Carbohydrate and fat substitutions

No. 2021/41Je, The Hague, November 16, 2021

Background document to:
Dutch dietary guidelines for people with type 2 diabetes.
No. 2021/41e, The Hague, November 16, 2021

Health Council of the Netherlands

contents

01 introduction

This background document belongs to the advisory report *Dutch dietary guidelines for people with type 2 diabetes.*[1] It describes the methodology for the search, selection and evaluation of the literature regarding the relationship of substitutions of carbohydrates and subtypes of fats with other macronutrients with health outcomes in people with type 2 diabetes. The current background document furthermore describes the evidence on this topic and the conclusions that have been drawn by the Health Council's Committee on Nutrition.

02 methodology

2.1 Questions

The Committee aimed to answer the following questions:

1. What is the association between substitution of dietary carbohydrates with subtypes of fat and proteins and the long-term health of people with type 2 diabetes?
2. What is the association between substitution of dietary subtypes of fat with other subtypes of fat and with a combination of carbohydrates and proteins and the long-term health of people with type 2 diabetes?

2.2 Definition of macronutrient substitutions

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 carbohydrate – fat substitutions as an example. For such substitutions, people with relatively low carbohydrate intakes and high fat intakes are compared to people with relatively high intakes of carbohydrates and low fat intakes, using multivariable statistical models. The results of such comparisons are then often interpreted as substitutions of carbohydrates with fats. However, the Committee stresses this is an interpretational step, and actually it is a comparison of people consuming high amounts of carbohydrates with people consuming high amounts of fats.

2.3 Outcomes

The Committee selected the following chronic disease outcomes for this advisory report: morbidity and mortality from coronary heart disease, stroke, heart failure, chronic obstructive pulmonary diseases, breast cancer, colorectal cancer, lung cancer, dementia, depression and chronic kidney disease. Also, all-cause mortality and morbidity and mortality from total cardiovascular disease (CVD) and total cancer were selected as outcomes.

A detailed description of the rationale for choosing those outcomes is given in the background document *Methodology for the evaluation of evidence*[2] for the advisory report *Dutch dietary guidelines for people with type 2 diabetes*.

Only literature on the outcomes of cardiovascular disease, cancer and kidney disease turned out to be available within the inclusion criteria of the Committee. Therefore, literature regarding the other outcomes is not evaluated in the current background document.

2.4 Selection and evaluation of literature

A detailed description of the approach used by the Committee for selecting and evaluating scientific literature is given in the background document *Methodology for the evaluation of evidence*[2] for the advisory report *Dutch dietary guidelines for people with type 2 diabetes*.
To summarise, the Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs) of prospective cohort studies and RCTs examining the relationships of dietary factors with health outcomes in people with type 2 diabetes.

For carbohydrate-fat and carbohydrate-protein substitutions, the current background document solely focuses on evidence from cohort studies. The evidence from RCTs is summarised in the background document *Reduced carbohydrate diets*.[3] An overview of the search strategies and the selection of articles is presented in **Annex A**. No MAs and SRs reporting evidence from cohort studies were found. Therefore, the Committee selected reports of individual studies. The Committee selected five articles on four studies authored by Campmans-Kuijpers et al. (2016)[4,5], Horikawa et al. (2017)[6], Jiao et al. (2019)[7] and Tanasescu et al. (2004)[8]. Three of those evaluated substitutions of carbohydrates with fats on CVD, and one on cancer outcomes. Two of those evaluated substitutions of carbo- hydrates with proteins on CVD outcomes, and one on kidney disease. The study of Jao et al. (2019)[7] also addressed substitutions of fat subtypes.

In addition, the Committee found an SR of Schwab et al.[9] that was published very recently. That report addressed the relationship of dietary fat intake (including substitutions with carbohydrates and fats) with CVD risk in people with type 2 diabetes and was additionally taken into account by the Committee in order to search for complementary studies to the above, addressing substitutions of fat subtypes. The already selected cohort studies into substitution of carbohydrates with fat and substitutions of fat subtypes were included in the SR of Schwab et al. In addition, one intervention study and one cohort study were included in the SR that addressed ratios of fatty acids (i.e. the ratios of saturated fat and specific subtypes of unsaturated fats). Those studies were excluded by the Committee since results of studies using such exposures are difficult to translate to dietary recommendations. Also, one additional prospective cohort study was included in the SR, authored by Trichopoulou et al.[10] That study investigated intakes of saturated fatty acids (SFAs) and polyunsaturated fatty acids (PUFAs) in association with CVD mortality and was additionally evaluated by the Committee.

2.5 Drawing conclusions

A detailed description of the approach used for drawing conclusions is given in the background document *Methodology for the evaluation of evidence*[2] for the advisory report *Dutch dietary guidelines for people with type 2 diabetes*. To summarise, conclusions on the certainty of the evidence regarding effects or associations of macronutrient substitutions with health outcomes were drawn based on the amount of studies and participants that contributed to the evaluation. Also, the quality of the evidence was taken into consideration. The Committee used the decision tree (**Annex B**) as tool to support consistency in drawing conclusions.

03 associations of carbohydrate substitutions with fats and proteins

Below, the scientific evidence for associations of substituting carbohydrates with fats and proteins on health outcomes in people with type 2 diabetes is described.

3.1 Carbohydrate – fat substitutions

Table 1 Associations of carbohydrates, and their substitutions with fats, with risk of all-cause mortality and morbidity and/or mortality from CVD and cancer: prospective cohort studies.

Cohort study; Study duration	Campmans-Kuijpers, 2016[4]; 9 years	Tanasescu, 2004[8]; 57 195 person-years	Jiao, 2019[7]; 11 years (124 362 person-years)
Cohort	EPIC; *Pooled analysis of 15 cohorts*	NHS	Pooled analysis of NHS & HPFS
Exposure	Substitution of 5 en% carbohydrates for fats	Substitution of 5 en% carbohydrates for fats	Highest vs. lowest quartile of intake of fats
Dietary assessment method	Validated country-specific dietary questionnaire at baseline, either quantitative dietary questionnaires with individual portion sizes or semi-quantitative food frequency questionnaires	Validated semi-quantitative food frequency questionnaires administered in 1980, 1984, 1986, 1990 and 1994	Validated semi-quantitative food frequency questionnaires administered in 1980, 1984, 1986, and every four years thereafter in the NHS and every four years since 1986 in the HPFS (until 2014)
Number of participants; number of cases	6192 participants; Total deaths: 791; CVD deaths: 268	5672 participants; CVD cases (fatal and nonfatal): 619	11264 participants; Total deaths: 2503; CVD deaths: 646; Cancer deaths: 406
Strength of the association: HR (95%CI) for CVD MORTALITY and/or MORBIDITY	Substitutions of carbohydrates with: Total fat: 1.03 (0.93, 1.15) SFA: 1.24 (0.98, 1.57) MUFA: 0.77 (0.58, 1.02) PUFA: 1.37 (1.03, 1.81) For CVD mortality	Substitution of carbohydrates with: Total fat: 1.01 (0.94, 1.08) SFA: 1.29 (1.02, 1.63) MUFA: 0.81 (0.63, 1.04) PUFA: 0.97 (0.68, 1.39) Animal fat: 1.01 (0.94, 1.09) Vegetable fat: 0.93 (0.82, 1.06) For CVD morbidity and mortality	Substitution of carbohydrates with: SFA: 1.13 (0.80, 1.59) MUFA: 0.99 (0.70, 1.39) PUFA: 0.76 (0.58, 0.99) For CVD mortality

Cohort study; Study duration	Campmans-Kuijpers, 2016[4]; 9 years	Tanasescu, 2004[8]; 57 195 person-years	Jiao, 2019[7]; 11 years (124 362 person-years)
Strength of the association: HR (95%CI) for CANCER MORTALITY	NR	NR	Substitution of carbohydrates with: SFA: 1.00 (0.85, 1.19) MUFA: 0.90 (0.76, 1.06) PUFA: 0.68 (0.60, 0.78)
Strength of the association: HR (95%CI) for ALL-CAUSE MORTALITY	Substitutions of carbohydrates with: Total fat: 1.08 (1.02, 1.16) SFA: 1.29 (1.13, 1.48) MUFA: 0.86 (0.73, 1.02) PUFA: 1.20 (1.00, 1.45)	NR	Substitution of carbohydrates with: SFA: 0.99 (0.67, 1.47) MUFA: 1.09 (0.74, 1.60) PUFA: 0.74 (0.55, 1.01)
Study population	People diagnosed with type 2 diabetes; diabetes duration[a]: 5 years; men and women; BMI[a]: 28.8 kg/m^2; diabetes medications[b]: oral agents, insulin; Europe	People diagnosed with type 2 diabetes; diabetes duration[a] ranging from 7 to 9 years over the quintiles of intake of fats; women; BMI[a] ranging from 27 to 29 kg/m^2 over the quintiles of intake of fats; diabetes medications[b]: oral agents, insulin; United States of America	People diagnosed with type 2 diabetes; diabetes duration[a] (age adjusted) ranging from 3 to 4 years over the quartiles of intake of fats; men and women; BMI[a] ranging from 27 to 30 kg/m^2 over the quartiles of intake of fats; diabetes medications[b]: oral agents, insulin; United States of America

BMI: body mass index; CVD: cardiovascular disease. EPIC, European Prospective Investigation into Cancer and Nutrition; NHS, Nurses' Health Study; NR, not reported; HPFS, Health Professionals Follow-Up Study; HR, Hazard Ratio; NR, not reported; SFA, saturated fat; PUFA, polyunsaturated fat; MUFA, monounsaturated fat.

[a] BMI and diabetes duration values represent the average in the study population.

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that all participants used those medications).

The Committee concluded the following:

Cohort studies show that replacing 5 energy percent of carbohydrates with saturated fat associates with approximately 25% higher long-term risk of morbidity or mortality due to CVD in people diagnosed with type 2 diabetes. 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. There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with SFAs with risk of CVD. There is one pooled analysis of 15 cohorts, a pooled analysis of two cohorts and one individual cohort study, with a total of >500 CVD cases, that address this topic. This is the first step required to mark the evidence as strong.
2. There is no heterogeneity in direction and size of associations between the different cohort studies.
3. The Nurses' Health Study was used in two analyses that contributed to the evidence. The outcomes and durations of follow-up in the analyses were different (CVD mortality [on average 11 years follow-up] vs. CVD morbidity plus mortality [maximum 8 years follow-up]). When one of the two would be discarded, the total number of CVD cases would still be >500, and the conclusion would not change due to the lack of heterogeneity between the studies.
4. There were no other considerations regarding the evaluated studies.

Cohort studies show contradictory associations of replacing carbohydrates with polyunsaturated fat on long-term risk of morbidity or mortality due to CVD in people diagnosed with type 2 diabetes.

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

1. There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with PUFAs with risk of CVD. There is one pooled analysis of 15 cohorts, a pooled analysis of two cohorts and one individual cohort study, with a total of >500 CVD cases, that address this topic. This is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as contradictory.
2. There is heterogeneity in directions of associations between the cohort studies. The pooled analysis of 15 studies showed a harmful association of substituting carbohydrates with PUFAs, whereas the pooled analysis of two cohorts showed a beneficial association and the individual cohort study showed a neutral association.
   The heterogeneous findings may be due to differences in underlying subtypes and/or food sources of fats and carbohydrates.
3. The Nurses' Health Study was used in two analyses that contributed to the evidence. The outcomes and durations of follow-up in the analyses were different (CVD mortality [on average 11 years follow-up] vs. CVD morbidity plus mortality [maximum 8 years follow-up]). When one of the two would be discarded, the heterogeneity in results between the different cohort studies would remain and therefore the conclusion would not change.

Cohort studies show inconclusive associations of replacing carbohydrates with monounsaturated fat on long-term risk of morbidity or mortality due to CVD in people diagnosed with type 2 diabetes.

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

1. There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with MUFAs with risk of CVD. There is one pooled analysis of 15 cohorts, a pooled analysis of two cohorts and one individual cohort study, with a total of >500 CVD cases, that address this topic. This is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as inconclusive.
2. There is heterogeneity in directions of associations between the cohort studies: The pooled analysis of 15 studies and the individual cohort study showed a (tendency towards a) beneficial association of substituting carbohydrates with MUFAs, whereas the pooled analysis of two cohorts showed a neutral association. The heterogeneous findings may be due to differences in underlying subtypes and/or food sources of fats and carbohydrates.
3. The Nurses' Health Study was used in two analyses that contributed to the evidence. The outcomes and durations of follow-up in the analyses

were different (CVD mortality [on average 11 years follow-up] vs. CVD morbidity plus mortality [maximum 8 years follow-up]). When one of the two would be discarded, the heterogeneity in results between the different cohort studies would remain and therefore the conclusion would not change.

There is too little research to draw conclusions regarding the associations of replacing carbohydrates with different types of fats on long-term cancer mortality in people diagnosed with type 2 diabetes.

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

There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with different types of fats with risk of cancer. There is one pooled analysis of two cohort studies that addresses this topic, which is too few to base conclusions on.

Cohort studies show inconclusive associations of replacing carbohydrates with saturated fat on long-term risk of all-cause mortality in people diagnosed with type 2 diabetes.

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

1. There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with SFAs with risk of all-cause mortality. There is one pooled analysis of 15 cohorts and a pooled analysis of two cohorts, with a total of >500 mortality cases, that address this topic. This is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as inconclusive.
2. There is heterogeneity in directions of associations between the cohort studies, with findings of both harmful and neutral associations. The pooled analysis of 15 studies showed a harmful association of substituting carbohydrates with SFAs, whereas the pooled analysis of two cohorts showed a neutral association. The heterogeneous findings may be due to differences in underlying subtypes and/or food sources of fats and carbohydrates. Due to this, the Committee marked the evidence as inconclusive.

Cohort studies show contradictory associations of replacing carbohydrates with polyunsaturated fat on long-term risk of all-cause mortality in people diagnosed with type 2 diabetes.

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

1. There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with PUFAs with risk of all-cause mortality. There is one pooled analysis of 15 cohorts and a pooled analysis of two cohorts, with a total of >500 mortality cases, that address this topic. This is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as contradictory.
2. There is a high level of heterogeneity in directions of associations between the cohort studies, with findings of both harmful and beneficial associations. The pooled analysis of 15 studies showed a harmful association of substituting carbohydrates with PUFAs, whereas the pooled analysis of two cohorts showed a beneficial association. The heterogeneous findings may be due to differences in underlying subtypes and/or food sources of fats and carbohydrates. Due to this, the Committee marked the evidence as contradictory.

Cohort studies show there is likely no association of replacing carbohydrates with monounsaturated fat on long-term risk of all-cause mortality in people diagnosed with type 2 diabetes.

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

1. There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with MUFAs with risk of all-cause mortality. There is one pooled analysis of 15 cohorts and a pooled analysis of two cohorts, with a total of >500 mortality cases, that address this topic. This is the first step required to mark the evidence as strong.
2. Both the pooled analysis of 15 studies and the pooled analysis of two cohorts showed a neutral association. There are no other considerations. Due to this, the Committee concluded there is likely no association.

Explanation:

The Committee did not find any MAs or SRs of cohort studies on the association of carbohydrate-fat substitutions with morbidity or mortality from chronic diseases. Two pooled analyses of cohorts and an analysis of an individual cohort were found that investigated associations of carbohydrate substitutions with fats in people with type 2 diabetes.

The outcomes were all-cause mortality, mortality from CVD, mortality from cancer, and CVD events (both fatal and non-fatal). The studies are further

explained below. All evaluations are of long-term associations (longer than one year).

The study of Campmans-Kuijpers et al.[4] (2016), evaluated substitutions of carbohydrates with different types of fats (SFA, MUFA, PUFA) and the risk of mortality due to CVD. The study included 6192 European participants with type 2 diabetes from 15 cohorts that contributed to the EPIC study. During a mean follow-up of 9 years, 268 participants died due to CVD. Diet was assessed at baseline. Substitution of 5 percent of energy intake of carbohydrates with SFA associated with a borderline significant increased risk of CVD mortality (HR 1.24 (95%CI 0.98, 1.57)). Substitution with PUFA also associated with increased risk of CVD mortality (HR 1.37 (95%CI 1.03, 1.81)). Substitution with MUFA associated with a borderline significant reduced risk of CVD mortality (HR 0.77 (95%CI: 0.58, 1.02)). Associations with all-cause mortality were in line with those of CVD mortality. The increased risk of (CVD) mortality with substituting PUFA for carbo- hydrates was particularly seen in northern European countries and not in middle or southern European countries. Dietary patterns and food sources contributing to PUFA and carbohydrate intake differ per European region. This may explain the (unexpected) increased risk.

The study of Jiao et al. (2019)[7] included 11264 US participants with type 2 diabetes from the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS). During a mean follow-up of 11 years, 2503 deaths occurred, of which 646 due to CVD and 406 due to cancer. Diet was assessed at baseline and repeatedly after that. Substitution of carbohydrates with SFA was associated with a non-significant higher risk of CVD mortality (HR in the highest versus lowest quartile of SFA intake: 1.13 (95%CI 0.80, 1.59)) but not with a risk of all-cause or cancer related mortality. Substitution with MUFA did not associate with risk of all-cause, CVD or cancer mortality. When MUFAs from animal sources were separately investigated, substitution of carbohydrates with those MUFAs associated non-significantly with an increased risk of CVD mortality. Substitution with PUFA associated with a lower risk of all-cause, CVD and cancer mortality. In particular, substitution of carbohydrates by n-3 marine PUFAs or linoleic acid was associated with reduced risk of CVD and/or all-cause mortality.

The cohort study of Tanasescu et al.[8] (2004) included 5672 individuals with type 2 diabetes from the NHS. During a maximum follow-up of 8 years, 619 CVD events (fatal and non-fatal combined) occurred. Diet was assessed at baseline and repeatedly after that. Substitution of 5 percent of energy intake of carbohydrates with SFA associated with a higher risk of CVD (RR 1.29 (95%CI 1.02, 1,63)). Substitution with MUFA tended to be associated with a lower CVD risk (RR 0.81 (95%CI 0.63, 1.04)). Substitution with PUFA was not associated with CVD risk. The authors noted the results did not materially change after further adjusting for use of hypoglycaemic or lipid-lowering drugs.

Inconsistencies in results between the different cohort studies regarding associations of substitutions of carbohydrates with MUFA and PUFA with CVD risk may be due to differences in underlying subtypes and/or food sources of fats and carbohydrates.

3.2 Carbohydrate – protein substitutions

Table 2 Association of carbohydrates and their substitution with proteins with risk of all-cause mortality, and morbidity and/or mortality from CVD and nephropathy: prospective cohort studies.

Cohort study; Study duration	Campmans-Kuijpers, 2015[5]; 9 years	Horikawa, 2017[6]; 8 years
Cohort	EPIC; Pooled analysis of 15 cohorts	Japan Diabetes Complications Study (JDCS)
Exposure	Substitution of 5 en% carbohydrates for proteins	Highest versus lowest tertile of carbohydrate intake
Dietary assessment method	Validated country-specific dietary questionnaire at baseline, either quantitative dietary questionnaires with individual portion sizes or semi-quantitative food frequency questionnaires	Food frequency questionnaire at baseline
Number of participants; number of cases	6107 participants; Total deaths: 787; CVD deaths: 266	1516 participants CVD events: 129; Overt nephropathy events: 81
Strength of the association: HR (95%CI) for CVD MORBIDITY and/ or MORTALITY	Substitutions of carbohydrates with: Total protein: 1.00 (0.82, 1.23) Animal protein: 1.02 (0.83, 1.25) Vegetable protein: 0.81 (0.33, 1.99) For CVD mortality	Substitutions of carbohydrates with: Total protein: 1.21 (0.76, 1.93) For CVD morbidity and mortality
Strength of the association: HR (95%CI) for OVERT NEPHROPATHY	NR	Substitutions of carbohydrates with: Total protein: 1.32 (0.71, 2.44)
Strength of the association: HR (95%CI) for ALL-CAUSE MORTALITY	Substitutions of carbohydrates with: Total protein: 1.00 (0.88, 1.12) Animal protein: 1.01 (0.90, 1.14) Vegetable protein: 0.55 (0.32, 0.93)	NR
Study population	People diagnosed with type 2 diabetes; diabetes duration[a]: 4 years; men and women; BMI: 28.4 kg/m^2; diabetes medications[b]: oral agents, insulin; Europe	People diagnosed with type 2 diabetes; diabetes duration[a]: 11 years; men and women; BMI: 22.9 kg/m^2; diabetes medications[b]: oral agents, insulin; Japan

BMI: body mass index; CVD: cardiovascular disease; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: Hazard Ratio; NR: not reported.

[a] Diabetes duration represents the average duration in the study population.

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that all participants used those medications).

The Committee concluded the following:

There is too little research regarding associations of replacing carbohydrates with proteins on long-term risk of morbidity or mortality due to CVD in people diagnosed with type 2 diabetes.

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

1. There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with proteins with risk of CVD. There is one pooled analysis of 15 cohort studies and one individual cohort study that address this topic, with a total of 395 CVD events. This excludes a conclusion with strong evidence (for which at least 500 CVD events are needed).

2. In both analyses, there was no association of replacement of carbohydrates with proteins with CVD risk. There are fewer than 500 cases included in the evaluation, which is too few to allow a conclusion of no association. Therefore, the Committee concludes there are too few studies to draw a conclusion.

There is too little research regarding associations of replacing carbohydrates with proteins on long-term risk of overt nephropathy in people diagnosed with type 2 diabetes.

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

There are no MAs of prospective cohort studies that address associations of substituting carbohydrates with proteins with risk of overt nephropathy. There is one individual cohort study that addresses this topic, which is too few to base conclusions on.

Cohort studies show that replacing carbohydrates with vegetable proteins associates with a lower long-term risk of all-cause mortality in people diagnosed with type 2 diabetes. The evidence is limited.

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

1. There are no MAs of prospective cohort studies that address associations of replacing carbohydrates with vegetable protein with risk of all-cause mortality. There is one pooled analysis of 15 cohorts, with more than 500 mortality cases, that addresses this topic. This is the first step required to mark the evidence as strong. However, there were other considerations to mark the evidence as limited.
2. There is an inverse association of replacing carbohydrates with vegetable protein with all-cause mortality. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. All cohorts in this pooled analysis are from the same consortium (EPIC) and therefore any dependency between cohorts cannot be ruled out. Because there is no other study that supports the result of the pooled analysis, the evidence was considered limited.

There is too little research to draw conclusions regarding the associations of replacing carbohydrates with total or animal protein on long-term risk of all-cause mortality in people diagnosed with type 2 diabetes.

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

1. There are no MAs of prospective cohort studies that address associations with risk of all-cause mortality. There is one pooled analysis of 15 cohorts, with more than 500 mortality cases, that addresses this topic.
2. There is no association of replacing carbohydrates with total or animal protein with all-cause mortality. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. All cohorts in this pooled analysis are from the same consortium (EPIC) and therefore any dependency between cohorts cannot be ruled out. Because there is no other study that supports the result of the pooled analysis, the evidence was considered limited. A conclusion of "*likely no association*" can only be drawn based on strong evidence.

Therefore, the Committee concludes there is too little research to draw a conclusion.

Explanation:

The Committee did not find any MAs or SRs of cohort studies on the association of carbohydrate-protein substitutions with morbidity or mortality from chronic diseases. One pooled analysis of 15 cohorts from the EPIC study and one individual prospective cohort (Japan Diabetes Complications Study [JDCS]) were found which investigated associations of carbohydrate substitutions with proteins in people with type 2 diabetes.[5,6] The outcomes were all-cause mortality, mortality from CVD, CVD events (both fatal and non-fatal) and overt nephropathy. The two reports are briefly explained below.

The pooled analysis of EPIC studies has already been explained in Section 3.1. The study found no associations of carbohydrate-protein substitutions on risk of CVD mortality and an inverse association of replacing carbohydrates with vegetable proteins on risk of all-cause mortality[5].

The study of Horikawa et al.[6] included 1516 participants with type 2 diabetes. Of those participants, 129 experienced CVD events and 81 overt nephropathy (severe nephropathy, defined as spot urinary albumin excretion >300 mg/g creatinine in two consecutive samples) events during 8 years follow-up. The study found no associations of substituting carbohydrates with total protein on both outcomes.

04 associations of fat subtype substitutions

Below, the scientific evidence for associations of substituting fat subtypes with health outcomes in people with type 2 diabetes is described.

Table 3 Association of saturated fat and its substitution with other fats with the risk of all-cause and cardiovascular mortality: prospective cohort studies.

Cohort study; **Study duration**	**Jiao, 2019[7];** **11 years (124 362 person-years)**
Cohort	Pooled analysis of NHS & HPFS
Exposure	Substitution of SFA with other fats, en% varies per substitution.
Dietary assessment method	Validated semi-quantitative food frequency questionnaires administered in 1980, 1984, 1986, and every four years thereafter in the NHS and every four years since 1986 in the HPFS (until 2014)
Number of participants; number of cases	11264 participants; Total deaths: 2503; CVD deaths: 646
Strength of the association: HR (95%CI) for CVD MORTALITY	Substitution of SFA with: PUFA (per 2 en%): 0.87 (0.77, 0.99) ALA (per 0.3 en%): 1.04 (0.88, 1.24) Marine n-3 (per 0.1 en%): 0.96 (0.89, 1.04) LA (per 2 en%): 0.85 (0.73, 0.99) AA (per 0.1 en%): 0.85 (0.58, 1.24) MUFA (per 2 en%): 0.99 (0.88, 1.11) Trans fat (per 2 en%): 1.02 (0.72, 1.43)
Strength of the association: HR (95%CI) for ALL-CAUSE MORTALITY	Substitution of SFA with: PUFA (per 2 en%): 0.88 (0.83, 0.94) ALA (per 0.3 en%): 0.92 (0.85, 1.00) Marine n-3 (per 0.1 en%): 0.92 (0.88, 0.96) LA (per 2 en%): 0.93 (0.86, 1.00) AA (per 0.1 en%): 0.96 (0.79, 1.16) MUFA (per 2 en%): 0.99 (0.94, 1.05) Trans fat (per 2 en%): 1.26 (1.06, 1.50)
Study population	People diagnosed with type 2 diabetes; diabetes duration[a] (age adjusted) ranging from 3 to 4 years over the quartiles of intake of fats; men and women; BMI[a] ranging from 27 to 30 kg/m^2 over the quartiles of intake of fats; diabetes medications[b]: oral agents, insulin; United States of America

BMI, body mass index; CVD, cardiovascular disease; en%, percentage of total energy intake; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-Up Study; HR, Hazard Ratio; SFA, saturated fat; PUFA, polyunsaturated fat; MUFA, monounsaturated fat, ALA, α-linolenic acid; Marine n-3, eicosapentaenoic acid and docosahexaenoic acid; LA, linoleic acid; AA, arachidonic acid.

[a] BMI and diabetes duration values represent the average in the study population.

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that all participants used those medications).

The Committee concluded the following:

There is too little research regarding associations of replacing saturated fat with other fat subtypes on long-term risk of all-cause mortality or mortality due to CVD in people diagnosed with type 2 diabetes.

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

The Committee found one pooled analysis of two cohort studies into the associations of substituting SFA with other fat subtypes with risk of all-cause and CVD mortality. Two cohort studies is too few to base conclusions on.

Explanation:

The Committee found a pooled analysis of the NHS and HPFS cohort studies on the association of substitutions of SFA with other fat subtypes with morbidity from all causes or CVD.[7] That study was already described in Section 3.1. Substitution of SFA with PUFA was associated with a lower risk of all-cause and CVD mortality. Substitution with MUFA was not associated with risk of all-cause and CVD mortality.

05 associations of substitutions of fat subtypes with combined proteins and carbohydrates

Below, the scientific evidence for associations of substituting fat subtypes with combined proteins and carbohydrates and health outcomes in people with type 2 diabetes is described.

Table 4 Association of saturated fat and polyunsaturated fat, and their substitution with combined proteins and carbohydrates, with risk of all-cause and cardiovascular mortality: prospective cohort studies.

Cohort study; **Study duration**	**Trichopoulou, 2006[10];** **4.5 years (4579 person-years)**
Cohort	EPIC Greece
Exposure	SFA per 10 g increment; PUFA per 9 g increment.
Dietary assessment method	Validated, interviewer-administered food frequency questionnaire at baseline
Number of participants; number of cases	1013 participants; Total deaths: 80; CVD deaths: 46
Strength of the association: HR (95%CI) for CVD MORTALITY	SFA (per 10 g/d): 1.93 (1.08, 3.42) PUFA (per 9 g/d): 1.20 (0.78, 1.84)
Strength of the association: HR (95%CI) for ALL-CAUSE MORTALITY	SFA (per 10 g/d): 1.82 (1.14, 2.90) PUFA (per 9 g/d): 1.44 (1.06, 1.96) MUFA (per 16 g/d): 1.28 (0.76, 2.16)
Study population	People diagnosed with diabetes (% type 2 diabetes NR); diabetes duration[a]: NR; men and women; BMI[a] ranging from <25 to ≥ 30 kg/m^2; diabetes medications[b]: oral agents, insulin; Europe (Greece)

BMI, body mass index; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; HR, Hazard Ratio; SFA, saturated fat; PUFA, polyunsaturated fat; NR, not reported.

[a] BMI and Diabetes duration values represent the average in the study population.

[b] Diabetes medications represent the types of medications that were used among the participants (it does not mean that all participants used those medications).

The Committee concluded the following:

There is too little research regarding associations of replacing saturated fat or polyunsaturated fat with carbohydrates and protein on long-term risk of all-cause and CVD mortality in people diagnosed with type 2 diabetes.

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

The Committee found one individual cohort study into the associations of substituting SFA and PUFA with proteins and carbohydrates with risk of all-cause and CVD mortality. One cohort study is too few to base conclusions on.

Explanation:

The Committee found one individual cohort study on the association of substitutions of SFA and PUFA with a combination of protein and carbohydrates with mortality from all causes or CVD. This study is described below.

Trichopoulou et al. (2006)[10] evaluated the associations of SFA and PUFA with risk of all cause and CVD mortality among 1013 participants with diabetes. During a mean follow-up of 4.5 years, 80 participants died. Diet was assessed at baseline with a food frequency questionnaire.

The associations were adjusted for intakes of the remaining fatty acids (e.g. associations of SFA with CVD mortality were adjusted for PUFA and MUFA intakes) and total energy intake. No adjustments for carbohydrate and protein intakes were made. The results can therefore be interpreted as substitutions of SFA or PUFA for a combination of proteins and carbohydrates. Each 10 g/d increment of SFA (as replacement for carbohydrates and proteins) associated with a statistically significant 93% higher risk of CVD mortality and 82% risk of all-cause mortality. Higher PUFA intake (as replacement for carbohydrates and proteins) also associated with a higher risk of all-cause mortality, but not with CVD mortality.

06 summary of conclusions

Table 5 Overview of conclusions regarding associations of carbohydrate and fat substitutions with other macronutrients with health outcomes in people diagnosed with type 2 diabetes, from cohort studies.

Health outcome[a]	Substitution	Conclusion
CVD morbidity and/or mortality	*Carbohydrate – SFA*	Substitution of 5 energy percent carbohydrates with SFA associates with a 25% higher risk; strong evidence
CVD morbidity and/or mortality	*Carbohydrate – PUFA*	Contradictory evidence
CVD morbidity and/or mortality	*Carbohydrate – MUFA*	Inconclusive evidence
All-cause mortality	*Carbohydrate – SFA*	Inconclusive evidence
All-cause mortality	*Carbohydrate – PUFA*	Contradictory evidence
All-cause mortality	*Carbohydrate – MUFA*	No association
CVD morbidity and/or mortality	*Carbohydrate – protein*	Too little research
All-cause mortality	*Carbohydrate – vegetable protein*	Substitution of carbohydrates with vegetable proteins associates with a lower risk; limited evidence
All-cause mortality	*Carbohydrate – total or animal protein*	Too little research
Cancer mortality	*Carbohydrate – SFA, MUFA, PUFA or protein*	Too little research
CVD mortality	*SFA – PUFA (subtypes), MUFA or Trans fat*	Too little research
All-cause mortality	*SFA – PUFA (subtypes), MUFA or Trans fat*	Too little research
CVD morbidity and/or mortality	*SFA – protein and carbohydrate*	Too little research
CVD morbidity and/or mortality	*PUFA – protein and carbohydrate*	Too little research
All-cause mortality	*SFA – protein and carbohydrate*	Too little research
All-cause mortality	*PUFA – protein and carbohydrate*	Too little research

[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.

references

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annex A
literature selection

The search for MA and SR regarding cohort studies into associations of carbohydrate substitutions with other macronutrients is described in the background document *Reduced carbohydrate diets*.[3] It yielded no relevant articles of cohort studies.

Since no MA and SR reporting evidence from cohort studies were found, external dietary diabetes guidelines for people with type 2 diabetes of the following organizations were searched for individual cohort studies with respect to associations of carbohydrate substitutions with other macronutrients on health outcomes:

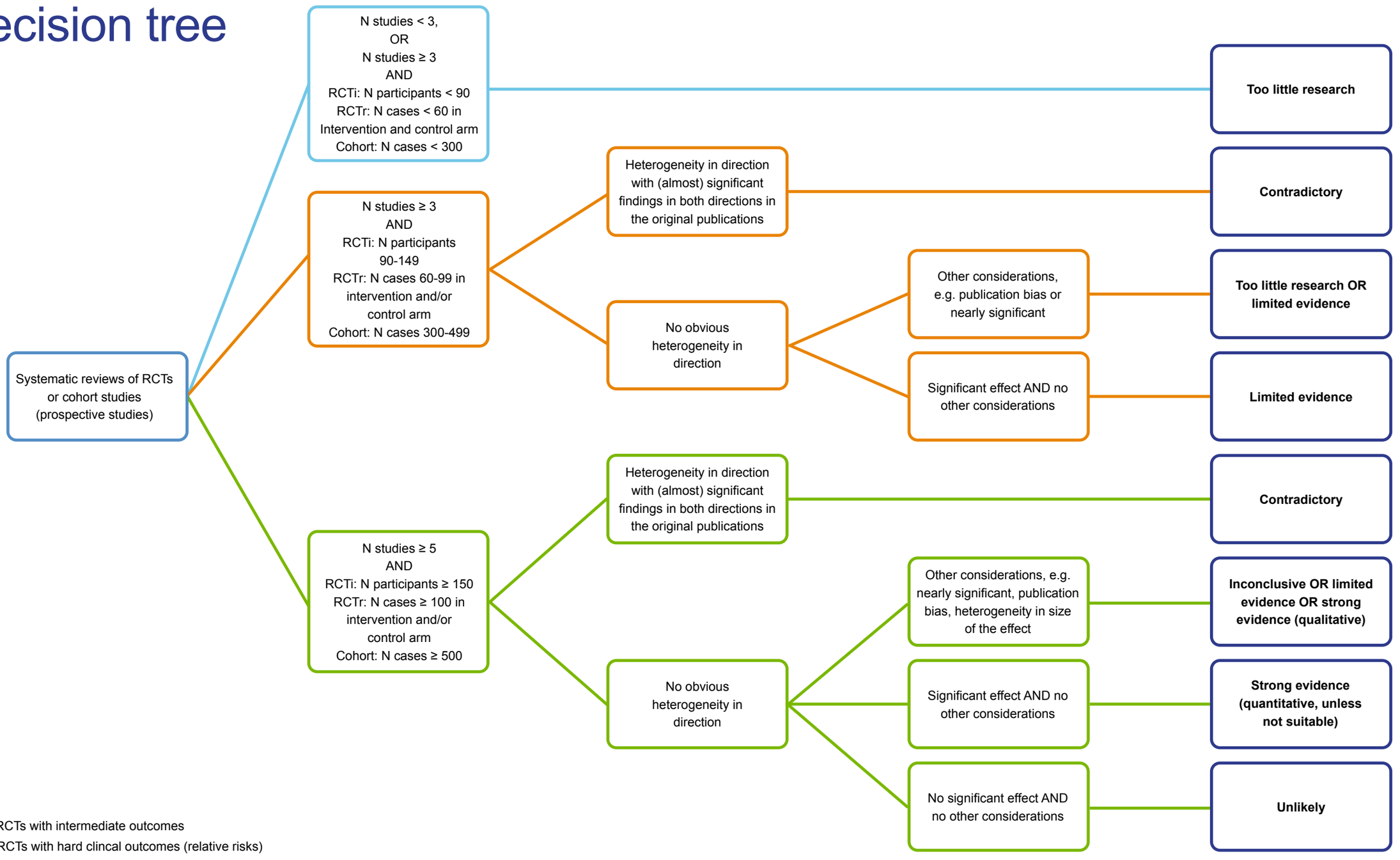
- Nederlandse Diabetes Federatie (NDF), 2020[11];
- European Association for the Study of Diabetes (EASD) & European Society of Cardiology (ESC), 2019[12];
- American Diabetes Association (ADA) 2019[13];
- Diabetes UK, 2018[14];
- Diabetes Canada, 2018[15];
- Swedish Council, 2010.[16]

One prospective cohort study was found in the guideline of Diabetes UK (Horikawa et al., 2017[6]). Next, articles citing this cohort study were searched in PubMed on 6 January 2021. This yielded 9 hits, of which all non-relevant. Then, similar articles were searched in Pubmed on 6 January 2021. This yielded 418 hits. Of those, 3 articles on cohort studies were selected, authored by Campmans-Kuijpers et al. (2015 and 2016)[4,5] and Tanasescu et al. (2004)[8]. Next, articles citing those 3 cohort studies were searched in Pubmed on 6 January 2021. This yielded 7 hits (citing Campmans-Kuijpers et al. (2015), 8 hits citing Campmans-Kuijpers et al. (2016) and 31 hits citing Tanasescu et al. (2004). From those, one additional cohort study was selected, that of Jiao et al. (2019)[7]. Thus, in total five prospective cohort studies were selected by the Committee:

- Horikawa et al., 2017[6];
- Campmans-Kuijpers et al., 2015[5];
- Campmans-Kuijpers et al., 2016[4];
- Tanasescu et al., 2004[8];
- Jiao et al., 2019.[7]

annex B

decision tree



RCTi: RCTs with intermediate outcomes
RCTr: RCTs with hard clincal outcomes (relative risks)

annex C
conflicts of interest

In the table below, the funding sources of the studies listed in this background document and conflicts of interests of authors contributing to those studies are reported.

Study's first author, year	Funding of the work	Conflicts of interest of authors
Campmans-Kuijpers, 2016[4]	It was reported that the paper was written without any funding. Financial support for the EPIC study came from the European Commission, national ministries and research councils.	One of the authors reported to have received research grants from FrieslandCampina and Unilever R&D for research on fatty acids and their food sources. No other authors declared a conflict of interest.
Horikawa, 2017[6]	This study was supported by the Ministry of Health, Labor and Welfare. It was reported that the funding sponsors had no role in the design of the study, the collection, analyses or interpretation of data, the writing of the manuscript or in the decision to publish the results.	The authors declared there were no conflicts of interest.
Jiao, 2019[7]	The study was sponsored by the National Institutes of Health. It was reported that the funders had no role in the design and conduct of the study, the collection, management, analysis and interpretation of the data, the preparation, review and approval of the manuscript, or the decision to submit the manuscript for publication.	One of the authors reported to have received research funding by Unilever R&D, and another author has received research support or honorariums from the California Walnut Commission and Diet Quality Photo Navigation, outside the submitted work. No other notable conflicts of interest were reported.
Tanasescu, 2004[8]	The study was supported by research grants from the National Institutes of Health and by an American Heart Association Established Investigator Award.	Not reported.
Trichopoulou, 2006[10]	The work was supported by the European Commission, the Greek Ministries of Health and Education, and the University of Athens.	The authors declared there were no conflicts of interest.
Campmans-Kuijpers, 2015[5]	It was reported that the paper was written without any funding. Financial support for the EPIC study came from the European Commission, national ministries and research councils.	The authors declared there were no conflicts of interest.

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.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity.
The reports are available to the public.

This publication can be downloaded from www.healthcouncil.nl.

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