Methodology for the evaluation of evidence

No. 2021/41Ae, 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 used by the Permanent Committee on Nutrition for the evaluation of the evidence regarding the relationships of dietary factors and health outcomes among people with type 2 diabetes.

The Dutch State Secretary for Health, Welfare and Sport requested the Health Council of the Netherlands to advise on the applicability of the *Dutch dietary guidelines,* that were published by the Health Council in 2015 (DDG2015)[2], for people with cardiometabolic diseases or at high risk of such diseases. In addition, the State Secretary requested the Health Council to specify, where applicable, which disease-specific modifications of the DDG2015 would be needed for those people. Based on this, the Permanent Committee on Nutrition of the Health Council formulated the following main- and sub-questions:

Main question:
Are the DDG2015 a suitable basis for a healthy diet for people with cardiometabolic diseases?

Sub-questions:

1. Which existing dietary recommendations in the DDG2015 should be modified?
2. Are there dietary recommendations that should be added to the DDG2015?
3. Should the dietary recommendations be different for subgroups of people based on sex, body weight status, comorbidities and medication use?

Cardiometabolic diseases include diabetes and cardiovascular diseases. Obesity and chronic kidney disease may also be considered part of this disease cluster. The Committee prioritized two topics within the domain of people with cardiometabolic diseases, for which separate recommendations were prepared. In the current background document, the Committee presents the methodology applied in evaluating the scientific evidence for the first advisory report regarding the DDG2015 for people with *type 2 diabetes*.

Since 2015, new studies, performed in the general population, have been published on the topics that were evaluated for the DDG2015. However, the Committee did not update the DDG2015 of 2015 for the general population. Rather, the Committee focused on evaluating the scientific evidence for people with type 2 diabetes, and pointed out where deviations from the DDG2015, as published in 2015, are recommended.

A healthy diet is part of a healthy lifestyle, but other lifestyle factors such as getting ample exercise and refraining from smoking are important for people's general health, including for those with type 2 diabetes. Lifestyle factors other than diet fall beyond the scope of the current advisory report. This report focuses on the applicability of the DDG2015 for people with type 2 diabetes.

Eleven background documents were prepared for the advisory report *Dutch dietary guidelines for people with type 2 diabetes*.[1] In the current methodological background document, the Committee describes how it evaluated the status of scientific knowledge. This evaluation resulted in 10 other background documents that describe the status of scientific evidence for the following nutritional topics:

- Fruit and vegetables[3];
- Whole grain foods[4];
- Dietary fibre[5];
- Legumes[6];
- Beverages with added sugar[7];
- Dairy products[8];
- Coffee[9];
- Sodium[10];
- Substitution of carbohydrates and fats[11];
- Reduced carbohydrate diets.[12]

In each background document, the Committee drew conclusions on the level of evidence for each of these nutritional topics in relation to health outcomes. Next, the Committee evaluated whether, based on those conclusions, there were indications for modifications of, or additional recommendations to the DDG2015 for people with type 2 diabetes.

In this introductory chapter, the Committee explains the target group (also called domain) covered by this advisory report. Chapter 2 describes the nutritional topics and health outcomes selected by the Committee. Chapter 3 describes the approach used for literature research, and Chapter 4 explains how the Committee drew conclusions in the background documents.

A working group 'Diabetes' of the Permanent Committee on Nutrition prepared the background documents and drew conclusions. The working group compiled and weighted the evidence and advised the Nutrition Committee regarding the formulation of recommendations. The Nutrition Committee takes final responsibility for the content of the advisory report and background documents. The composition of the Diabetes working group and Nutrition Committee is presented in **Annex A**.

1.1 Domain of the advisory report

The Committee selected the subgroup of people with type 2 diabetes within the domain of people with cardiometabolic diseases. This subgroup was selected since cardiometabolic diseases are among the disorders with the highest mortality, disease burden and prevalence in the Netherlands[13], and there are suggestions that the composition of the diet can impact the health of people with type 2 diabetes.[14-16]

The advisory report is applicable to people with type 2 diabetes with all types of diabetes treatment (diet, oral anti-hyperglycaemic agents, and/or insulin). Also, the Committee assumes the advisory report is applicable to both children (of 2 years and older) and adults with type 2 diabetes. The evaluation of the Committee only included research performed among adults with type 2 diabetes. From existing dietary guidelines for people with type 2 diabetes, the Committee noted that such research in children and adolescents is sparse.[17-23] For the DDG2015, the research was primarily based on adults and then applied to people aged 2 years and older. For the current advice, the Committee sees no reason to deviate from this.

The recommendations in the advisory report do not apply to people with type 2 diabetes who already require dietary advice for other conditions, such as celiac disease (gluten intolerance).

In addition, the advisory report is not applicable to women with gestational diabetes since this a pregnancy-related complication, and a *risk factor* for type 2 diabetes.

The Committee often found studies that excluded people with major complications of diabetes (clinically established micro- and macro-vascular disorders such as proliferative retinopathy and blindness, renal failure, myocardial infarction, heart failure). Due to this, there is some uncertainty regarding the applicability of this advisory report to this group. The Committee notes that the DDG2015 can be applied to this group as long as there is no evidence that suggests otherwise.

Finally, the recommendations of the Committee are aimed at improving the long-term health of people with type 2 diabetes (i.e. prevention of common chronic diseases, as is explained in Section 2.2), similar to the approach taken for the DDG2015. For people with type 2 diabetes, management of daily blood glucose levels is of importance as well. The consumption of foods rich in complex carbohydrates and dietary fibre, which are recommended in the DDG2015, contribute to that.[24,25] However, the Committee did not evaluate the effects of diet on acute postprandial effects since (individual) short-term regulation of blood glucose levels is not in the scope of the DDG2015, which focus on prevention of common chronic diseases in long term.

02 selection of nutritional topics and health outcomes

The Committee used recent (national and international) evidence-based dietary guidelines for people with type 2 diabetes to select relevant nutritional topics and health outcomes for its evaluation, as explained further in Sections 2.1 and 2.2. Reports of the following organizations were considered:

- European Association for the Study of Diabetes (EASD) & European Society of Cardiology (ESC), 2020[17];
- American Diabetes Association (ADA), 2019[20];
- Diabetes UK, 2018[19];
- Diabetes Canada, 2018[18];
- Joint Scientific Advisory Committee Nutrition (SACN), 2021[22];
- Netherlands Diabetes Federation (NDF), 2020[21];
- Swedish Council, 2010.[23]

2.1 Nutritional topics

The Committee assumes that the DDG2015 are applicable to people with type 2 diabetes because they are based on research performed in the general population (and not just in the healthy population). Since part of the general population has type 2 diabetes, this group was implicitly included in the evaluations on which the DDG2015 are based.

The DDG2015 focus on the prevention of common chronic diseases such as coronary heart disease and stroke, which people with type 2 diabetes have an increased risk of developing. However, studies carried out entirely on people already suffering from type 2 diabetes were not considered in preparing the DDG2015. An evaluation of such research could help formulate possible disease-specific adaptations or additions to the DDG2015 for people with type 2 diabetes.
The Committee used the DDG2015 as a starting point and considered whether there were any indications that adaptations or additions might be needed for people with type 2 diabetes. This means that the Committee recommends that people with type 2 diabetes follow the DDG2015, unless proven otherwise.

In this advisory report, the Committee uses the term ‘dietary factors’ as an umbrella term for foods, beverages, nutrients and dietary patterns.

For eight of the current dietary recommendations in the DDG2015, the Committee saw reasons to conduct a specific evaluation for people with type 2 diabetes, namely the guidelines on fruits and vegetables, whole grain foods, legumes, sugar-containing beverages, dairy products, coffee and salt. In addition, the Committee opted to evaluate carbohydrate-restricted dietary patterns.

In selecting these topics, the Committee used Dutch and international reports with dietary guidelines for people with type 2 diabetes.[17-23]
The dietary factors covered in these reports were compared with the dietary factors evaluated for the DDG2015. All dietary factors for which the DDG2015 contain recommendations were also covered in the aforementioned reports. All conclusions or recommendations for a dietary factor that differed from the DDG2015 or that had not been evaluated for the DDG2015 were considered eligible for evaluation by the Committee.
The following considerations were also taken into account in selecting the dietary factors to be evaluated:

1. Coverage of the dietary factor in one or more of the aforementioned reports.
2. Limited scientific evidence on this dietary factor in people with type 2 diabetes in the aforementioned reports.
3. Expert judgement of the Committee (for example: a dietary factor is under discussion among caregivers, policy officers, researchers and/or patients).

A more detailed explanation of the selection of these individual dietary factors is given in Table 1.

Only dietary factors that fit into a conventional dietary pattern were selected, and dietary supplements or specific weight-loss diets (such as intermittent fasting or diets with strict energy restriction and meal replacements) were not considered.

For those dietary factors from the DDG2015 that were not evaluated by the Committee for the current advisory report, the Committee assumes that they are important for people with type 2 diabetes but that no adjustments are necessary for this group, based on the aforementioned reports.[17-23]

As many people with type 2 diabetes are overweight or obese and dietary intake is inextricably linked to energy balance, the Committee also addresses the importance of weight reduction. However, the Committee does not make any recommendations on how people with type 2 diabetes can best lose weight and therefore does not specifically address weight-loss diets.

Some of the intervention studies on dietary factors from the DDG2015 that have been evaluated in people with type 2 diabetes were carried out in combination with mild energy restriction. However, weight reduction was not a primary goal of these studies. In interpreting these studies, the Committee considered whether the prescribed amounts of energy materially differed between the intervention group and the control group.

When evaluating intervention studies on carbohydrate-restricted dietary patterns, it appeared that most of these studies were carried out with the underlying aim of losing weight, but the Committee did not necessarily select this diet as a weight-loss diet. Moreover, this dietary pattern is not only used for weight reduction, as it can also improve blood glucose levels, which is why the Committee still included this dietary pattern in its advisory report.

For people with type 2 diabetes looking to watch their weight (maintain their body weight or limit weight gain), the Committee has included in Chapter 5 several pointers with regard to choices that can be made within the food groups on which the Committee advises, such as product type and quantity.

Table 1 Nutritional topics selected for evaluation.

Nutritional topic	Explanation
Dairy products, including whole fat versus (semi) skimmed	The following DDG2015 recommendation applies to dairy products: Take a few portions of dairy products daily, including milk or yogurt. Cohort studies show that higher consumption of certain subgroups of dairy products, such as yoghurt, is associated with a lower risk of developing type 2 diabetes.[2] This raised the question among the Committee members as to whether dairy products are also beneficial for people who already have type 2 diabetes. The Committee wished to evaluate whether the dairy recommendation could be made more specific with regard to the fat content of the dairy for people with type 2 diabetes. This issue is addressed by only one of the reports with dietary guidelines for people with type 2 diabetes[21] and, according to the Committee, it is currently the subject of debate.
Coffee	Concerning coffee, the 2015DDG Committee derived the following guideline: Replace unfiltered coffee by filtered coffee. There is strong evidence from cohort studies that higher coffee consumption is associated with a lower risk of developing type 2 diabetes.[2] This raised the question among the Committee members of whether coffee consumption also benefits the long-term health of people who already have type 2 diabetes. The association between coffee consumption and the long-term health of people already suffering from type 2 diabetes was addressed in only one of the reports with dietary guidelines for people with type 2 diabetes, dating from 2010.[23] In order to gain a good understanding of the current state of scientific knowledge by examining more recent literature, the Committee decided to include this topic in its evaluation.
Salt	The following DDG2015 recommendation applies to sodium intake: Limit salt intake to 6 grams daily (equals 2400 mg/d sodium). The DDG2015 recommend eating no more than 6 grams of salt per day, which is equivalent to 2400 mg of sodium per day. According to the Committee, it has been debated whether the maximum sodium intake should be lower for people with type 2 diabetes, given their higher risk of developing chronic kidney disease and cardiovascular disease.[26] The Committee wished to evaluate whether the recommended maximum salt intake should be adjusted for people with type 2 diabetes. Salt is a topic that was also addressed in the reports with dietary guidelines for people with type 2 diabetes.[17-21,23]

Nutritional topic	Explanation
Carbohydrate-restricted dietary patterns & carbohydrate food sources: fruit and vegetables, whole grain products, legumes, sugar-containing beverages	Several dietary patterns, such as Mediterranean, DASH and vegetarian dietary patterns, were evaluated for the DDG2015. These dietary patterns were found to be beneficial for overall health. Since the diets in question shared many similarities, such as a relatively high intake of plant-based products and fish and a relatively low intake of red and processed meats and hard fats, the findings on these dietary patterns were ultimately reflected in the overarching recommendation to: 'Follow a dietary pattern that involves eating more plant-based and less animal-based food'. The underlying principles of these dietary patterns are also reflected in the guidelines on the level of foods and beverages. The Committee found no discrepancies in conclusions about the dietary patterns in question, such as the Mediterranean diet, in reports with guidelines for people with type 2 diabetes. However, it did note that these reports do cover carbohydrate-restricted dietary patterns, which had not been evaluated for the DDG2015.[17-23] These dietary patterns are of particular interest with respect to people with type 2 diabetes, due in part to the fact that carbohydrates directly affect blood glucose levels.[27-33] The Committee has therefore considered whether the *Dutch dietary guidelines for people with type 2 diabetes* should set a limit for the maximum recommended percentage of energy derived from carbohydrates. As the DDG2015 make recommendations about foods and given the fact that the quantity of carbohydrates and the quality of carbohydrate food sources (such as fruit and cereal products) can both matter for health[34], the Committee evaluated the carbohydrate food sources about which the DDG2015 made recommendations, for people with type 2 diabetes. This includes vegetables, fruit, whole grain products, legumes and sugar-containing beverages. The Committee also evaluated the literature on dietary fibre from vegetables, fruit, wholemeal and oat products for people with type 2 diabetes. These dietary factors were also addressed in reports presenting dietary guidelines for people with type 2 diabetes.[17-21,23] The following DDG2015 recommendations apply to carbohydrate food sources: • Eat at least 200 grams of vegetables and at least 200 grams of fruit daily; • Eat at least 90 grams of brown bread, wholemeal bread or other; wholegrain products daily; • Eat legumes weekly; • Replace refined cereal products by whole-grain products; • Minimise consumption of sugar-containing beverages.*

* This includes beverages with added sugars, and beverages that naturally contain sugars, such as fruit juices.

Nutritional topics not selected for evaluation

The remaining nutritional topics addressed in the DDG2015 were not evaluated for people with type 2 diabetes. According to the expert judgement of the Committee and existing evidence-based dietary guidelines for people with type 2 diabetes[17-23], there were no indications that deviations would be required.
Those are:
Follow a dietary pattern that involves eating more plant-based and less animal-based food, as recommended in the following guidelines:

- Eat at least 15 grams of unsalted nuts daily;
- Eat one serving of fish weekly, preferably oily fish;
- Drink three cups of tea daily;
- Replace butter, hard margarines, and cooking fats by soft margarines, liquid cooking fats, and vegetable oils;
- Limit the consumption of red meat, particularly processed meat;
- Don´t drink alcohol or no more than one glass daily;
- Nutrient supplements are not needed*, except for specific groups for which supplementation applies.**

* This guideline applies to (multi)vitamins and minerals.
** For example: certain subgroups of the population are advised to use Vitamin D supplements, including children up to the age of 3 years, people with a dark skin and low exposure to sunlight, pregnant women, women aged 50 years and older, men aged 70 years and older.

2.2 Health outcomes

Table 2 shows an overview of the health outcomes selected for evaluation by the Committee. The Committee distinguished long-term health outcomes and short-term, surrogate outcomes. In preparing the background documents, the Committee searched for literature regarding all outcomes listed below. Next, the scientific evidence for outcomes with available relevant literature was described in the background documents.

Table 2 Health outcomes selected for evaluation.

Long-term health outcomes	Short-term surrogate outcomes
• Morbidity and mortality from coronary heart disease, stroke, heart failure, type 2 diabetes, chronic obstructive pulmonary diseases, breast cancer, colorectal cancer, lung cancer, dementia, depression.* • Morbidity and mortality from chronic kidney disease.** • All-cause mortality.* • Morbidity and/or mortality from total cardiovascular disease and total cancer.*	• Glycated haemoglobin (HbA1c).** • Fasting blood glucose.** • Body weight.* • Systolic blood pressure.* • Low-density lipoprotein (LDL) cholesterol.* • Estimated glomerular filtration rate (eGFR).**

* Those outcomes were selected since they were also considered for all or a selection of evaluations that contributed to the DDG2015;

** Those outcomes were additionally selected since they are common long-term complications of diabetes or markers relevant in diabetes management.

2.2.1 Long-term health outcomes

The guidelines were drawn up to prevent common chronic diseases in people with type 2 diabetes (similar to the DDG2015 approach), including, but not solely focusing on, diabetes-related complications.

The Committee selected long-term health outcomes similar to the DDG2015 advisory report. For the DDG2015 advisory report, the top 10 diseases in the Netherlands with respect to mortality, years of potential life lost and burden of disease were selected. These were coronary heart disease, stroke, heart failure, type 2 diabetes mellitus, chronic obstructive pulmonary diseases, breast cancer, colorectal cancer, lung cancer, dementia, and depression.[2] The Committee noted that those were also among the top 10 diseases in more recent years.[13]

In addition, chronic kidney disease was selected as an outcome since this is a long-term complication of diabetes, and was not yet covered in the aforementioned list of outcomes. Retinopathy and neuropathy are also important complications of type 2 diabetes. However, existing evidence-based dietary guidelines for people with type 2 diabetes pointed out there is a scarcity of literature regarding the direct effects of diet on retinopathy and neuropathy[17-23], and therefore they were discarded as outcomes in this advisory report. Instead, key underlying risk factors such as glycaemic control and blood pressure were considered (see Section 2.2.2).

The Committee also evaluated all-cause mortality, mortality and morbidity from multiple types of cardiovascular diseases combined (total cardiovascular disease), and mortality and morbidity from multiple types of cancer combined (total cancer).

2.2.2 Short-term, surrogate outcomes

Clarifying the effect of diet on morbidity and mortality outcomes in randomized controlled trials (RCTs) requires an intervention period of (at least) several years and a large number of participants. Such studies are difficult to implement and are expensive and therefore few in number. A frequently used alternative has been the use of surrogate outcomes in RCTs. The Committee applies the definition proposed by DeMets et al. for surrogate outcomes. DeMets et al. explains that surrogate outcomes can be seen as replacement endpoints for the disease of interest, and are thought to capture the causal pathway that leads to the disease outcome.[35] An example is the use of LDL cholesterol or systolic blood pressure as surrogate endpoints for coronary heart disease. The advantage of using surrogate endpoints in experimental studies is that they involve significantly fewer participants and shorter study durations than the outcomes morbidity or mortality. For instance, dietary effects on LDL cholesterol or systolic blood pressure can be identified in just a few weeks, compared to several years for coronary heart disease.

For the current advisory report, the Committee accepted a surrogate outcome as sufficiently verified surrogate outcome when there is evidence from cohort studies showing that it predicts the risk of disease, and when RCT results demonstrate that one (or preferably multiple) intervention(s) on the surrogate outcome leads to a change in the surrogate outcome and in the risk of disease[a]. Evidence from Mendelian randomization studies (described in the box below) pointing towards causal associations of surrogate outcomes with disease risk were additionally used to accept a surrogate outcome as sufficiently verified, but were not defined as necessary evidence.

Mendelian randomization studies

More recently, Mendelian randomization (MR) studies have been introduced to help to elucidate the causality of relationships between modifiable surrogate endpoints and disease outcomes. In such studies, the relationship between genetic variations that predict the surrogate endpoints and disease risk is investigated using observational data. Such studies can be seen as natural experiments since genetic factors are randomly assigned by nature. MR studies are less likely to be affected by confounding or reverse causation than conventional observational studies, given that three key MR assumptions are met. Those assumptions are that the genetic variants associate with the surrogate endpoint of interest; that the genetic variants have no other influence on the outcome, except through the surrogate outcome; and that there are no confounders of the genetic variants-outcome association.[36]

[a] Even if an intervention had the intended effect on the surrogate outcome, the effect of the intervention on the disease outcome of interest may be affected by other mechanisms that are not captured by the surrogate outcome (a so-called off-target effect). The Committee makes the assumption there are no or minimal off-target effects of the dietary interventions that were evaluated in relation to the surrogate outcomes. The Committee believes this is a valid assumption since the dietary interventions under study were of foods that are already consumed by the general population. Also, the levels of intakes of those foods in the studies are within a range that is consumed by the general population. It would be expected that any serious off-target effects would already have been found in the general population, for instance in large-scale population based cohort studies. Such off-target effects have not been reported for the evaluated nutritional topics.

The Committee selected short term, surrogate outcomes similar to the DDG2015 approach (body weight, systolic blood pressure and LDL cholesterol). Furthermore, markers of glucose control and kidney function were selected since those are relevant in diabetes management according to treatment guidelines.[37,38] The selected (and some unselected) outcomes are explained below.

Body weight, systolic blood pressure and LDL cholesterol

Body weight, systolic blood pressure and LDL cholesterol were selected in line with the approach used for the DDG2015. As explained in the DDG2015 methodology document[39], those markers have been shown to have a causal relationship with at least one of the following chronic diseases: coronary heart disease, stroke, heart failure and type 2 diabetes. Below, additional, more recent evidence that confirms the causality is presented, as well as evidence for such relationships in people with type 2 diabetes.

Body weight

Recent evidence from Mendelian randomization studies confirmed a causal association between the level of adiposity and coronary heart disease risk.[40,41] Among people with diabetes, weight loss of at least 5% improves glycaemic control, lipid levels, and blood pressure.[42]

Systolic blood pressure

Recent evidence from Mendelian randomization studies supports that blood pressure is causally associated with the risk of coronary heart disease and stroke.[43,44] Among people with diabetes, blood pressure lowering therapies also lead to improvements in cardiovascular outcomes: A meta-analysis of RCTs with a median duration of 3.6 years showed that every 10 mmHg reduction in systolic blood pressure associated with an 11% lower risk of cardiovascular events (myocardial infarction, sudden cardiac death, revascularization, fatal and nonfatal stroke and fatal and nonfatal heart failure), a 27% reduction in stroke risk, and a 12% reduction in the risk of coronary heart disease.[45]

LDL cholesterol

Recent reports confirmed that numerous and different types of studies, including prospective cohort studies, RCTs and Mendelian randomization studies, have convincingly shown higher LDL cholesterol to cause atherosclerotic cardiovascular disease.[46] Furthermore, among people with type 2 diabetes, LDL-lowering therapies lead to statistically significant improvements in cardiovascular disease outcomes: A meta-analysis of RCTs showed that every 1 mmol/L reduction in LDL cholesterol was associated with a 22% lower risk of major vascular events (coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke) at one year. The risk of coronary death or non-fatal myocardial infarction was reduced by 24% and the risk of stroke by 16%.[47]

Markers of glucose control and kidney function

In addition to the outcomes described above, the Committee made a selection of outcomes reflecting glucose control and kidney function. These outcomes were selected since they are relevant for diabetes management and important (potentially causal) predictors of long-term diabetes complications.

Glucose control: Glycated haemoglobin (HbA1c) and fasting glucose

HbA1c reflects the average blood glucose concentrations of the past 2 to 3 months whereas fasting glucose reflects a blood glucose concentration at one point in time. Large observational studies have shown continuous associations between various measures of glycaemia, including fasting glucose levels and HbA1c, and the risk of cardiovascular disease.[48] Moreover, Mendelian randomization studies have shown a causal association of HbA1c with coronary heart disease risk.[49,50] Meta-analyses of RCTs have shown that long-term (average of 5 years) intensive glucose control therapies, accompanied by a reduction in HbA1c of 0.9%, reduce microvascular complications (progression of retinopathy and nephropathy) in people with type 2 diabetes compared to conventional glucose control therapies.[51] With respect to cardiovascular outcomes, meta-analyses of RCTs have shown that a 0.9% reduction in HbA1c has a modest benefit on major cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction and non-fatal stroke; 9% risk reduction), particularly non-fatal myocardial infarctions (17% reduced risk) and coronary heart diseases (15% reduced risk), but not stroke, with long-term (average of 5 years) intensive glucose control therapies. Those effects were particularly apparent for people who were relatively young and early in the course of diabetes.[48,52]

Estimated glomerular filtration rate

The estimated glomerular filtration rate (eGFR, estimated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]-formula), is generally used as measure of kidney function in epidemiological studies. The definition of chronic kidney disease is (among other things) based on this marker.[53] Cohort studies have shown that eGFR is an independent risk factor for cardiovascular morbidity and mortality.[54] Also in high-risk groups, such as people with diabetes, eGFR independently predicted cardiovascular mortality.[55] Moreover, RCTs that studied effects of therapies with sodium-glucose cotransporter-2 (SGLT-2) inhibitors, or inhibitors of the renin-angiotensin-aldosterone system (RAAS), showed that such therapies reduced the progression of eGFR decline, leading to less cases of end stage kidney disease in people with type 2 diabetes.[56]

Markers of the lipid profile that were not selected

Small dense LDL cholesterol was not selected as an outcome by the Committee. There are pathophysiological theories stating that the small particles of total LDL cholesterol, in particular, may be a risk factor for atherosclerotic cardiovascular disease. This was confirmed in a few

cohort studies, and in the placebo group of a large statin trial, where small particles of LDL, but not the large particles of LDL, predicted cardiovascular disease outcomes, independent of total LDL cholesterol. However, there is currently no convincing evidence that interventions targeted at reducing small dense LDL lead to reductions in cardiovascular disease outcomes.[57]

HDL cholesterol was not selected as an outcome, despite that cohort studies have shown that higher HDL cholesterol levels are associated with reduced cardiovascular disease outcomes.[58] There is currently no convincing evidence that increasing HDL cholesterol leads to reductions of cardiovascular disease outcomes.[59] In addition, Mendelian randomizations studies showed no evidence for a causal relation of HDL cholesterol with cardiovascular disease outcomes.[60] The Committee does not rule out specific HDL functions and particles may lower cardiovascular disease risk, but there is currently no convincing evidence from human RCTs to support this.[61,62]

Triglycerides were not included as an outcome by the Committee. Although cohort studies and genetic epidemiological studies convincingly suggested a causal role of triglycerides in atherosclerotic cardiovascular disease development[63,64], evidence that intervening on triglycerides, particularly with fibrates, reduces cardiovascular events is limited.[65] Also, among people with diabetes, lowering triglycerides by fibrates did not reduce cardiovascular disease outcomes.[66]

2.2.3 Remaining outcomes

In more recent scientific reports, diabetes remission and reversion have been introduced as outcomes in type 2 diabetes.[14] These are based on a combination of outcomes, and defined as follows:

- Diabetes remission: HbA1c < 48 mmol/mol and no use of diabetes medication for ≥1 year;
- Diabetes reversion: HbA1c < 53 mmol/mol and less medication use for ≥1 year.

These were included as outcomes by the Committee as well.

03 types of studies included in the advisory report

3.1 Pooled analyses, meta-analyses and systematic reviews

The Committee principally used systematic reviews (SRs), meta-analyses (MAs) and pooled analyses of RCTs and prospective cohort studies published in peer-reviewed journals as the basis for evaluation of the evidence. In pooled analyses and MAs, the findings from several original studies that used similar research questions and approaches are combined to create a new overall effect size. Combining findings from several studies creates greater statistical power and yields more accurate estimates of the relationship or effect in comparison with the original studies.

In addition, the Committee complemented the evidence from SRs and MAs into RCTs with individual reports of RCTs published after the most recent search date of those publications. Pooled analyses of prospective cohort studies were supplemented with individual prospective cohort studies. The Committee searched for such prospective cohort studies in existing dietary guidelines for people with type 2 diabetes.[17-23]

The 10 background documents on the nutritional topics provide details of the scientific evidence that was identified and considered relevant for the purpose of this advisory report. Where certain publications were disregarded, the reasons behind the decision were explained. Older SRs and MAs that included only a fraction of the published studies were excluded if more recent, good-quality publications were available.

3.2 RCTs and cohort studies

Both RCTs and prospective cohort studies have advantages and disadvantages, and the two are complementary. The value of prospective cohort studies lies in their (potentially) long follow-up period, and the (potentially) large number of participants. For the purposes of research into the aetiology of chronic diseases – which arise gradually over long periods of time – the long follow-up is a major asset. Another value of cohort studies lies in the representativeness of the participants to the general population or the relevant population group (with various levels of intake). The strength of RCTs lies in the fact that this kind of study can provide strong evidence of a causal relationship by eliminating confounding effects. The Committee evaluated RCTs in which only the dietary component was different from the control group. RCTs in which, for example, diet and physical activity were different from the control group are beyond the scope of the advisory report.

The Committee drew its conclusions based on 10 background documents with regard to the current status of scientific knowledge in relation to the following types of studies:

- RCTs into effects of dietary factors on the incidence of morbidity/mortality due to a disease;
- RCTs into effects of dietary factors on surrogate outcomes;
- Prospective cohort studies into associations of dietary factors with morbidity/mortality due to disease.

In view of the differences between RCTs and cohort studies, the Committee evaluated the evidence from RCTs and cohort studies separately in the background documents. Based on evidence from RCTs, the Committee drew conclusions about the *effects* of food consumption on chronic diseases or surrogate outcomes and on the strength of the evidence supporting those conclusions. In the case of evidence from prospective cohort studies, the Committee drew conclusions about the *associations* between food consumption and chronic diseases. In addition, the Committee judged the strength of the evidence supporting those conclusions.

3.3 Sources and search strategies

For its literature search, the Committee used PubMed and Scopus. The exact search strategy per nutritional topic is explained in the background document of each nutritional topic.

In the evaluation of the evidence regarding carbohydrate-restricted dietary patterns, the Committee used a report of SACN (2021) as a basis for the selection of literature.[22] This report contains an overview of the scientific evidence regarding the effects of carbohydrate-restricted dietary patterns on a selection of health outcomes in people with type 2 diabetes. The Committee supplemented the literature selected by SACN with searches for additional, more up-to-date literature and literature on additional health outcomes. For the remaining topics, the Committee itself performed literature searches.

3.4 Study populations

People with pre-diabetes or types of diabetes other than type 2 diabetes, such as type 1 diabetes, were excluded from the evaluation of the Committee. For pragmatic reasons, study populations of combined type 2 diabetes and pre-diabetes, or other types of diabetes, were included only when the vast majority (approximately 90% or more) of participants in those studies had type 2 diabetes.

The Committee aimed to further distinguish subgroups within the group of people with type 2 diabetes, such as men versus women, people with overweight or obesity compared to normal-weight people, people with certain medication use or with comorbidities. However, based on the available literature, the Committee could not draw conclusions on differences in effects or associations between subgroups.

3.5 Risk of bias

The Committee used the risk of bias assessments that were reported in the selected articles of SRs and MAs. Mostly, the Cochrane collaboration tool 2011 was used for the evaluation of RCTs.[67] This tool addresses seven specific domains of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other biases. For recently published, individual RCTs, the Committee assessed the risk of bias itself, using the Cochrane collaboration tool 2019.[68] This tool allowed the evaluation of the following five domains: bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result.

3.6 Public comments

Draft versions of the advisory report and background documents (except the document *Methodology for the evaluation of evidence*) were temporarily put on the Council's website in July and August 2021 to give stakeholders the opportunity to comment on their content. By doing so, the Committee sought to answer two main questions:

1. Did the Committee miss any important publications that fit within the method used?
2. Are there any errors in the documents?

No additional publications on the nutritional topics that were evaluated by the Committee, and that fit within the method used by the Committee, were detected from this. The comments received and the Committee's responses to them are published on the Health Council's website.

04 evaluations of literature and drawing conclusions

In the background documents, the Committee evaluated the current status of scientific knowledge in relation to the effects (in case of RCTs) and associations (in case of cohort research) of each nutritional topic. Below, the Committee describes how the conclusions regarding effects and associations were established.

4.1 Evaluation of the literature

The Committee aimed to determine the evidence base for the relationship of each of the selected nutritional topics with each of the selected outcomes. Each individual assessment began with a table summarizing the MAs and/or SRs (Table 3; for MAs). When individual RCTs or (pooled analyses of) cohorts were evaluated, a table was provided summarizing those RCTs (**Annex B**; Table A1) or cohorts (**Annex B**; Table A2). For SRs (without MAs), the relevant individual RCTs listed in the SRs were summarized in a table (similar format as for individual RCTs; Table A1). All tables have a standardised format. Where needed, the tables were extended with additional columns of information to clarify relevant design aspects of the included studies, such as descriptions of the dietary interventions.

Table 3 Summary table for each effect or association in the background documents: meta-analyses.

Summary	Explanation
Selected studies	Specification, per meta-analysis, of the number of RCTs or cohort studies, the number of participants, and the number of disease or mortality cases (where applicable) on which its conclusion is based.
Heterogeneity	Yes/no; where 'yes', the Committee provided an explanation where possible. Tests for heterogeneity between the original studies were evaluated. If the test revealed little or no heterogeneity (I^2<0.25), the summary table showed 'no'. For moderate heterogeneity (I^2 0.25 to 0.50), the summary table showed 'no' as well. In this situation, heterogeneity was explained in the accompanying text. For substantial heterogeneity (I^2 >0.50 and p-value <0.10), the summary table showed 'yes'. Where a heterogeneity test was not available, the Committee assessed the degree of overlap between the confidence intervals from initial studies or meta-analyses and the direction of the effect or risk estimators. The Committee distinguished heterogeneity in terms of the size and the direction of the effect or risk estimates. In case of heterogeneity with regard to the size of the effect/association, it is not possible to quantify the effect/association. In case of heterogeneity with regard to the direction, the findings on the effect/association are considered to be contradictory, and it is not possible to quantify the effect/association.
Strength of the effect / association	Specification of the effect estimate or risk estimate with a 95% confidence interval, where possible in relation to (change in) the nutritional factor. In case a meta-analysis presented effects based on both 'fixed effects' and 'random effects', the Committee used the results of the 'random effects' model.
Population studied	Specification of the participant characteristics, such as the body weight status, the use of diabetes medications, and the sex (men, women or both), and specification of the continent in which the research took place.

4.2 Choice from five options for the conclusion of each evaluation

Below the summary table, the Committees conclusion was given, chosen from one of five fixed options (Table 4). The formulation was different for RCTs than for cohort studies: intervention studies allowed statements

about effects (causality) to be made, whereas cohort studies only allowed statements about associations, relationships and coherence to be made. In case the available publications suggested an effect or association, the Committee additionally indicated whether it considered the evidence strong or limited. The conclusion was followed by a text in which the conclusion was explained and in which the Committee presented the publications assessed in connection with the conclusion. In said text and in the corresponding table or tables, the Committee presented the research data used for the summary table.

Table 4 Formulation of conclusions in the background documents.

Option	Formulation of conclusion	Explanation
1	*High or low exposure increases or decreases the risk of disease (based on RCTs), or high or low exposure is associated with a higher or lower risk of disease (based on cohort studies). The level of evidence is strong or limited.*	For conclusions of this type, the Committee specified the level of evidence based on the availability of studies, the presence or absence of heterogeneity in the direction and size of the effect or association, the strength of the effect or association (confidence interval, statistical significance, and in some instances also the size of the effect), and any additional considerations that were described in the explanation section. Where the conclusion related to a specific population or a specific level of exposure, the relevant details were provided. In case the level of evidence was strong and there was little heterogeneity in the direction and size of the effect or association, the Committee quantified the effect or association. In case there was a strong level of evidence but significant heterogeneity in the size of the effect or association, or if there was a limited level of evidence, the Committee gave a qualitative conclusion.
2	*An effect or association is unlikely.*	This conclusion was drawn when there was sufficient research that indicated no effect or association. In the case of surrogate outcome measures, the effect estimator is close to zero (no effect), with a narrow confidence interval; in the case of disease or mortality as outcome measure, the relative risk ratio (such as odds ratio or relative risk) is close to 1.00 (no effect or association) with a narrow confidence interval.
3	*Evidence for the effect or association is contradictory.*	This conclusion indicates that there was uncertainty about the direction of the effect/association. One or more of the following situations applied: 1) In a meta-analysis or pooled analysis, considerable and unexplained heterogeneity was noted in the direction of the effect or association. 2) No measure of heterogeneity was available, but the findings of the original studies showed significant differences in the direction of effects or associations, with (near) significant findings in both directions.
4	*There is too little research to draw a conclusion about an effect or association.*	One or more of the following situations applied: 1) No more than two original studies were summarized in a systematic review, or there were more than two studies summarized but the number of participants / cases was insufficient. 2) There were three or four studies summarized but the available studies were of insufficient quality to make a statement about the association or effect, for instance due to publication bias or insufficient correction for confounding. 3) There were three or four studies summarized but all available studies were from one research group and were therefore not independent.
5	*No conclusion can be based on the available studies.*	Five or more original studies were summarized in a systematic review, but there was some degree of uncertainty as to whether an effect/association existed (the width of the confidence interval did not allow one to draw a conclusion and the original publications did not demonstrate convincing heterogeneity with regard to the direction of the effect or association).

4.3 Decision tree

The Committee used a decision tree in order to improve objectivity and consistency in the judgement of the evidence, and drawing conclusions on the certainty of the evidence (**Annex C**). In doing so, it applied criteria listed in the decision tree for the required number of studies, number of participants and number of cases that contributed to the evaluation. In addition, the decision tree takes the risk of bias and heterogeneity between studies into account. These included aspects were based on experience with the *Physical Activity Guidelines 2017*, and *Dietary recommendations for pregnant women (2021)* by the Health Council.[69,70]

Regarding the required number of studies, participants and cases, the conclusion that the evidence is strong or that an effect or association is unlikely implies that there were at least 5 studies involving a total of at least 150 participants (RCTs into surrogate outcomes) or 500 cases (cohort studies); the conclusion that there was a limited level of evidence implies 3 or 4 studies and at least 90 participants (RCTs into surrogate outcomes) or 300 cases (cohort studies); one or two studies indicates a conclusion of too little research. The required number of participants in individual RCTs naturally depends on the variation in outcome measure and the expected size of the effect. The experience of the Committee is that these cut-off values are helpful in practice.

The decision tree was initially developed for evaluating results from MA and pooled analyses. The Committee also used the decision tree as a basis for the evaluation of the totality of evidence from individual cohort studies or RCTs.

4.4 From conclusions to recommendations

At the end of the background documents, the Committee summarized the conclusions for each nutritional topic per health outcome, and per type of study (RCTs and cohort studies). In addition, the Committee indicated whether the level of evidence was strong or limited. Next, the Committee evaluated, per nutritional topic, the totality of the evidence, in line with the approach used by the DDG2015 Committee (explained in the text box below). Only convincing evidence among people with type 2 diabetes could give reason to change an existing recommendation of the DDG2015 for people with type 2 diabetes. For nutritional topics where no conclusions could be drawn, the Committee advised maintaining the DDG2015 for people with type 2 diabetes.

Convincing and plausible evidence

The following approach was used by the 2015DDG Committee in evaluating the totality of evidence: Where strong conclusions from RCTs and cohort studies were mutually supportive, the Committee took the view that it has been convincingly demonstrated that the nutritional factor in question has an adverse or beneficial effect on health outcome(s). The same applies when there was exclusively strong evidence from RCTs. Where only strong conclusions based on cohort studies was available, the Committee took the view that an association is plausible. The difference between 'convincing' and 'plausible' evidence is usually reflected in the wording of the associated guideline. Where an effect has been convincingly demonstrated, the associated guideline will usually contain a quantitative recommendation (eat or drink so much); where an effect is merely 'plausible', no quantitative recommendation is normally made.[39]

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annex A

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- Dr. K.A.C. Berk, Registered Dietitian and Postdoc Researcher Department of Internal Medicine at Erasmus MC, Rotterdam (structurally consulted expert since 24 June 2020)
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annex B

summary tables for the evaluation of individual RCTs and cohort studies

Table A1 Summary table for each effect in the background documents: individual RCTs.

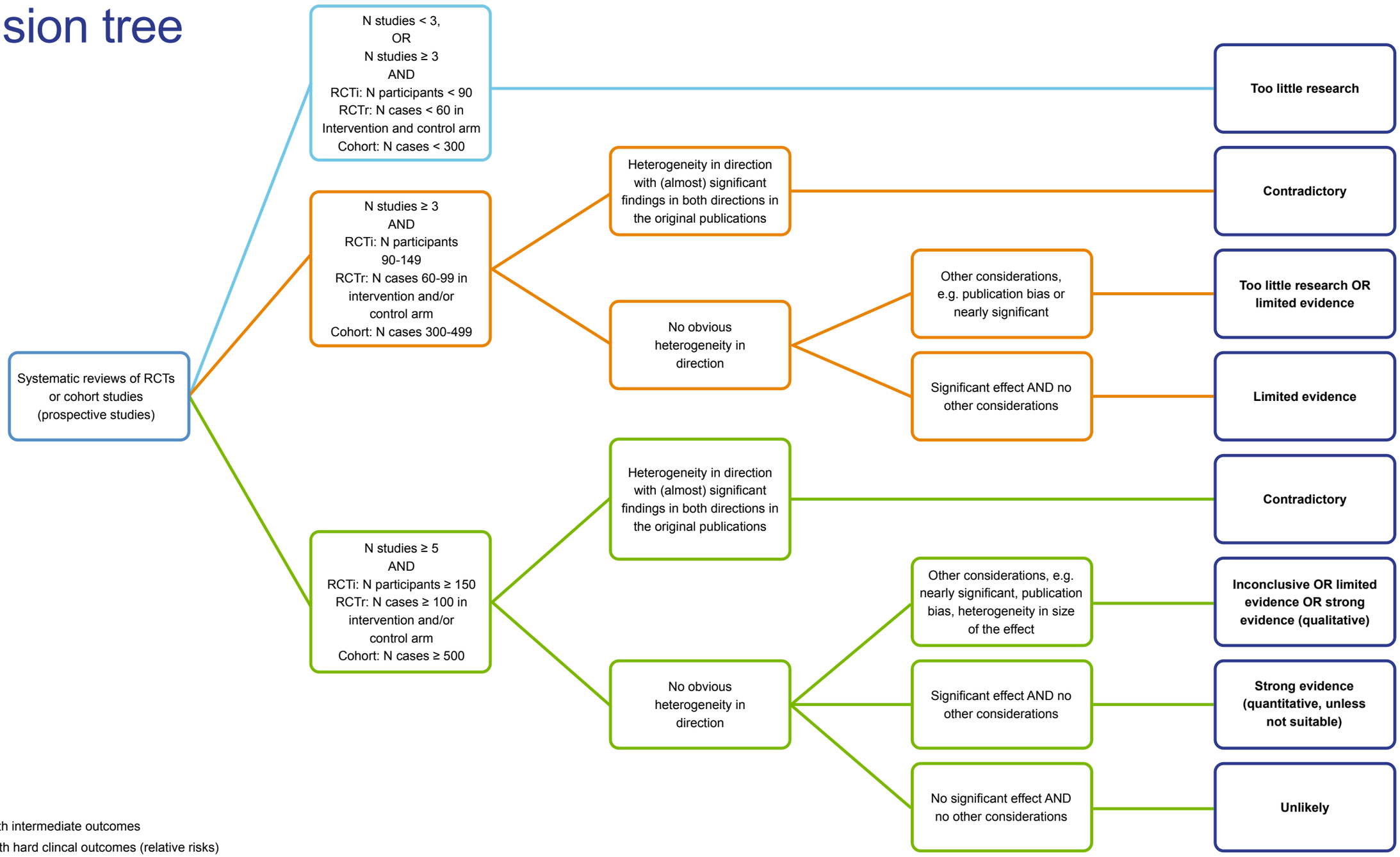
Summary	Explanation
Intervention (i) and control (c)	Specification of the composition of the study diets.
Number of participants in intervention (i) and control (c) group	Specification of the number of participants in the study.
Strength of the effect	Specification of the effect estimate with a 95% confidence interval in relation to (change in) the nutritional factor.
Study population	Specification of the participant characteristics, such as the body weight status, the use of diabetes medications, and the sex (men, women or both), and specification of the continent or country in which the research took place.

Table A2 Summary table for each association in the background documents: individual or pooled cohort studies.

Summary	Explanation
Cohort	Specification of the name of the cohort(s).
Exposure	Specification of the dietary factor under study.
Dietary assessment method	Specification of the method of dietary assessment.
Number of participants; number of cases	Specification of the total number of participants in the analysis and the total number of participants that developed the chronic disease outcome during follow-up.
Strength of the effect	Specification of the risk estimate with a 95% confidence interval in relation to (levels of intake of) the nutritional factor.
Study population	Specification of the participant characteristics, such as the body weight status, the use of diabetes medications, the sex (men, women or both), and specification of the continent or country in which the research took place.

annex C

decision tree



RCTi: RCTs with intermediate outcomes

RCTr: RCTs with hard clincal outcomes (relative risks)

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