# Saturated fat substitution

No. 2023/02Fe, The Hague, February 7, 2023

Background document to the advisory report:
Dutch dietary guidelines for people with atherosclerotic cardiovascular disease
No. 2023/02e, The Hague, February 7, 2023

Health Council of the Netherlands

# Contents

# 1 Introduction

This background document belongs to the advisory report on *Dutch dietary guidelines for people with atherosclerotic cardiovascular disease* (ASCVD).[1] It describes the methodology for the search, selection and evaluation of the literature regarding the relationship between substitutions of saturated fatty acid (SFA) with other macronutrients and health outcomes in people with ASCVD. It also describes the scientific evidence on this topic and the conclusions that have been drawn by the Health Council's Committee on Nutrition.

## 1.1 Saturated fat recommendation and intake in the Netherlands

The Health Council of the Netherlands recommends that the adult population derives at least 20% up to 40% of total energy intake (en%) from the diet out of fat, of which the energy intake out of saturated fat should be as low as possible and not rise above 10 en%.[2] The average saturated fat intake of the Dutch adult population is 13 en% according to the most recent *Dutch National Food Consumption Survey*.[3] There are no Health Council recommendations regarding saturated fat intake for people with ASCVD.

# 2 Methodology

## 2.1 Questions

The Committee aimed to answer the following question: What is the relationship (effect or association) between substitution of SFA with subtypes of other fats, protein or carbohydrate and health outcomes in people with ASCVD?

## 2.2 Definition of substitution

Given that the effects of substitution could differ depending on whether SFA would be substituted with (subgroups of) other fats, carbohydrates or protein, the Committee separated evidence of studies that substituted 1) SFA with other fats, 2) SFA with carbohydrate and 3) SFA with protein, where possible. The Committee preferred to further evaluate substitutions of SFA with subgroups of fat (e.g. monounsaturated fatty acid [MUFA], polyunsaturated fatty acid [PUFA]) and protein (e.g. derived from animal versus vegetable sources). However, such distinctions could only be made for PUFA since there were too few studies available for MUFA, and no studies in which substitution with proteins or carbohydrates were the focus.

In observational cohort studies with dietary intake assessed once at baseline, actual substitution of macronutrients cannot be observed. Here, the Committee further explains this using SFA-PUFA substitutions as an example. For such substitutions, people with relatively low SFA intakes and high PUFA intakes are compared to people with relatively high intakes of SFA and low PUFA intakes, using multivariable statistical models. The results of such comparisons are then often interpreted as substitutions of SFA with PUFA. However, the Committee stresses this is an interpretational step, and it is a comparison of people consuming high amounts of PUFA with people consuming high amounts of SFA.

## 2.3 Target group

The target group of the current advisory report is people with ASCVD. The Committee defines this group as people with clinically established coronary heart disease (CHD, consisting of acute coronary syndromes [myocardial infarction and unstable angina], stable angina and revascularisation procedures such as percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]), peripheral arterial disease (PAD) or cerebrovascular disease (consisting of stroke and transient ischemic attack). In the target population, atherosclerosis in the coronary arteries, aorta, iliac and femoral arteries, and cerebral arteries is the main underlying pathological process. Groups with a high risk (but no manifestation) of ASCVD, such as people with

hypertension or elevated LDL cholesterol levels, fall outside this definition. Also, the target group of this advice does not include people with heart failure (except when those people also suffer from ASCVD). A detailed description of the target group of this advisory report is provided in the background document *Methodology for the evaluation of the evidence*.[4]

In the present background document, the Committee also considered studies performed in people with cardiovascular disease (CVD) in general (not further specified) because it assumes that the majority of this population will have ASCVD.

## 2.4 Health outcomes

The Committee selected the following health outcomes for this advisory report (further explained in the background document *Methodology for the evaluation of the evidence*[4]):

- surrogate outcomes:
  - body weight
  - systolic blood pressure
  - low-density lipoprotein (LDL) cholesterol
  - estimated glomerular filtration rate (eGFR)
  - glycated haemoglobin (HbA1c) and fasting blood glucose
- long-term health outcomes:
  - all-cause mortality
  - morbidity and/or mortality from total CVD, CHD, stroke (cerebrovascular disease), heart failure, atrial fibrillation, type 2 diabetes, chronic obstructive pulmonary diseases (COPD), total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression
  - subtypes of CHD, such as myocardial infarction, angina pectoris and revascularisation procedures (i.e., coronary artery bypass surgery and percutaneous coronary intervention)

For cohort studies, the Committee included only studies in the above-described category named long-term health outcomes.

## 2.5 Selection and evaluation of the literature and drawing conclusions

### 2.5.1 Search and selection of studies

The Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs) and pooled analyses, of randomised

controlled trials (RCTs) and/or prospective cohort studies examining the relationship of SFA substitution with other fats, carbohydrate or protein with above-described health outcomes in people with ASCVD. To identify such publications, the Committee searched PubMed and Scopus in November 2021. The search strategy and specification of the study selection are presented in Annex A.

The Committee found 2 MAs that included 6 RCTs, by Schwingshackl & Hoffmann (2014)[5] and Hooper et al. (2020)[6], and one MA that included 4 RCTs, by Mozaffarian et al. (2010)[7], on SFA-PUFA substitution in people with ASCVD. The included RCTs entirely overlapped between the MAs, but the reported health outcomes differed (to some extent) between the MAs. The MA reports originally included studies in both people with and without ASCVD, but only RCTs performed in people with ASCVD were used for the Committee's evaluation. The Committee obtained pooled estimates of the 6 RCTs from the MA report by Schwingshackl & Hoffmann (2014)[5] for the outcomes of all-cause mortality and CVD mortality, CVD events and MI. For the CHD events outcome, and for additional analyses excluding specific studies (for all outcomes), the Committee itself pooled estimates from the individual studies reported in one or multiple of the MA reports. A random effects approach was used for the MAs.
The MA by Hooper et al. also reported on effects of substitution with other macronutrients. For people with ASCVD, one RCT on substitution of SFA with MUFA was found to be use for the Committee's evaluation. No RCTs in which substitution of SFA with proteins or carbohydrates was the main focus were found.

The 6 RCTs that were evaluated for the current advisory report were also included as part of the evaluation of studies for the advisory report *Dutch Dietary Guidelines 2015* (DDG2015).[2] In the *DDG2015* evaluation, RCTs performed in people with and without ASCVD were combined, with a large share of studies performed in people with ASCVD. The current evaluation focuses specifically on the studies in people with ASCVD. However, it should be noted there is a large amount of overlap.

**Literature search individual RCTs**
The most recent MA, by Hooper et al. (2020),[6] searched for studies published up to October 2019. The Committee additionally searched for individual RCTs that mainly focused on substitution of SFA with other macronutrients published after 2019, in March 2022. The search yielded 571 hits, of which 3 were selected based on title and abstract. All were excluded after full text screening since the studies addressed a dietary exposure or outcome outside the inclusion criteria of the Committee.

**Literature search individual prospective cohort studies**

The Committee was aware of 2 relevant prospective cohort studies via its network and via the search for SRs and MAs. These were the publications by Mölenberg et al. (2017)[8] and Puaschitz et al. (2015).[9] The reference lists of these publications and articles that cited these publications were checked, which yielded one more prospective cohort study, namely that of Pertiwi et al. (2020).[10] The studies addressed substitutions of SFA with unsaturated fatty acids (2 studies) in relation to the outcomes type 2 diabetes (1 study) and mortality due to CVD and CHD (1 study). Furthermore, one study addressed the association of SFA in general (without specified substitution) in relation to all-cause mortality and coronary events.

The Committee additionally searched for individual cohort studies published after 2019, in January 2022. The search strategy and specification of the study selection are presented in Annex A. The search yielded 716 hits, of which 48 were selected based on title and abstract. None of the studies were selected after full-text screening.

To sum up, the Committee found six RCTs and three prospective cohort studies that were relevant for its evaluation. These studies are described in the next chapter.

### 2.5.2 Drawing conclusions

A detailed description of the approach used for drawing conclusions is provided in the background document *Methodology for the evaluation of the evidence*.[4] In short, the Committee drew conclusions on (the certainty of) the evidence regarding the associations between SFA substitution and the risk of health outcomes in people with ASCVD, based on the number of studies, the number of participants and the number of cases which contributed to the evaluation. Also, it took the quality of the studies, in particular the risk of bias, and the heterogeneity between studies into account. The Committee used the decision tree (presented in the background document *Methodology for the evaluation of the evidence*[4]) as a tool to support consistency in drawing conclusions.

# 3 Effects and associations of saturated fat substitution

In this chapter the Committee describes the scientific evidence for effects and associations of SFA substitution with health outcomes in people with ASCVD.

## 3.1 RCTs

### 3.1.1 SFA – PUFA substitution

Table 1 summarises the results and characteristics of the RCTs presented in the MAs by Hooper et al. (2020),[6] Schwingshackl & Hoffmann (2014)[5] and Mozaffarian et al. (2010),[7] which provided evidence regarding the effect of SFA substitution with PUFA on long-term health outcomes in men with CHD.

**Table 1** The effects of saturated fat substitution with PUFA on health outcomes in men with CHD: meta-analyses of RCTs

| Aspect | Explanation |
|---|---|
| Number of studies | 6 RCTs performed in people with CHD were identified from 3 MA reports[a] |
| Number of participants and cases in the intervention group (i) and control group (c) | Total number of participants: 3405<br>Total number of cases:<br>All-cause mortality: i: 225, c: 231<br>CVD mortality: i: 203, c: 200<br>CVD events[b]: i: 308, c: 342<br>CHD mortality: i: 199, c: 196<br>CHD events[c]: i: 283, c: 323<br>MI: i: 149, c: 168<br>Non-fatal MI: i: 148, c: 168<br>Stroke: i: 4, c: 2 |
| Study design (number of RCTs) | Factorial (1), parallel (5) |
| Study duration | 1 to 6 years |
| Diet of intervention | Advised[d] increased mean intake of 6.0 en% of PUFA. Substituted for SFA.[e] |
| Strength of the effect:<br>Pooled RR (95% CI) and heterogeneity ($I^2$).<br><br>Based on:<br>(1) The pooled estimate of all 6 RCTs; | ALL-CAUSE MORTALITY<br>(1) 0.99 (0.75, 1.29), $I^2$ =44%<br>(2) 0.90 (0.75, 1.08), $I^2$ =13%<br><br>CVD MORTALITY<br>(1) 1.05 (0.76, 1.44), $I^2$ =51%<br>(2) 0.93 (0.75, 1.14), $I^2$ =22% |

| | |
|---|---|
| (2) The pooled estimate excluding the SDHS (thus 5 RCTs). | CVD EVENTS<br>(1) 0.93 (0.72, 1.19), $I^2$ =61%<br>(2) 0.85 (0.73, 0.97), $I^2$ =34%<br><br>CHD MORTALITY*<br>(1) 1.05 (0.77, 1.41), $I^2$ =52%<br>(2) 0.93 (0.58, 1.13), $I^2$ =25%<br><br>CHD EVENTS<br>(1) 0.99 (0.73, 1.34), $I^2$ =59%<br>(2) 0.86 (0.74, 1.00), $I^2$ =27%<br><br>MI<br>(1) 0.91 (0.65, 1.29), $I^2$ =54%<br>(2) 0.78 (0.60, 1.00), $I^2$ =0%<br><br>NON-FATAL MI*<br>(1) 0.84 (0.64, 1.09), $I^2$ =0%<br><br>*For the outcomes stroke (3 studies), non-fatal MI (4 studies) and CHD mortality (5 studies) effect estimates were presented in only a selection of the RCTs. For the stroke outcome there were too little cases to present a pooled estimate.<br>The risk estimates per RCT are presented in Annex B. |
| Study population | Adults with CHD; BMI: 23.6-29.1 kg/m$^2$; men (100%); use of medication: NR; UK, Europe (Norway), Australia. |

Abbreviations: BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; en: energy; MA: meta-analysis; MI: myocardial infarction; NR: not reported; PUFA: polyunsaturated fatty acid; RCT: randomised controlled trial; RR: relative risk; SDHS: Sydney Diet Heart Study; SFA: saturated fatty acid; UK: United Kingdom.

Footnotes:

[a] The pooled effects of the 6 RCTs, and an additional pooled effect based on 5 RCTs, were abstracted from the MA reports or, in case these pooled effects were not reported in any of the MA reports, calculated by the Committee based on the effects reported for the individual studies.

[b] CVD events include myocardial infarction or stroke.

[c] CHD events include myocardial infarction, CHD death and/or sudden death.

[d] With exception of the Rose-corn/ Rose-olive trial,[11] which provided besides dietary advice 80 g/d olive oil or corn oil in the intervention arms.

[e] The diets of the intervention groups and control groups are further explained in Annex B.

**Conclusions:**
**Intervention studies show that advising substitution of 6 en% SFA with PUFA has likely no effect on the risk of all-cause mortality and CVD mortality in men with CHD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1 Number of studies and cases:
There are 6 RCTs that addressed the effect of SFA substitution with PUFA on the risks of all-cause mortality and CVD mortality. In total, there were >150 participants in the intervention groups and >100 cases in these studies. This is the first step required to mark the evidence as strong (for which at least 5 studies are needed, 150 participants in the intervention groups and 100 cases).

2 Heterogeneity of the study findings and considerations regarding the quality of the evidence:
The pooled estimates of 6 studies showed no statistically significant effects on all-cause mortality and CVD mortality when 6 en% of SFA was substituted with PUFA, with moderate to high heterogeneity between studies ($I^2$=44% and 51%, respectively). The Committee has serious concerns about one of the included RCTs (Sydney Diet Heart Study (SDHS)[12,13]), for which the margarine that was given to the intervention group may have been high in trans fatty acids (TFA). Also, this study had a high and unexplained loss-to-follow-up and it is unsure whether lifestyle factors of study participants were equally distributed. Therefore, the Committee decided to base its conclusion on the remaining 5 RCTs, thereby discarding the results of the SDHS. The effects on all-cause mortality and CVD mortality remained non-significant after excluding the SDHS.

3 After excluding the SDHS, little to moderate heterogeneity ($I^2$=13% for all-cause mortality and $I^2$=22% for CVD mortality) remained between the studies. The remaining heterogeneity may to some extent be due to variation between studies in the dietary advice that was given and the type of PUFA that was advised (n-6 PUFA, plant-based n-3 PUFA and/or marine PUFA). It is not expected these variations in diet contributed to the lack of effect since there was no substantial heterogeneity.

4 Generalisability:
The Committee has the following considerations regarding the generalisability of the study findings: (A) The studies only included men, possibly limiting

generalisability to women. The advisory report of the *DDG2015* included 2 MAs, which both included a RCT that included women for the effect of SFA-PUFA substitution on CVD outcomes. These studies found no different findings for women compared to men.[14,15] Therefore, the Committee does not expect the effect would be different for women. Moreover, RCTs into the effects of SFA on LDL cholesterol, performed in both men and women of the general population, showed no indications for differences in effects between men and women.[16] (B) The medical treatment guidelines of CHD have changed since the RCTs were performed (1965-1992). For instance, currently the use of statins and beta-blockers are part of the regular treatment. The Committee expects use of such medication might attenuate potential health effects of dietary interventions.[17] However, the lack of effect of SFA-PUFA substitution on all-cause mortality and CVD mortality is expected to be also present in a population with a high background use of lipid- and blood pressure-lowering medication. (C) All but one of the included RCTs provided dietary advice, which increases generalisability to dietary recommendations, but likely underestimated the real effect due to noncompliance.

**There is too little research from intervention studies to draw a conclusion on the effect of advising substitution of 6 en% SFA with PUFA on the risk of CHD mortality in men with CHD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1 Number of studies and cases:
There are 5 RCTs that addressed the effect of SFA substitution with PUFA on CHD mortality. In total, there were >150 participants in the intervention groups and >100 cases in these studies. This is the first step required to mark the evidence as strong (for which at least 5 studies are needed, 150 participants in the intervention groups and 100 cases). However, there were other considerations to conclude there is too little research to draw a conclusion.

2 Heterogeneity of the study findings and considerations regarding the quality of the evidence:
The pooled estimates of 5 studies showed no statistically significant effects on CHD mortality when 6 en% of SFA was substituted with PUFA, with high heterogeneity ($I^2$=52%) between studies. The Committee has serious concerns about one of the included RCTs (SDHS[12,13]), for which the margarine that was given to the intervention group may have been high in TFA. Also, this study had a

high and unexplained loss-to-follow-up and it is unsure whether lifestyle factors of study participants were equally distributed. Therefore, the Committee decided to base its conclusion on the remaining 4 RCTs, thereby discarding the results of the SDHS. The effects on CHD mortality remained non-significant after excluding the SDHS. However, this excludes a conclusion of 'an effect is unlikely', for which at least 5 studies are required.

3 After excluding the SDHS, moderate heterogeneity remained between the studies ($I^2$=25%*)*. The remaining heterogeneity may to some extent be due to variation between studies in the dietary advice that was given and the type of PUFA that was advised (n-6 PUFA, plant-based n-3 PUFA or marine PUFA). It is not expected these variations in diet contributed to the lack of effect since there was no substantial heterogeneity.

4 Generalisability:
The Committee has the following considerations regarding the generalisability of the study findings: (A) The studies only included men, possibly limiting generalisability to women. The advisory report of the *DDG2015* included 2 MAs which both included a RCT that included women for the effect on SFA-PUFA substitution on CVD outcomes. These studies found no different findings for women compared to men.[14,15] Therefore, the Committee does not expect the effect would be different for women. Moreover, RCTs into the effects of SFA on LDL cholesterol, performed in both men and women of the general population, showed no indications for differences in effects between men and women.[16] (B) The medical treatment guidelines of CHD have changed since the RCTs were performed (1965-1992). For instance, currently the use of statins and beta-blockers are part of the regular treatment options. The Committee expects use of such medication might attenuate potential health effects of dietary interventions.[17] However, the lack of effect of SFA-PUFA substitution on CHD mortality is expected to be also present in a population with a high background use of lipid- and blood pressure-lowering medication. (C) All but one of the included RCTs provided dietary advice, which increases generalisability to dietary recommendations, but likely underestimated the real effect due to noncompliance.

**Intervention studies show that advising substitution of 6 en% SFA with PUFA reduces the risk of events of CVD, CHD and MI with approximately 15% (for CVD and CHD) to 20% (for MI) in men with CHD. The evidence is strong.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1 Number of studies and cases:
There are 6 RCTs that addressed the effect of SFA substitution with PUFA on the risks of events of CVD, CHD or MI. In total, there were >150 participants in the intervention groups and >100 cases in these studies. This is the first step required to mark the evidence as strong (for which at least 5 studies are needed, 150 participants in the intervention groups and 100 cases).

2 Heterogeneity of the study findings and considerations regarding the quality of the evidence:
The pooled estimates of 6 studies showed no statistically significant effects on events of CVD, CHD and MI when 6 en% of SFA was substituted with PUFA, with moderate to high heterogeneity between studies ($I^2$=61%, 59% and 54%, respectively). The Committee has serious concerns about one of the included RCTs (SDHS[12,13]), for which the margarine that was given to the intervention group may have been high in TFA. Also, this study had a high and unexplained loss-to-follow-up and it is unsure whether lifestyle factors of study participants were equally distributed. Therefore, the Committee decided to base its conclusion on the remaining 5 RCTs, thereby discarding the results of the SDHS. Based on these 5 RCTs, there were (borderline for CVD events and CHD events) statistically significant reduced risks.

3 After excluding the SDHS, no to moderate heterogeneity remained between the studies ($I^2$=34%, 27% and 0% for CVD, CHD and MI, respectively). The remaining heterogeneity may to some extent be due to variation between studies in the dietary advice that was given and the type of PUFA that was advised (n-6 PUFA, plant-based n-3 PUFA and/or marine PUFA).

4 Generalisability:
The Committee has the following considerations regarding the generalisability of the study findings: (A) The observed effects on CVD events are likely explained by effects on coronary events since the majority of events were due to CHD and the reported effects on CVD events and CHD events were very similar. (B) The studies only included men, possibly limiting generalisability to women. The advisory report of the *DDG2015* included 2 MAs which both included a RCT that included women for the effect of SFA-PUFA substitution on CVD outcomes. These studies found no substantially different findings for women compared to men.[14,15] Moreover, RCTs into the effects of SFA on LDL cholesterol, performed in both

men and women of the general population, showed no indications for differences in effects between men and women.[16] Therefore, the Committee does not expect the effect would be different for women. (C) The medical treatment guidelines for CHD have changed since the RCTs were performed (1965-1992). For instance, currently the use of statins and beta-blockers are part of the regular treatment options. The Committee expects use of such medication might attenuate potential health effects of dietary interventions.[17] The observed effects of SFA-PUFA substitution might therefore be weaker in populations with a high background use of lipid- and blood pressure-lowering medication. However, there are currently no RCTs into SFA-PUFA substitution in users of lipid- and blood pressure-lowering medication that could support such an expectation. A cohort study showed that SFA-PUFA substitution associated with less CVD-related outcomes in people with a previous MI and high use of lipid- and blood pressure-lowering medication.[8] Although one such study provides too little evidence to base conclusions on, it suggests the effects may still be visible on top of such medication use. (D) All but one of the included RCTs provided dietary advice, which increases generalisability to dietary recommendations, but likely underestimated the real effect due to noncompliance.

**There is too little research from intervention studies to draw a conclusion on the effect of SFA substitution with PUFA on the risk of non-fatal MI in people with ASCVD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1 Number of studies and cases:
There are 4 RCTs that addressed the effect of SFA substitution with PUFA on non-fatal MI. In total, there were >150 participants in the intervention groups and >100 cases in these studies. This excludes a conclusion with strong evidence, for which >5 studies are required, including the conclusion of ‘an effect is unlikely’ or ‘evidence is inconclusive’.

2 Heterogeneity of the study findings, and considerations regarding the quality of the evidence:
The pooled estimates of 4 studies showed no statistically significant effects on non-fatal MI when 6 en% of SFA was substituted with PUFA, with no heterogeneity between studies.

3 Generalisability:
The Committee has the following considerations regarding the generalisability of the study findings: (A) The studies only included men, possibly limiting generalisability to women. The advisory report of the DDG-2015 included 2 MAs which both included a RCT that included women for the SFA-PUFA substitution on CVD outcomes. These studies found no substantially different findings for women compared to men.[14,15] Moreover, RCTs into the effects of SFA on LDL cholesterol, performed in both men and women of the general population, showed no indications for differences in effects between men and women.[16] Therefore, the Committee does not expect the effect would be different for women. (B) The medical treatment guidelines of CHD have changed since the RCTs were performed (1965-1992). For instance, currently the use of statins and beta-blockers are part of the regular treatment options. The Committee expects use of such medication might attenuate potential health effects of dietary interventions.[17] However, the lack of effect of SFA-PUFA substitution on non-fatal MI is expected to be also present in a population with a high background use of lipid- and blood-pressure lowering medication. (C) All but one of the included RCTs provided dietary advice, which increases generalisability to dietary recommendations, but likely underestimated the real effect due to noncompliance.

**There is too little research from intervention studies to draw conclusions regarding the effect of SFA substitution with PUFA on the risk of stroke in people with ASCVD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:
There are three RCTs with six cases in total that addressed the effect of SFA substitution with PUFA on the risk of stroke. These are too few cases to base conclusions on.

**Regarding subtypes of ASCVD:**
The evidence that contributed to the above given conclusions is entirely driven by studies performed in people with CHD, and beneficial effects of SFA-PUFA substitution were found for CHD outcomes. The effects on stroke could not be properly evaluated, since there were only a few stroke cases in the 3 RCTs that reported on stroke outcomes (Supplemental Table 2 in Annex B). Moreover, studies performed specifically in people with stroke or PAD were not found. The Committee sees no reason to believe the effects on CHD outcomes would be different in people with stroke or PAD. The Committee notes that people with stroke may be in particular at risk for developing a

subsequent stroke,[18] and based on the current evidence no conclusions can be drawn on whether SFA-PUFA substitution would influence that risk.

**Explanation of the studies that contributed to the conclusions:**
The Committee found three MAs that together reported on six RCTs on SFA-PUFA substitution in people with ASCVD. The findings based on these six RCTs are described in brief below, as well as assessments of bias and quality of the evidence. Detailed information regarding the individual RCTs, and in particular the diets advised to the intervention and control groups, are provided in Annex B.

The studies evaluated a substitution of, on average, 6 en% SFA with PUFA in men with existing CHD. All but one study were of dietary advice (thus not providing diets to participants). Mean SFA intake was 10.7 en% (range 8.5-14 en%) in the intervention groups and 16.4 en% (range 13.5-26.4 en%) in the control groups. Mean PUFA intake was 14.9 en% (range 8.7-20.7 en%) in the intervention groups and 6.6 en% (range 4.4-8.9 en%) in the control groups. The pooled analyses showed no effect of SFA-PUFA substitution on all evaluated health outcomes (all-cause mortality, CVD mortality, CVD events, CHD events, MI), with a moderate to high amount of heterogeneity. After excluding the SDHS[12,13], heterogeneity substantially reduced, and (borderline) statistically significant reduced risks for CVD, CHD and MI events were found. No effects on all-cause mortality and CVD mortality were found.

It is worth noting that the composition of the advised diets to the intervention groups and control groups varied between studies, which may have contributed to the heterogeneity. For instance, 2 studies (Rose et al. and Woodhill et al.) replaced SFA solely with n-6 PUFA and generally found (a tendency towards) unfavourable health effects, whereas the remaining RCTs replaced SFA with a mix of n-6 and n-3 (mostly both plant and marine based) PUFA and generally reported favourable or neutral health effects. The study by Rose et al. was likely too small to cause substantial heterogeneity. The study by Woodhill et al. caused substantial heterogeneity, but possibly (also) because of other concerns. This is further explained in the next paragraph. Furthermore, the RCT of Leren et al. (1970)[19] provided, in addition to the main advice to consume soybean oil, sardines to the intervention group, so that observed benefits may be at least partly related to marine n-3 PUFA rather than total PUFA consumption. The results of this RCT are generally in line with the majority of other RCTs, though slightly stronger.

As stated above, particularly a large extent of the heterogeneity can be explained by the SDHS (RCT of Woodhill et al. (1978)[12,13]). As described in the background

document of the advisory report of the *DDG2015*[2]*,* there are some serious concerns about the RCT by Woodhill et al. (1978), which are shared by the Committee. First, the intervention group consumed margarine with safflower oil. At that time, margarines were generally high in TFA. Therefore, a high intake of TFA in the intervention group can possibly explain part of the harmful health effects observed in the RCT. Second, approximately 2/3rd of study participants was lost to follow up during the study duration. The original publication gave no information regarding the reason why these participants were lost to follow up. Last, the authors stated that their study may not have been adequate to test the effect of SFA substitution with PUFA, since the intervention coincided with other changes in lifestyle factors as smoking, weight loss and physical activity. The authors did not provide an overview of such risk factors in the SDHS study population, and therefore it is not known whether there were inequalities in these factors between groups, despite the randomisation. In line with the approach taken for the *DDG2015*, the Committee discarded the results of the SDHS when drawing conclusions.

Schwingshackl & Hoffmann (2014)[5] reported that some of the studies included in the MAs provided limited information on the quality of their respective setup. Possibly this has to do with the fact that the publications of the studies date back to more than 50 years ago. Schwingshackl & Hoffmann graded the overall quality of evidence using GRADE as moderate. This judgement was not further explained. Studies were also assessed for methodological quality by using the risk of bias assessment tool of the Cochrane Collaboration. Selective reporting (reporting bias) was overall rated as 'low risk of bias' and blinding of participants and personnel (performance bias) as 'high risk of bias'. This is likely due to the fact that all RCTs were single-blinded, which raises the possibility of a possible overestimated benefit of the intervention. Random sequence generation (selection bias), allocation concealment (selection bias) and incomplete outcome data (attrition bias) were overall rated as 'moderate risk of bias'. Furthermore, the authors noted that the examination of funnel plots showed little to moderate asymmetry suggesting that publication bias cannot be completely excluded as a confounder of the MA.

Mozaffarian et al. (2010)[7] judged the overall quality of the studies using the validated Jadad scale, which includes criteria related to randomisation, blinding, and withdrawal and dropouts. On the scale from 0 (lowest quality score) to 5 (highest quality score), the overall quality was rated as moderate with all studies having a score of 2. This was in particular due to the fact that all RCTs were single-blinded. This raises the possibility of a possible overestimated benefit of the intervention. This is in line with the quality judgement of Schwingshackl & Hoffmann.

No notable funding sources or conflicts of interests were reported in the studies besides in the study by Watts et al. (1992; STARS). This RCT was partially financed by Unilever. The involvement of the sponsor was not reported and therefore the impact on the study findings remains unclear. Conflicts of interest were generally not reported in the RCT reports, except for the SDHS, where no notable conflicts of interest were reported.

### 3.1.2 SFA – MUFA substitution

**Conclusion:**
**There is too little research from cohort studies to draw conclusions regarding the effect of SFA substitution with MUFA on the risk of long-term health outcomes in people with ASCVD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:
There is one RCT that addressed the effect of SFA substitution with MUFA on the risk of long-term health outcomes. One study provides too little evidence to base conclusions on (according to the decision tree).

**Explanation:**
Only one RCT was found and therefore it is only described in short, since one study provides too little evidence to base conclusions on.

Rose et al. (1965)[11] examined the effects of a restricted fat diet in combination with a 80 g/d olive oil supplement versus usual health care in a small-scale RCT of 52 men with CHD, for 2 years. The RCT included 2 intervention arms, of which one was high in PUFA (corn oil) and the other high in MUFA (olive oil). The comparison with the PUFA arm was used for the evaluation of SFA-PUFA substitution. The comparison with the MUFA arm was used for the current evaluation of SFA-MUFA substitution. Details about the intervention and control diet are given in Annex B. Average SFA and MUFA intakes of the study population were not reported. The RCT only reported the number of cases in the intervention group and control group per health outcome. No risk estimates were reported. Risk estimates were retrieved from the MA by Hooper et al. (2020).[6] No effects were found on all-cause mortality, CVD mortality, CVD events, CHD mortality, CHD events, MI or non-fatal MI.
The involvement of the sponsor was not reported and therefore the impact on the study findings remains unclear. Conflicts of interest of the authors were not reported.

## 3.2 Prospective cohort studies

### 3.2.2 SFA – unsaturated fatty acid substitution

**Conclusion:**
**There is too little research from cohort studies to draw conclusions regarding the association between SFA substitution with total unsaturated fatty acids, PUFA and MUFA and the risk of CVD mortality and CHD mortality in people who survived a MI.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:
There is one prospective cohort study that addressed the associations between SFA substitution with total unsaturated fatty acids (UFA), PUFA and MUFA and the risk of CVD mortality and CHD mortality. One study provides too little evidence to base conclusions on.

**Explanation:**
Only one prospective cohort study was found and therefore it is only described in short, since one study provides too little evidence to base conclusions on.

The study by Mölenberg et al. (2017)[8] reported on associations between 5 en% isocaloric replacement of SFA with total UFA, PUFA or cis-MUFA and cardiovascular mortality outcomes in 4146 people with a previous MI from the Alpha Omega Cohort. The follow-up was 7 years. For the CVD mortality outcome, the authors reported a 31% risk reduction (95% CI 0.55, 0.87) for SFA-UFA replacement, a 35% risk reduction (95% CI 0.48, 0.97) for SFA-PUFA replacement and a 26% risk reduction (95% CI 0.56, 0.97) for SFA-cisMUFA replacement. For the CHD mortality outcome, the authors reported a 40% risk reduction (95% CI 0.45, 0.80) for SFA-UFA replacement, a 49% risk reduction (95% CI 0.35, 0.73) for SFA-PUFA replacement and a 32% risk reduction (95% CI 0.48, 0.96) for SFA-cisMUFA replacement. The associations were adjusted for total energy intake, intake of TFA, protein, carbohydrates, MUFA (in PUFA analyses) or PUFA (in cis-MUFA analyses), age, sex, Alpha Omega treatment code, body mass index (BMI), prevalent diabetes, anti-thrombotic drugs, anti-hypertensive drugs, lipid-lowering drugs, level of education, smoking status, alcohol intake, physical activity, dietary cholesterol and dietary fibre. Dietary data was collected by a biomarker-validated food frequency questionnaire (FFQ). Participants consumed on average 17.5% of energy of total UFA and 13.0% of energy of SFA.

No notable funding sources were reported. In addition, none of the authors had any conflicts of financial or personal interest with the financial sponsor of this research.

**Conclusion:**
**There is too little research from cohort studies to draw conclusions regarding the association between SFA substitution with linoleic acid and the risk of type 2 diabetes in people with ASCVD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:
There is one prospective cohort study that addressed associations of SFA substitution with linoleic acid (LA) and the risk of type 2 diabetes. One study provides too little evidence to base conclusions on.

**Explanation:**
Only one prospective cohort study was found and therefore it is only described in short, since one study provides too little evidence to base conclusions on.

The study by Pertiwi et al. (2020)[10] found no association between substitution of SFA with LA and the risk of type 2 diabetes in 3257 people with a previous MI from the Alpha Omega Cohort (hazard ratio (95% CI) per 5 en% 1.18 (0.59, 2.35)). Participants were followed up for a median of 3.5 years. The associations were adjusted for total energy intake, protein, carbohydrates, n-3 PUFA, MUFA, age, sex, Alpha Omega treatment code, BMI, prevalent diabetes, anti-thrombotic drugs, anti-hypertensive drugs, lipid-lowering drugs, level of education, smoking status, alcohol intake, physical activity, dietary cholesterol and dietary fibre. Dietary data was collected via a biomarker-validated FFQ. Participants consumed on average 6% of energy of LA and 13% of energy of SFA.
No notable funding sources were reported. In addition, none of the authors had any conflicts of financial or personal interest with the financial sponsor of this research.

### 3.2.3 SFA – unspecified macronutrient substitution

**Conclusion:**
**There is too little research from cohort studies to draw conclusions regarding the association between SFA with unspecified macronutrient substitution and the risk of all-cause mortality, CHD mortality, CHD events and MI in people with ASCVD.**

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:
There is one prospective cohort study that addressed associations between SFA substitution with unspecified macronutrient substitution and the risk of all-cause mortality, CHD mortality, CHD events and MI. According to the decision tree, one study provides too little evidence to base conclusions on.

**Explanation:**
Only one prospective cohort study was found and therefore it is only described in short, since one study provides too little evidence to base conclusions on.

The study by Puaschitz et al. (2015)[9] found no associations of SFA intake (en%) and different health outcomes in 2412 participants with CHD from the Western Norway B-Vitamin Intervention Trial (hazard ratio (95% CI) for Q4 vs. Q1: all-cause mortality: 1.02 (0.64, 1.62); CHD mortality: 1.29 (0.69, 2.42); CHD events: 0.83 (0.59, 1.16); MI: 0.90 (0.61, 1.32)). The median follow-up was 4.8 years. The health outcomes were all-cause mortality, CHD mortality, total CHD events and acute MI. Dietary intake was collected with a semi quantitative FFQ. SFA intake was energy-adjusted. The associations were adjusted for acute coronary syndrome, age, diabetes, hypertension, left ventricular ejection fraction, sex, current smoker and use of statins. It should be noted that intake of energy and other macronutrients were not taken into account in the multivariable model. Therefore, the results can be interpreted as a substitution of SFA with 'the rest of the diet'. From the baseline table, it can be seen that higher SFA intake particularly goes together with lower carbohydrate intake. In additional analyses, adjustments for SFA-rich foods were applied. Although this likely leads to over-adjustment, it did not change the results.
No notable funding sources were reported. In addition, none of the authors had any conflicts of financial or personal interest with the financial sponsor of this research.

### 3.3 Summary of conclusions

The Committee's conclusions regarding effects and associations of SFA substitution with other macronutrients with health outcomes in people with ASCVD are summarised in Table 2.

**Table 2** Overview of conclusions regarding the effects and associations of SFA substitution with other macronutrients with health outcomes in people with ASCVD

| Substitution | Health outcome[a] | Study design | Conclusion |
|---|---|---|---|
| SFA-total UFA | CVD mortality | Cohort studies | Too little research |
| SFA-total UFA | CHD mortality | Cohort studies | Too little research |
| SFA-PUFA | All-cause mortality | RCTs | Likely no effect |

| | | | |
|---|---|---|---|
| SFA-PUFA | CVD mortality | RCTs | Likely no effect |
| SFA-PUFA | CVD mortality | Cohort studies | Too little research |
| SFA-PUFA | CVD events | RCTs | 6 en% substitution reduced the risk with 15% |
| SFA-PUFA | CHD mortality | RCTs | Too little research |
| SFA-PUFA | CHD mortality | Cohort studies | Too little research |
| SFA-PUFA | CHD events | RCTs | 6 en% substitution reduced the risk with 15% |
| SFA-PUFA | MI | RCTs | 6 en% substitution reduced the risk with 20% |
| SFA-PUFA | Non-fatal MI | RCTs | Too little research |
| SFA-PUFA | Stroke | RCTs | Too little research |
| SFA-MUFA | All-cause mortality | RCTs | Too little research |
| SFA-MUFA | CVD mortality | RCTs | Too little research |
| SFA-MUFA | CVD mortality | Cohort studies | Too little research |
| SFA-MUFA | CVD events | RCTs | Too little research |
| SFA-MUFA | CHD mortality | RCTs | Too little research |
| SFA-MUFA | CHD mortality | Cohort studies | Too little research |
| SFA-MUFA | CHD events | RCTs | Too little research |
| SFA-MUFA | MI | RCTs | Too little research |
| SFA-MUFA | Non-fatal MI | RCTs | Too little research |
| SFA-LA | Type 2 diabetes | Cohort studies | Too little research |
| SFA-unspecified macronutrient | All-cause mortality | | Too little research |
| SFA-unspecified macronutrient | CHD mortality | Cohort studies | Too little research |
| SFA-unspecified macronutrient | CHD events | Cohort studies | Too little research |
| SFA-unspecified macronutrient | MI | Cohort studies | Too little research |

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; CVD: cardiovascular disease; en: energy; LA: linoleic acid; MI: myocardial infarction; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; RCT: randomised controlled trial; SFA; saturated fatty acid; UFA: unsaturated fatty acid.
Footnotes:

[a] The table contains the health outcomes for which (relevant) studies were found. For the health outcomes that are not listed in the table, no (relevant) studies were found.

On the topic of SFA-PUFA substitution in relation to CVD mortality and CHD mortality, both RCTs and a cohort study were available for the Committee's evaluation. The cohort study found reduced risks of CVD mortality and CHD mortality with SFA-PUFA substitution.[8] This is in contrast to the findings from RCTs, that found no effect on CVD mortality and CHD mortality.[11-13,19-22] There was only one cohort study on this topic. This provides too little evidence to base separate cohort-based conclusions on, and this limits the comparison of evidence from cohort studies with the evidence from the

RCTs. Nevertheless, a possible explanation for the contrasting findings of RCTs and the cohort study may be differences in study design and/or underlying subtypes of cardiovascular diseases that contributed to the endpoints, such as heart failure. Such information on subtypes underlying the CVD and CHD mortality was not available for the (majority of) studies, and therefore there remains uncertainty on this matter.

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# Annexes

## Annex A Search strategy and study selection

### A.1 Search strategy for SRs/MAs

**PubMed**

("Coronary disease" [MeSH] OR "Acute coronary syndrome" [MeSH] OR "Angina pectoris" [MeSH] OR "Coronary artery disease" [MeSH] OR "Myocardial infarction" [MeSH] OR "Peripheral arterial disease" [MeSH] OR "Intermittent claudication" [MeSH] OR "Stroke" [MeSH] OR "Brain ischemia" [MeSH] OR "Cerebrovascular disorders" [MeSH] OR "Percutaneous coronary intervention" [MeSH] OR "Coronary artery bypass" [MeSH] OR "Coronary disease" [TIAB] OR "Coronary heart disease" [TIAB] OR "Acute coronary syndrome" [TIAB] OR "Angina pectoris" [TIAB] OR "Angina" [TIAB] OR "Ischemic heart disease" [TIAB] OR Ischaemic heart disease [TIAB] OR Coronary artery disease [TIAB] OR "Coronary Arteriosclerosis" [TIAB] OR "Myocardial infarction" [TIAB] OR "Heart attack" [TIAB] OR "Peripheral arterial disease" [TIAB] OR "Peripheral vascular disease" [TIAB] OR "Intermittent claudication" [TIAB] OR "Stroke" [TIAB] OR "Acute stroke" [TIAB] OR "Cerebrovascular Apoplexy" [TIAB] OR "Apoplexy" [TIAB] OR "Ischemic stroke" [TIAB] OR "Ischaemic stroke" [TIAB] OR "Hemorrhagic stroke" [TIAB] OR "Haemorrhagic stroke" [TIAB] OR "Cerebrovascular accident" [TIAB] OR "Acute cerebrovascular accident" [TIAB] OR "Cerebrovascular stroke" [TIAB] OR "Brain vascular accident" [TIAB] OR "Brain ischemia" [TIAB] OR "Cerebral ischemia" [TIAB] OR "Cerebral stroke" [TIAB] OR "Brain accident" [TIAB] OR "Brain infarction" [TIAB] OR "Cerebral infarction" [TIAB] OR "Transient ischemic attack" [TIAB] OR "TIA" [TIAB] OR "Cerebrovascular*" [TIAB] OR "Subarachnoid haemorrhage" [TIAB] OR "Intracerebral hemorrhage" [TIAB] OR "Intracranial hemorrhages" [TIAB] OR "Coronary revascularization" [TIAB] OR "Percutaneous coronary intervention" [TIAB] OR "Coronary artery bypass graft surgery" [TIAB] OR "Percutaneous transluminal coronary angioplasty" [TIAB] OR "Percutaneous transluminal angioplasty" [TIAB] OR "Coronary angioplasty" [TIAB] OR "Atherosclerotic cardiovascular disease" [TIAB] OR "Carotid artery disease" [TIAB] OR "CHD" [TIAB] OR "ACS" [TIAB] OR "IHD" [TIAB] OR "CAD" [TIAB] OR "MI" [TIAB] OR "AMI" [TIAB] OR "PAD" [TIAB] OR "CVA" [TIAB] OR "CVAs" [TIAB] OR "TIA" [TIAB] OR "PCI" [TIAB] OR "CABG" [TIAB] OR "PTCA" [TIAB] OR "PTA" [TIAB] OR "ASCVD" [TIAB])

AND

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**Scopus**

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### A.2 Search strategy for RCTs

**PubMed**

("Coronary disease" [MeSH] OR "Acute coronary syndrome" [MeSH] OR "Angina pectoris" [MeSH] OR "Coronary artery disease" [MeSH] OR "Myocardial infarction" [MeSH] OR "Peripheral arterial disease" [MeSH] OR "Intermittent claudication" [MeSH] OR "Stroke" [MeSH] OR "Brain ischemia" [MeSH] OR "Cerebrovascular disorders" [MeSH] OR "Percutaneous coronary intervention" [MeSH] OR "Coronary artery bypass" [MeSH] OR "Coronary disease" [TIAB] OR "Coronary heart disease" [TIAB] OR "Acute coronary syndrome" [TIAB] OR "Angina pectoris" [TIAB] OR "Angina" [TIAB] OR "Ischemic heart disease" [TIAB] OR Ischaemic heart disease [TIAB] OR Coronary artery disease [TIAB] OR "Coronary Arteriosclerosis" [TIAB] OR "Myocardial infarction" [TIAB] OR "Heart attack" [TIAB] OR "Peripheral arterial disease" [TIAB] OR "Peripheral vascular disease" [TIAB] OR "Intermittent claudication" [TIAB] OR "Stroke" [TIAB] OR "Acute stroke" [TIAB] OR "Cerebrovascular Apoplexy" [TIAB] OR "Apoplexy" [TIAB] OR "Ischemic stroke" [TIAB] OR "Ischaemic stroke" [TIAB] OR "Hemorrhagic stroke" [TIAB] OR "Haemorrhagic stroke" [TIAB] OR "Cerebrovascular accident" [TIAB] OR "Acute cerebrovascular accident" [TIAB] OR "Cerebrovascular stroke" [TIAB] OR "Brain vascular accident" [TIAB] OR "Brain ischemia" [TIAB] OR "Cerebral ischemia" [TIAB] OR "Cerebral stroke" [TIAB] OR "Brain accident" [TIAB] OR "Brain infarction" [TIAB] OR "Cerebral infarction" [TIAB] OR "Transient ischemic attack" [TIAB] OR "TIA" [TIAB] OR "Cerebrovascular*" [TIAB] OR "Subarachnoid haemorrhage" [TIAB] OR "Intracerebral hemorrhage" [TIAB] OR "Intracranial hemorrhages" [TIAB] OR "Coronary revascularization" [TIAB] OR "Percutaneous coronary intervention" [TIAB] OR "Coronary artery bypass graft surgery" [TIAB] OR "Percutaneous transluminal coronary angioplasty" [TIAB] OR "Percutaneous transluminal angioplasty" [TIAB] OR "Coronary angioplasty" [TIAB] OR "Atherosclerotic cardiovascular disease" [TIAB] OR "Carotid artery disease" [TIAB] OR "CHD" [TIAB] OR "ACS" [TIAB] OR "IHD" [TIAB] OR "CAD"

[TIAB] OR “MI” [TIAB] OR “AMI” [TIAB] OR “PAD” [TIAB] OR “CVA” [TIAB] OR “CVAs” [TIAB] OR “TIA” [TIAB] OR “PCI” [TIAB] OR “CABG” [TIAB] OR “PTCA” [TIAB] OR “PTA” [TIAB] OR “ASCVD” [TIAB])

AND

(“Saturated Fat*”[TIAB] OR “Saturated Fatty Acid*”[TIAB] OR “Fat Diet”[TIAB] OR "Diet, Fat-Restricted"[Mesh] OR “restricted fat”[TIAB] OR “restricted fat diet”[TIAB] OR “modified fat”[TIAB] OR “modified fat diet”[TIAB] OR “fat substitution”[TIAB] OR “low fat diet” OR "Dietary Proteins"[Mesh] OR “dietary protein*”[TIAB] OR "Dietary Fats"[Mesh] OR “dietary fat*”[TIAB] OR "Dietary Carbohydrates"[Mesh] OR “dietary carbohydrate*”[TIAB] OR “Diet, Carbohydrate-Restricted”[Mesh] OR “carbohydrate restricted”[tiab] OR “low carbohydrate diet”[tiab] OR “low-carbohydrate diet”[tiab] OR “carbohydrate-restricted”[tiab] OR “low-Carbohydrate Diet*”[tiab] OR “Carbohydrate Restricted Diet*”[tiab] OR “carbohydrate restriction”[tiab] OR “carbohydrate quantity”[tiab] OR “diet, low carbohydrate”[TIAB] OR “diet, low-carbohydrate”[TIAB] OR "Diet, High-Protein"[Mesh] OR “high protein diet*”[TIAB] OR "Diet, Protein-Restricted"[Mesh] OR “protein restrict*”[TIAB] OR “low protein diet*”[TIAB])

AND

("Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [publication type] OR "Cross-Over Studies"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Historically Controlled Study"[Mesh] OR randomized[tiab] OR randomised[tiab] OR RCT[tiab] OR controlled*[tiab] OR placebo[tiab] OR clinical trial[tiab] OR trial[tiab] OR intervention[tiab])

NOT

("Fatty Acids, Omega-3"[Mesh] OR "Systematic Review"[Publication Type] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Review"[Publication Type] OR "meta analysis"[Publication Type] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Network Meta-Analysis"[MeSH Terms] OR "Primary Prevention"[MeSH Terms])

Limit: from 2019

**Scopus**

TITLE-ABS("Coronary disease") OR TITLE-ABS("Acute coronary syndrome") OR TITLE-ABS("Angina pectoris") OR TITLE-ABS("Coronary artery disease") OR TITLE-ABS("Myocardial infarction") OR TITLE-ABS("Peripheral arterial disease") OR TITLE-ABS("Intermittent claudication") OR TITLE-ABS(Stroke) OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebrovascular disorders") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass") OR TITLE-ABS("Coronary heart disease") OR TITLE-ABS(Angina) OR TITLE-ABS("Ischemic heart disease") OR TITLE-ABS("Ischaemic heart disease") OR TITLE-ABS("Coronary Arteriosclerosis") OR TITLE-ABS("Heart attack") OR TITLE-ABS("Peripheral vascular disease") OR TITLE-ABS("Acute stroke") OR TITLE-ABS("Cerebrovascular Apoplexy") OR TITLE-ABS(Apoplexy) OR TITLE-ABS("Ischemic stroke") OR TITLE-ABS("Ischaemic stroke") OR TITLE-ABS("Hemorrhagic stroke") OR TITLE-ABS("Haemorrhagic stroke") OR TITLE-ABS("Cerebrovascular accident") OR TITLE-ABS("Acute cerebrovascular accident") OR TITLE-ABS("Cerebrovascular stroke") OR TITLE-ABS("Brain vascular accident") OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebral ischemia") OR TITLE-ABS("Cerebral stroke") OR TITLE-ABS("Brain accident") OR TITLE-ABS("Brain infarction") OR TITLE-ABS("Cerebral infarction") OR TITLE-ABS("Transient ischemic attack") OR TITLE-ABS(TIA) OR TITLE-ABS(Cerebrovascular*) OR TITLE-ABS("Subarachnoid haemorrhage") OR TITLE-ABS("Intracerebral hemorrhage") OR TITLE-ABS("Intracranial hemorrhages") OR TITLE-ABS("Coronary revascularization") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass graft surgery") OR TITLE-ABS("Percutaneous transluminal coronary angioplasty") OR TITLE-ABS("Percutaneous transluminal angioplasty") OR TITLE-ABS("Coronary angioplasty") OR TITLE-ABS("Atherosclerotic cardiovascular disease") OR TITLE-ABS("Carotid artery disease") OR TITLE-ABS(CHD) OR TITLE-ABS(ACS) OR TITLE-ABS(IHD) OR TITLE-ABS(CAD) OR TITLE-ABS(MI) OR TITLE-ABS(AMI) OR TITLE-ABS(PAD) OR TITLE-ABS(CVA) OR TITLE-ABS(CVAs) OR TITLE-ABS(TIA) OR TITLE-ABS(PCI) OR TITLE-ABS(CABG) OR TITLE-ABS(PTCA) OR TITLE-ABS(PTA) OR TITLE-ABS(ASCVD)

AND

TITLE-ABS(“Saturated Fat”) OR TITLE-ABS(“Saturated Fatty Acid”) OR TITLE-ABS(“Fat Diet”) OR TITLE-ABS(“restricted fat”) OR TITLE-ABS(“fat restricted”) OR TITLE-ABS(“fat restriction”) OR TITLE-ABS(“modified fat”) OR TITLE-ABS(“modified fat diet”) OR TITLE-ABS(“fat substitution”) OR TITLE-ABS(“low fat diet”) OR TITLE-ABS(“Saturated Fatty Acids”) OR TITLE-ABS(“Saturated Fats”) OR TITLE-

ABS(“dietary protein”) OR TITLE-ABS(“dietary proteins”) OR TITLE-ABS(“dietary fat”) OR TITLE-ABS(“dietary fats”) OR TITLE-ABS(“dietary carbohydrate”) OR TITLE-ABS(“dietary carbohydrates”) OR TITLE-ABS(“carbohydrate restriction”) OR TITLE-ABS(“carbohydrate diet”) OR TITLE-ABS(“carbohydrate restricted”) OR TITLE-ABS(“low carbohydrate diet”) OR TITLE-ABS(“low-carbohydrate diet”) OR TITLE-ABS(“carbohydrate-restricted”) OR TITLE-ABS(“carbohydrate quantity”) OR TITLE-ABS(“high protein diet”) OR TITLE-ABS(“high-protein diet”) OR TITLE-ABS(“protein restriction”) OR TITLE-ABS(“protein restricted”) OR TITLE-ABS(“low protein diet”) OR TITLE-ABS(“low-protein diet”)

AND

TITLE-ABS-KEY ("Clinical Trial") OR TITLE-ABS-KEY ("Cross-Over Studies”) OR TITLE-ABS-KEY("Double-Blind Method") OR TITLE-ABS-KEY("Single-Blind Method") OR TITLE-ABS-KEY("Controlled Before-After Studies") OR TITLE-ABS-KEY("Historically Controlled Study") OR TITLE-ABS-KEY(randomized) OR TITLE-ABS-KEY(randomised) OR TITLE-ABS-KEY(RCT) OR TITLE-ABS-KEY(controlled*) OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY(“clinical trial”) OR TITLE-ABS-KEY(trial) OR TITLE-ABS-KEY(intervention)

AND NOT

TITLE-ABS(“omega 3 fatty acid”) OR TITLE-ABS(“n-3 fatty acid”) OR TITLE-ABS(“n-3 PUFA”) OR TITLE-ABS(“primary prevention”) OR TITLE-ABS-KEY ("Systematic Review ") OR TITLE-ABS-KEY ("Systematic Reviews") OR TITLE-ABS-KEY ("Review") OR TITLE-ABS-KEY ("meta analysis") OR TITLE-ABS-KEY ("meta-analysis") OR TITLE-ABS-KEY ("Network Meta-Analysis")

Limit: from 2019

### A.3 Search strategy for prospective cohort studies

**PubMed**

(“Coronary disease” [MeSH] OR “Acute coronary syndrome” [MeSH] OR “Angina pectoris” [MeSH] OR “Coronary artery disease” [MeSH] OR “Myocardial infarction” [MeSH] OR “Peripheral arterial disease” [MeSH] OR “Intermittent claudication” [MeSH] OR “Stroke” [MeSH] OR “Brain ischemia” [MeSH] OR “Cerebrovascular disorders” [MeSH] OR “Percutaneous coronary intervention” [MeSH] OR “Coronary artery bypass” [MeSH] OR “Coronary disease” [TIAB] OR “Coronary heart disease” [TIAB] OR “Acute

coronary syndrome” [TIAB] OR “Angina pectoris” [TIAB] OR “Angina” [TIAB] OR “Ischemic heart disease” [TIAB] OR Ischaemic heart disease [TIAB] OR Coronary artery disease [TIAB] OR “Coronary Arteriosclerosis” [TIAB] OR “Myocardial infarction” [TIAB] OR “Heart attack” [TIAB] OR “Peripheral arterial disease” [TIAB] OR “Peripheral vascular disease” [TIAB] OR “Intermittent claudication” [TIAB] OR “Stroke” [TIAB] OR “Acute stroke” [TIAB] OR “Cerebrovascular Apoplexy” [TIAB] OR “Apoplexy” [TIAB] OR “Ischemic stroke” [TIAB] OR “Ischaemic stroke” [TIAB] OR “Hemorrhagic stroke” [TIAB] OR “Haemorrhagic stroke” [TIAB] OR “Cerebrovascular accident” [TIAB] OR “Acute cerebrovascular accident” [TIAB] OR “Cerebrovascular stroke” [TIAB] OR “Brain vascular accident” [TIAB] OR “Brain ischemia” [TIAB] OR “Cerebral ischemia” [TIAB] OR “Cerebral stroke” [TIAB] OR “Brain accident” [TIAB] OR “Brain infarction” [TIAB] OR “Cerebral infarction” [TIAB] OR “Transient ischemic attack” [TIAB] OR “TIA” [TIAB] OR “Cerebrovascular*” [TIAB] OR “Subarachnoid haemorrhage” [TIAB] OR “Intracerebral hemorrhage” [TIAB] OR “Intracranial hemorrhages” [TIAB] OR “Coronary revascularization” [TIAB] OR “Percutaneous coronary intervention” [TIAB] OR “Coronary artery bypass graft surgery” [TIAB] OR “Percutaneous transluminal coronary angioplasty” [TIAB] OR “Percutaneous transluminal angioplasty” [TIAB] OR “Coronary angioplasty” [TIAB] OR “Atherosclerotic cardiovascular disease” [TIAB] OR “Carotid artery disease” [TIAB] OR “CHD” [TIAB] OR “ACS” [TIAB] OR “IHD” [TIAB] OR “CAD” [TIAB] OR “MI” [TIAB] OR “AMI” [TIAB] OR “PAD” [TIAB] OR “CVA” [TIAB] OR “CVAs” [TIAB] OR “TIA” [TIAB] OR “PCI” [TIAB] OR “CABG” [TIAB] OR “PTCA” [TIAB] OR “PTA” [TIAB] OR “ASCVD” [TIAB])

AND

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AND

(“cohort studies”[MeSH] OR “cohort stud*”[TIAB] OR “longitudinal studies”[MeSH] OR “longitudinal stud*”[TiAB] OR “prospective studies”[MeSH] OR “prospective stud*”[TIAB] OR “Observational study”[publication type])

NOT

("Fatty Acids, Omega-3"[Mesh] OR "Systematic Review"[Publication Type] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Review"[Publication Type] OR "meta analysis"[Publication Type] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Network Meta-Analysis"[MeSH Terms] OR "Primary Prevention"[MeSH Terms])

Limit: from 2000

**Scopus**

TITLE-ABS("Coronary disease") OR TITLE-ABS("Acute coronary syndrome") OR TITLE-ABS("Angina pectoris") OR TITLE-ABS("Coronary artery disease") OR TITLE-ABS("Myocardial infarction") OR TITLE-ABS("Peripheral arterial disease") OR TITLE-ABS("Intermittent claudication") OR TITLE-ABS(Stroke) OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebrovascular disorders") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass") OR TITLE-ABS("Coronary heart disease") OR TITLE-ABS(Angina) OR TITLE-ABS("Ischemic heart disease") OR TITLE-ABS("Ischaemic heart disease") OR TITLE-ABS("Coronary Arteriosclerosis") OR TITLE-ABS("Heart attack") OR TITLE-ABS("Peripheral vascular disease") OR TITLE-ABS("Acute stroke") OR TITLE-ABS("Cerebrovascular Apoplexy") OR TITLE-ABS(Apoplexy) OR TITLE-ABS("Ischemic stroke") OR TITLE-ABS("Ischaemic stroke") OR TITLE-ABS("Hemorrhagic stroke") OR TITLE-ABS("Haemorrhagic stroke") OR TITLE-ABS("Cerebrovascular accident") OR TITLE-ABS("Acute cerebrovascular accident") OR TITLE-ABS("Cerebrovascular stroke") OR TITLE-ABS("Brain vascular accident") OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebral ischemia") OR TITLE-ABS("Cerebral stroke") OR TITLE-ABS("Brain accident") OR TITLE-ABS("Brain infarction") OR TITLE-ABS("Cerebral infarction") OR TITLE-ABS("Transient ischemic attack") OR TITLE-ABS(TIA) OR TITLE-ABS(Cerebrovascular*) OR TITLE-ABS("Subarachnoid haemorrhage") OR TITLE-ABS("Intracerebral hemorrhage") OR TITLE-ABS("Intracranial hemorrhages") OR TITLE-ABS("Coronary revascularization") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass graft surgery") OR TITLE-ABS("Percutaneous transluminal coronary angioplasty") OR TITLE-ABS("Percutaneous transluminal angioplasty") OR TITLE-ABS("Coronary angioplasty") OR TITLE-ABS("Atherosclerotic cardiovascular disease")

OR TITLE-ABS("Carotid artery disease") OR TITLE-ABS(CHD) OR TITLE-ABS(ACS) OR TITLE-ABS(IHD) OR TITLE-ABS(CAD) OR TITLE-ABS(MI) OR TITLE-ABS(AMI) OR TITLE-ABS(PAD) OR TITLE-ABS(CVA) OR TITLE-ABS(CVAs) OR TITLE-ABS(TIA) OR TITLE-ABS(PCI) OR TITLE-ABS(CABG) OR TITLE-ABS(PTCA) OR TITLE-ABS(PTA) OR TITLE-ABS(ASCVD)

AND

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AND

TITLE-ABS-KEY ("cohort studies") OR TITLE-ABS-KEY ("cohort study") OR TITLE-ABS-KEY ("longitudinal studies") OR TITLE-ABS-KEY ("longitudinal study") OR TITLE-ABS-KEY ("prospective studies") OR TITLE-ABS-KEY ("prospective study") OR TITLE-ABS-KEY ("Observational study") OR TITLE-ABS-KEY ("Observational studies")

AND NOT

TITLE-ABS(“omega 3 fatty acid”) OR TITLE-ABS(“n-3 fatty acid”) OR TITLE-ABS(“n-3 PUFA”) OR TITLE-ABS(“primary prevention”) OR TITLE-ABS-KEY ("Systematic Review ") OR TITLE-ABS-KEY ("Systematic Reviews") OR TITLE-ABS-KEY ("Review") OR TITLE-ABS-KEY ("meta analysis") OR TITLE-ABS-KEY ("meta-analysis") OR TITLE-ABS-KEY ("Network Meta-Analysis")

Limit: from 2000

### A.4 Selection of SRs/MAs

**Step 1. Identification**
2415 records retrieved:

- PubMed: 443
- Scopus: 1972
- Other sources: 1

337 duplicates excluded

**Step 2. Screening**
2079 records screened,
2029 records excluded after first selection

**Step 3. Eligibility**
50 full-texts assessed,
47 records excluded after second selection due to:

- No exposure of interest: 1
- No outcome of interest: 8
- Different study population (<90% ASCVD): 15
- Different study design: 6
- Updated version available: 2
- Not a *systematic* review: 15

**Step 4. Inclusion**
3 records included

### A.5 Selection of prospective cohort studies

**Step 1. Identification**
885 records retrieved:

- PubMed: 675
- Scopus: 207
- Other sources: 3

169 duplicates excluded

**Step 2. Screening**
716 records screened,
668 records excluded after first selection

**Step 3. Eligibility**
48 full-texts assessed,
45 records excluded after second selection due to:

- No exposure of interest: 6
- No outcome of interest: 2
- Different study design: 3
- Updated version available: 1
- No subgroups: 8
- Primary prevention: 19
- Language: 1
- RCTs: 4
- Duration too short: 1

**Step 4. Inclusion**
3 records included

## Annex B Characteristics of the RCTs and reported effects

**Supplemental Table B1** Characteristics of the individual RCTs included in the MAs

| Study (author and/or year) | Study duration | N participants; N intervention group (i); N control group (c) | Study design | Diet of intervention (i) and control (c) group | PUFAs in dietary intervention |
|---|---|---|---|---|---|
| DART (Burr et al. 1989)[20] | 2 years | 2033; i: 1018; c: 1015 | Factorial | i: advice to reduce fat intake to 30 en% and to increase PUFA/SFA ratio to 1:0<br>c: NR | n-3 + n-6 (amount unknown) |
| Oslo Diet-Heart (Leren et al. 1970)[19] | 5 years | 412; i: 206; c: 206 | Parallel | i: advice to consume 39 en% of fat. Sources of fat: soybean oil (72%), fish fat (11.6%), animal fat (8.8%), cereal fat (5%) and other sources (2.6%). Of the mean amount of dietary fat, 21.6% was SFA, 25.7% MUFA and 52.7% PUFA<br>c: NR | n-3 + n-6 |
| MRC (1968)[21] | 5 years | 393; i: 199; c: 194 | Parallel | i: advice to remove SFA from diet. Additional advice to take 85 g/d of soybean oil, of which 43 g/d unheated. A maximum of 35 g/d of other fat was allowed. 14g of this was taken as moderately unsaturated margarine. Foods allowed were lean meat (with a maximum of 85 g), fish, skimmed milk and clear soups. Forbidden foods were butter, other margarines, cooking-fat, other oils, fat meat, whole milk, cheese, egg yolk, biscuits and cakes.<br>c: normal diet | n-3 + n-6 |
| Rose et al. (1965)[11] | 2 years | 80; i: 28; c: 26 | 3-arm parallel | i: supplement of 80 g/d of corn oil (i1; mainly PUFA) or olive oil (i2; mainly MUFA) plus advice to avoid fried foods, fatty meat, sausages, pastry, ice cream, cheese, cakes. | n-6 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Restriction of milk, eggs and butter.<br>c: no advice on dietary fats | |
| STARS (Watts et al. 1992)[22] | 3 years | 90; i: 27; c: 28 | 3-arm parallel | i: advice to reduce total fat to 27 en%, SFA to 8-10 en% and dietary cholesterol to 100 mg/1000 kcal. Advice to increase PUFA to 8 en% and plant-derived soluble fibre intake was increased to the equivalent of 3.6g polygalacturonate/1000 kcal.<br>c: normal cardiological treatment and advice to reduce weight if BMI was >25 kg/m$^2$ | n-3 + n-6 |
| Sydney Diet Heart (Woodhill et al. 1978; Ramsden et al. 2013)[12,13] | 5 years | 458; i: 221; c: 237 | Parallel | i: advice of a diet of <10 en% of SFA and >15 en% of PUFA. PUFA came entirely from provided advised safflower oil and safflower margarine (which contains only n-6 LA). Safflower oil/margarine replaced animal fats, other margarines or butter, cooking oils, salad dressings, baked goods, other products and was taken as a supplement<br>c: no specific dietary instruction | n-6 (+ TFA) |

Abbreviations: BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; en: energy; LA: linoleic acid; MI; myocardial infarction; MUFA: monounsaturated fatty acid; NR: not reported; PUFA: polyunsaturated fatty acid; RCT: randomised controlled trial; SFA: saturated fatty acid; TFA: trans fatty acid.

**Supplemental table B2** Effects reported in individual RCTs for substitution of SFA with PUFA on health outcomes in men with CHD

| Outcome | Author/study name; risk estimate (95% CI); N cases in intervention group (i); N cases in control group (c) |
|---|---|
| All-cause mortality | Burr et al. **0.99 (0.76, 1.25)**; i: 111; c: 113<br>Leren et al. **0.75 (0.52, 1.06)**; i: 41; c: 55<br>MRC **0.88 (0.55, 1.41)**; i: 28; c: 31<br>Rose et al. **4.64 (0.58, 37.15)**; i: 5; c: 1<br>Watts et al. **0.35 (0.04, 3.12)**; i: 1; c: 3<br>Woodhill et al. **1.49 (0.95, 2.34)**; i: 39; c: 28 |

| | |
|---|---|
| CVD mortality | Burr et al. **1.00 (0.76, 1.30)**; i: 97; c: 97<br>Leren et al. **0.73 (0.50, 1.06)**; i: 38; c: 52<br>MRC **1.05 (0.63, 1.75)**; i: 27; c: 25<br>Rose et al. **4.64 (0.58, 37.15)**; i: 1; c: 5<br>Watts et al. **0.35 (0.04, 3.12)**; i: 1; c: 3<br>Woodhill et al. **1.71 (1.03, 2.82)**; i: 35; c: 22 |
| CVD events | Burr et al. **0.91 (0.73, 1.14)**; i: 132; c: 144<br>Leren et al. **0.75 (0.57, 0.99)**; i: 61; c: 81<br>MRC **0.82 (0.62, 1.07)**; i: 62; c: 74<br>Rose et al. **1.27 (0.72, 2.23)**; i: 15; c: 11<br>Watts et al. **0.31 (0.10, 1.01)**; i: 3, c: 10<br>Woodhill et al. **1.71 (1.03, 2.82)**; i: 35, c: 22 |
| MI | Burr et al. **0.74 (0.48, 1.14)**; i: 35; c: 47<br>Leren et al. **0.63 (0.43, 0.92)**; i: 34; c: 54<br>MRC **1.00 (0.67, 1.48)**; i: 40; 39<br>Rose et al. **0.93 (0.30, 2.84)**; i: 5; c: 5<br>Watts et al. **0.52 (0.05, 5.39)**; i: 1; c: 2<br>Woodhill et al. **1.74 (1.04, 2.90)**; i: 34; 21 |
| Non-fatal MI | Burr et al. **0.74 (0.48, 1.14)**; i: 35; c: 47<br>MRC **0.97 (0.58, 1.64)**; i: 25; c: 25<br>Leren et al. **0.77 (0.47, 1.27)**; i: 24; c: 31<br>Rose et al. **1.30 (0.47, 3.59)**; i: 7; c: 5 |
| CHD mortality | Burr et al. **1.00 (0.76, 1.30)**; i: 97; c: 97<br>MRC **0.97 (0.58, 1.64)**; i: 25; c: 25<br>Leren et al. **0.74 (0.51, 1.08)**; i: 37; c: 50<br>Rose et al. **4.64 (0.58, 37.15)**; i: 5; c :1<br>Woodhill et al. **1.63 (1.00, 2.67)**; i: 35; c: 23 |
| CHD events | Burr et al. **0.91 (0.73, 1.14)**; i: 132; c: 144<br>MRC **0.86 (0.61, 1.22)**; i: 45; c: 51<br>Leren et al. **0.75 (0.57, 0.99)**; i: 61; c: 81<br>Rose et al. **1.86 (0.82, 4.22)**; i :12 ; c :6<br>Watts et al. **0.41 (0.09, 1.96)**; i :2 ; c :5<br>Woodhill et al. **1.76 (1.04, 2.92)**; NR |
| Stroke | MRC **4.88 (0.24, 100.89)**; i: 2; c: 0<br>Leren et al. **2.00 (0.18, 21.89)**; i: 2; c: 1<br>Watts et al. **0.35 (0.01, 8.12)**; i: 0; c: 1 |

Abbreviations: CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; MI; myocardial infarction; NR: not reported; PUFA: polyunsaturated fatty acid; RCT: randomised controlled trial; SFA: saturated fatty acid.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
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