 0.89 (0.78 to 1.03)	5 fewer per 1000 (from 10 fewer to 1 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; MUFA: monounsaturated fatty acids; RR: relative risk; TFA: *trans*-fatty acids.

Explanations

a. Data from only one or two studies are unlikely to be generalizable to other peoples or countries.
b. CIs contain both a null and strong effect.

What is the effect of replacing 2% TFA in the diet of adults with MUFA from plants?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
ALL-CAUSE MORTALITY										
2	observational studies	serious [a]	not serious	not serious	not serious	dose response gradient	41 344/93 378 (44.3%)	RR 0.90 (0.85 to 0.96)	44 fewer per 1000 (from 66 fewer to 18 fewer)	⨁⨁ LOW
CHD INCIDENCE										
2	observational studies	serious [a]	not serious	not serious	not serious	dose response gradient	4419/93 384 (4.7%)	RR 0.80 (0.70 to 0.92)	9 fewer per 1000 (from 14 fewer to 4 fewer)	⨁⨁ LOW
CVD INCIDENCE										
2	observational studies	serious [a]	serious b	not serious	serious [c]	none	4588/93 378 (4.9%)	RR 0.97 (0.71 to 1.32)	1 fewer per 1000 (from 14 fewer to 16 more)	⨁ VERY LOW

CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; MUFA: monounsaturated fatty acids; RR: relative risk; TFA: *trans*-fatty acids.

Explanations

a. Data from only one or two cohorts are unlikely to be generalizable to other peoples or countries.
b. Initial heterogeneity was high.
c. CIs contain both a null and strong effect.

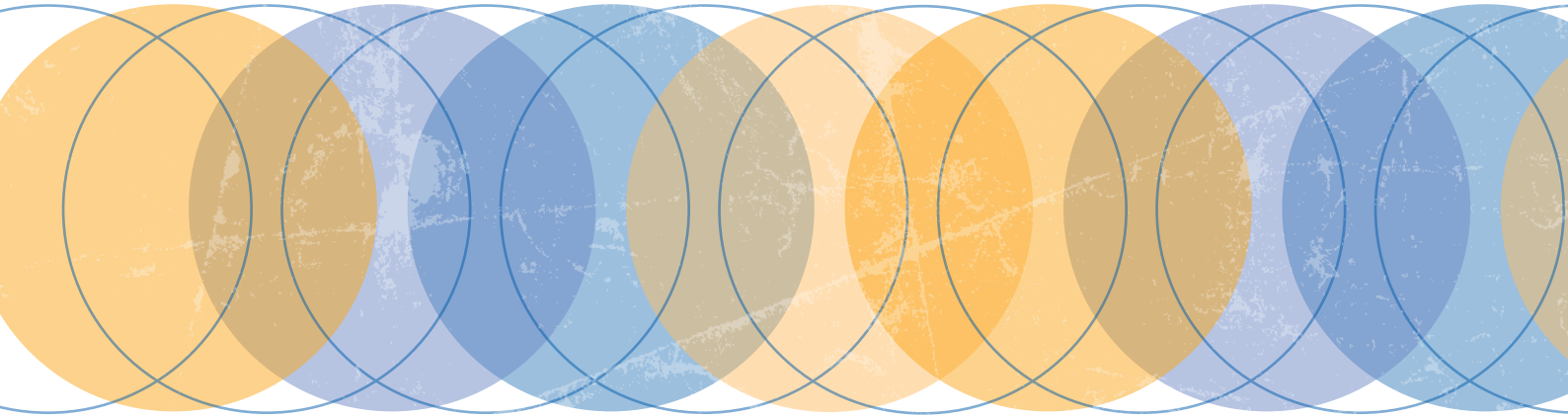
What is the effect of replacing 2% TFA in the diet of adults with refined CHO and sugar?

CERTAINTY ASSESSMENT							Nº OF PATIENTS	EFFECT		CERTAINTY
Nº OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS		RELATIVE (95% CI)	ABSOLUTE (95% CI)	
CHD INCIDENCE										
2	observational studies	serious [a]	serious [b]	not serious	not serious	none	7667/127 536 (6.0%)	RR 0.95 (0.80 to 1.13)	3 fewer per 1000 (from 12 fewer to 8 more)	⨁ VERY LOW

CHD: coronary heart disease; CHO: carbohydrates; CI: confidence interval; RR: relative risk; TFA: *trans*-fatty acids.

Explanations

a. Data from only one or two studies are unlikely to be generalizable to other peoples or countries.
b. Initial heterogeneity was high.



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