Methodology for the evaluation of evidence

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

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

Health Council of the Netherlands

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1 Introduction

This background document belongs to the advisory report *Dutch dietary guidelines for people with atherosclerotic cardiovascular disease* (ASCVD).[1] It describes the methodology used by the Permanent Committee on Nutrition for the evaluation of the evidence regarding the relationships between dietary factors and health outcomes in people with ASCVD (cardiovascular disease [CVD] due to atherosclerosis).

1.1 Background

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*, which 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 or use of medication?

Cardiometabolic diseases include diabetes and CVD. Obesity and chronic kidney disease may also be considered part of this disease cluster. The Committee prioritised two topics within the domain of cardiometabolic diseases, for which it prepared separate recommendations: type 2 diabetes and ASCVD. The advisory report on the applicability of the DDG2015 for people with type 2 diabetes was published in 2021.[3] In the current background document, the Committee presents the methodology applied in evaluating the scientific evidence for the second advisory report, which concerns the DDG2015 for people with ASCVD.

1.2 Starting points and outline of the evaluation

Since 2015, new studies (performed in the general population) have been published on the nutritional topics that were evaluated for the DDG2015. However, the Committee did not re-evaluate the dietary recommendations from the DDG2015 for the general

population. Instead, the Committee focused on evaluating the scientific evidence on people with ASCVD and pointed out where deviations from the DDG2015 are recommended for this specific group. The Committee also evaluated a few dietary factors that were not covered in the DDG2015. For those factors, the Committee made an exception to the above principle, as is further explained in paragraph 2.1.

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 as well, including for people with ASCVD. 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 ASCVD.

Twelve background documents were prepared for the advisory report *Dutch dietary guidelines for people with ASCVD*.[1] In the current methodological background document, the Committee describes how it evaluated the status of scientific knowledge. This evaluation resulted in eleven other background documents that describe the status of scientific evidence for the following dietary factors:

- alcohol[4]
- coffee[5]
- dairy products[6]
- eicosapentaenoic acid (EPA) & docosahexaenoic acid (DHA)[7]
- fats & oils[8]
- fish[9]
- foods fortified with plant sterols and stanols[10]
- meat[11]
- supplements with monacolin K from red yeast rice[12]
- saturated fat substitution[13]
- sodium[14]

In each background document, the Committee drew conclusions on the level of evidence for each of these dietary factors in relation to health outcomes. Based on the totality of conclusions drawn in the background documents for the dietary factors, the Committee evaluated whether there were indications for modifications of or additional recommendations to the DDG2015 for people with ASCVD. The general approach used for evaluating the totality of the evidence is described in the current document (Chapter 4). The Committee's conclusion on whether the evidence was supportive of the DDG2015 or gave cause for adaptation of the DDG2015 for people with ASCVD is described in the advisory report.

A 'Cardiovascular disease' working group of the Permanent Committee on Nutrition prepared the background documents. The working group compiled and weighted the evidence from all background documents and advised the Permanent Committee on

Nutrition regarding the formulation of recommendations. The Committee takes final responsibility for the content of the advisory report and background documents. The compositions of the Committee and working group are presented in Annex A. The working group and Committee consulted several experts, including a cardiologist and internist-vascular medicine specialist for a cardiovascular perspective on the advisory report. The incidentally consulted experts are listed in Annex A as well.

1.3 Domain of the advisory report

The advisory report is applicable to people with CVD due to atherosclerosis, known as ASCVD. The Committee defines ASCVD according to the definition of the European Society of Cardiology (ESC), which comprises both documented ASCVD and unequivocally documented ASCVD on imaging.[15] Documented ASCVD includes clinically established acute coronary syndromes (i.e. myocardial infarction [MI] and unstable angina pectoris), stable angina pectoris, coronary revascularisation (percutaneous intervention [PCI], coronary artery bypass graft surgery [CABG] and other arterial revascularisation procedures), cerebrovascular disease (i.e. stroke and transient ischemic attack [TIA]) and peripheral arterial disease (PAD). Unequivocally documented ASCVD on imaging relates to those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or a CT scan (multivessel coronary disease with two major epicardial arteries having more than 50% stenosis) or on carotid ultrasound.

People with a high risk but no manifestation of ASCVD, such as those with hypertension or elevated LDL cholesterol levels, fall outside this definition (although, for a selection of nutritional topics, studies performed among people with elevated LDL cholesterol levels were considered, as is further explained in paragraph 2.1). The target group of this advice also excludes people with heart failure that has no atherosclerotic cause (unless those persons also suffer from ASCVD). This report may also not (entirely) be applicable to people with major complications of ASCVD, such as (partial) paralysis, swallowing problems or functional disability. In addition, it is unknown whether the recommendations in the advisory report (entirely) apply to people with ASCVD who already require dietary advice for other conditions, such as kidney disease, since this was not part of the Committee's evaluation.

Finally, the recommendations of the Committee are aimed at improving the long-term health of people with ASCVD (i.e. prevention of common chronic diseases, as is explained in paragraph 2.2), similar to the approach taken for the DDG2015. Consequently, the Committee did not examine acute effects (effects that occur within a few hours or days), for example, effects of supplementation with fish fatty acids on the occurrence of atrial fibrillation within two to four days after surgery (postoperative atrial fibrillation).

1.4 Reading guide

Chapter 2 describes the dietary factors and health outcomes selected by the Committee. Chapter 3 describes the approach used for the literature research, and Chapter 4 explains how the Committee drew conclusions in the background documents and how it used the totality of the evidence to conclude whether the DDG2015 are applicable for people with ASCVD.

2 Selection of dietary factors and health outcomes

The Committee used recent (national and international) evidence-based (dietary) guidelines for people with ASCVD or risk factors for ASCVD, such as hyperlipidaemia and hypertension, to select relevant dietary factors and health outcomes for its evaluation, as explained further in paragraphs 2.1 and 2.2. Reports of the following organisations were considered:

- European Society of Cardiology (ESC)[a]
  - 2021 Guidelines on cardiovascular disease prevention in clinical practice[16]
  - 2020 Guidelines for the management of acute coronary syndromes[17]
  - 2019 Guidelines for the diagnosis and management of chronic coronary syndromes[18]
  - 2019 Guidelines for the management of dyslipidaemias[15]
  - 2018 Guidelines for the management of arterial hypertension[19]
- American Heart Association (AHA)[b]
  - 2021 Dietary guidance to improve cardiovascular health[20]
  - 2013 Guideline on lifestyle management to reduce cardiovascular risk[21]
  - 2011 Secondary prevention guidelines for patients with coronary and other atherosclerotic vascular disease[22]
  - 2014 Guidelines for the prevention of stroke and transient ischemic attack[23]
  - 2012 Guidelines for the diagnosis and management of patients with stable ischemic heart disease[24]
  - 2018 Guideline on the management of blood cholesterol[25]
  - 2017 Guideline for the prevention, detection, evaluation and management of high blood pressure[26]
- Nederlands Huisartsen Genootschap (NHG, *Dutch College of General Practitioners*)
  - NGH-Standaard Cardiovasculair risicomanagement (CVRM, *cardiovascular risk management*)[27]
  - NHG-Standaard Beroerte (*stroke*), 2018[28]
  - NHG-Standaard Stabiele angina pectoris (*stable angina pectoris*), 2019[29]

2.1 Dietary factors

The Committee used the DDG2015 as its starting point. The Committee assumes that the DDG2015 are appropriate for people with ASCVD, because they are based on

[a] Some reports were prepared in collaboration with other organisations, such as the European Society of Hypertension and the European Atherosclerosis Society.

[b] Some reports were prepared in collaboration with other organisations, such as the American College of Cardiology Foundation and the American Stroke Association.

research in the general population and not just in the healthy population. Since part of the general population has ASCVD, this group was implicitly included in the evaluations on which the DDG2015 are based.

Based on Dutch and international reports with dietary guidelines for people with ASCVD (Annex B) and its expert opinion, the Committee considered for which dietary factors there were indications that adaptations or additions might be needed to the DDG2015 for people with ASCVD and for what dietary factors there is a need for a guideline for this group. The Committee uses the term 'dietary factors' as an umbrella term for foods, beverages, nutrients and dietary patterns. In selecting the dietary factors to be evaluated, the following questions were considered:

1 Which dietary factors are (especially) relevant for people with ASCVD and the health outcomes that are evaluated in this regard?
2 For which dietary factors are deviations to be expected for people with ASCVD compared to the DDG2015? For this, the Committee compared conclusions and recommendations underlying the DDG2015 with reports that include dietary guidelines for people with ASCVD.
3 Which dietary factors are the subject of discussion among healthcare professionals?

For seven of the current dietary recommendations in the DDG2015, the Committee saw reasons to conduct a specific evaluation for people with ASCVD. This concerns the following:

- dairy products
- fish
- fats and oils
- coffee
- meat
- alcohol
- table salt

For the other dietary recommendations addressed in the DDG2015, such as those on fruits and vegetables or whole grain products, and for the overarching recommendation to follow a dietary pattern that involves more plant-based and less animal-based food, the Committee believes that these are important for people with ASCVD, but saw, based on the aforementioned evidence-based dietary guidelines from other organisations and its expert judgment, no indications that deviations would be required for this group. From the foregoing, it follows that the Committee recommends that people with ASCVD follow the DDG2015, unless proven otherwise.

The DDG2015 includes the recommendation that, in general, nutrient supplements are not necessary, except for specific groups for which supplementation applies.[2] For the

group of people with ASCVD, the Committee opted to evaluate the following products (in addition to the aforementioned dietary factors that were already covered in the DDG2015):

- products fortified with plant sterols and/or stanols
- supplements with monacolin K from red yeast rice
- supplements with EPA and DHA (fish fatty acids)

Based on its expertise, the Committee assumes that these dietary factors may especially be of interest with respect to people with ASCVD. Those three dietary factors are also addressed in existing dietary guidelines for people with ASCVD (Annex B) and are a frequent topic of conversation in (clinical) practice.

The Committee is aware that products fortified with plant sterols and/or stanols (functional foods), supplements with high doses of monacolin K from red yeast rice and supplements with high doses of EPA and DHA (higher than what can be achieved via consumption of usual foods) lie at the interface of what can be seen as a food and as a medicine. The European Union (EU) considers those products as foods, and therefore, in line with the EU, the Committee evaluated products with plant sterols and/or stanols, supplements with monacolin K from red yeast rice and supplements with EPA and DHA using the methodology for foods (as described in the current document).

As many people with ASCVD 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 ASCVD can best lose weight and therefore does not specifically address weight-loss diets.

People with ASCVD may participate in a cardiac rehabilitation programme or another (combined) lifestyle intervention in which diet plays an important role. In studies that examined the effect of lifestyle interventions, the effect of the dietary component is often difficult to isolate from the other components (such as exercise and smoking cessation). Moreover, the evaluated dietary component of such intervention often concerns a dietary pattern rather than a specific food or beverage (or nutrient). Dietary patterns are not part of the Committee's evaluation. The Committee therefore did not evaluate lifestyle interventions and only evaluated studies that addressed the dietary factors listed above.

The starting principle of the Committee is to advise people with ASCVD to follow the DDG2015, unless proven otherwise. As stated above, the Committee assumes that the DDG2015 are appropriate for people with ASCVD, since they are based on research in the general population (part of the general population has ASCVD). However, research that has been entirely conducted in people who already have ASCVD has been considered only to a limited extent in preparing the DDG2015. The Committee has now

focused exclusively on such research, which may contribute to formulating any disease-specific adaptations or additions to the DDG2015 for people with ASCVD. An exception to this concerns the evaluation of the dietary factors that were not evaluated for the DDG2015 and for which insufficient research was available in people with ASCVD. This concerns products fortified with plant sterols and/or stanols and supplements with monacolin K from red yeast rice. For these dietary factors, the Committee has included studies that were performed in (mainly) high-risk groups, namely people with elevated LDL cholesterol levels (without established ASCVD). The reason is as follows. The Committee recommends that people with ASCVD should follow the DDG2015, unless proven otherwise. This means that, when too little research is available in people with ASCVD to draw conclusions on a certain dietary factor, the respective recommendation from the DDG2015 is recommended for people with ASCVD. Since products with plant sterols and/or stanols and supplements with monacolin K from red yeast rice were not included in the DDDG2015, this approach could not be applied for these dietary factors. By evaluating the evidence in (mainly) people with elevated LDL cholesterol levels, the same approach could be used as for dietary factors that were included in the DDG2015. The Committee notes that people with ASCVD often have elevated LDL cholesterol levels and that products fortified with plant sterols and/or stanols and supplements with monacolin K from red yeast rice are specifically targeted at reducing LDL cholesterol levels. The Committee therefore expects that effects of these products on LDL cholesterol observed in people with elevated LDL cholesterol levels would also be applicable to people with ASCVD.

2.2 Health outcomes

The health outcomes evaluated in the DDG2015 were a starting point for the selection of health outcomes for the current advisory report. In addition, the Committee selected health outcomes that are listed as relevant in cardiovascular risk management in the Netherlands.[16,27] The Committee distinguished long-term health outcomes and short-term, surrogate outcomes. The selected health outcomes are listed below:

- long-term health outcomes:
  - all-cause mortality
  - morbidity and/or mortality from total CVD, coronary heart disease (CHD; this includes acute coronary syndromes and stable angina pectoris), stroke, heart failure, atrial fibrillation, type 2 diabetes mellitus, chronic kidney disease (CKD), chronic obstructive pulmonary diseases (COPD), total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression
  - subtypes of CHD, such as MI, (stable and unstable) angina pectoris and revascularisation procedures (i.e. CABG and PCI)
- short-term surrogate outcomes
  - body weight
  - systolic blood pressure

- low-density lipoprotein (LDL) cholesterol
- estimated glomerular filtration rate (eGFR)
- glycated haemoglobin (HbA1c) and fasting blood glucose

In preparing the background documents, the Committee searched for literature regarding the aforementioned health outcomes. Subsequently, the scientific evidence for health outcomes with available relevant literature was described in the background documents.

2.2.1 Long-term health outcomes

In line with the DDG2015 approach, the dietary guidelines are drawn up to prevent common chronic diseases in people with ASCVD, including, but not solely focusing on, CVD-related outcomes. The Committee selected the long-term health outcomes evaluated in the DDG2015 advisory report. In that report, the top 10 diseases in the Netherlands with respect to mortality, years of potential life lost and burden of disease were selected, which include: CHD, stroke, heart failure, type 2 diabetes, COPD, breast cancer, colorectal cancer, lung cancer, dementia and depression.[2] The Committee noted that these were also among the top 10 diseases in more recent years.[30]

In addition to the above, the Committee selected atrial fibrillation, since this health outcome is relevant in cardiovascular risk management according to treatment guidelines.[16,27] Moreover, all-cause mortality, mortality and morbidity from multiple types of CVD combined (total CVD) and mortality and morbidity from multiple types of cancer combined (total cancer) were selected as outcomes. These latter health outcomes were not included as outcome measure in the DDG2015 (with a few exceptions), as mortality regardless of cause of death and total CVD or total cancer convey nothing or little about the aetiology of individual diseases. However, the Committee now considers that these outcomes do reflect disease burden, which is (more) relevant for people who already have been diagnosed with a chronic disease such as ASCVD. Moreover, those health outcomes are frequently measured in studies and generally provide more cases than disease subtypes, which increases the evidence base for the current advisory report.

Lastly, where possible, the Committee additionally evaluated more specific outcomes of CHD, such as MI, angina pectoris and revascularisation procedures. For stroke, such specifications were not possible based on the available literature.

2.2.2 Short-term, surrogate outcomes

Clarifying the effect of diet on morbidity and mortality outcomes in randomised 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 expensive,

and are 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.[31] An example is the use of LDL cholesterol or systolic blood pressure as surrogate endpoints for CHD. The advantage of using surrogate endpoints in experimental studies is that they involve significantly fewer participants and shorter study durations than the outcomes of 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 CHD.

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

Mendelian randomisation studies

More recently, Mendelian randomisation studies have been introduced to help to elucidate the causality of relationships between modifiable surrogate outcomes and disease outcomes. In such studies, the relationship between genetic variations that predict the surrogate outcomes and disease risk is investigated using observational data. Such studies can be seen as natural experiments since genetic factors are randomly assigned by nature. Mendelian randomisation studies are less likely to be affected by confounding or reverse causation than conventional observational studies, given that three key Mendelian randomisation assumptions are met. These assumptions are that the genetic variants associate with the surrogate outcome 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.[32]

[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 that there are no or minimal off-target effects of the dietary factors that were evaluated in relation to the surrogate outcomes in the DDG2015. 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 observed in the general population, for instance in large-scale population-based cohort studies. Such off-target effects have not been reported for the evaluated dietary factors. The Committee cannot make this assumption with regard to foods fortified with plant sterols and/or stanols, supplements with monacolin K from red yeast rice or supplements with EPA and DHA. In these products, the doses of the active ingredient are much higher than can be obtained from usual foods.

The Committee selected short-term, surrogate outcomes similar to the DDG2015 approach, which include: body weight, systolic blood pressure and LDL cholesterol. Furthermore, markers of kidney function (eGFR) and glucose metabolism (HbA1c and fasting blood glucose) were selected, since these are listed as relevant in cardiovascular risk management[16,27] and are (potentially causal) predictors of above listed long-term health outcomes.

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,[33] those markers have been shown to have a causal relationship with at least one of the following chronic diseases: CHD, stroke, heart failure and type 2 diabetes. Below, additional, more recent evidence that confirms the causality and, where available, evidence for such relationships in people with ASCVD is presented.

Body weight: Recent evidence from Mendelian randomisation studies confirmed a causal association between the level of adiposity and CHD risk.[34,35] Moreover, a MA of cohort studies showed that (predominantly) overweight or obese people with CVD who (purposefully) lost at least 5% of their body weight had a lower risk of mortality and CVD than people with a stable (too high) body weight.[36]

Systolic blood pressure: Recent evidence from Mendelian randomisation studies supports the notion that blood pressure is causally associated with the risk of CHD and stroke.[37,38] Among people with CVD, blood pressure-lowering therapies also lead to improvements in cardiovascular outcomes: a meta-analysis of RCTs with a median duration of 4.2 years showed that every 5 mmHg reduction in systolic blood pressure was associated with an 11% lower risk of cardiovascular events (fatal or non-fatal MI, fatal and non-fatal stroke, CHD or heart failure causing death or requiring hospital admission), an 11% reduction in stroke risk and a 10% reduction in the risk of CHD.[39]

LDL cholesterol: Recent reports of numerous and different types of studies, including prospective cohort studies, RCTs and Mendelian randomisation studies, have convincingly shown higher LDL cholesterol causes ASCVD.[40] Furthermore, among people with CHD, LDL-lowering therapies lead to statistically significant improvements in cardiovascular outcomes: a meta-analysis of RCTs showed that every 1 mmol/L reduction in LDL cholesterol was associated with a 21% lower risk of major vascular events (coronary death, non-fatal MI, coronary revascularisation or stroke) at one year. The risk of non-fatal MI was reduced by 29% and the risk of ischaemic stroke by 31%.[41]

Markers of kidney function and glucose metabolism
In addition to the outcomes described above, the Committee selected outcomes reflecting kidney function and glucose metabolism.

Estimated glomerular filtration rate (eGFR): The 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.[42] Cohort studies have shown that eGFR is an independent risk factor for cardiovascular morbidity and mortality.[43] Also, in high-risk groups, such as people with CVD, eGFR independently predicted cardiovascular mortality.[43]

Glycated haemoglobin (HbA1c) and fasting glucose: HbA1c reflects the average blood glucose concentrations of the past two to three 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 CVD.[44] Moreover, Mendelian randomisation studies have shown a causal association between HbA1c and CHD risk.[45,46] Among people who have both type 2 diabetes and ASCVD, glucose-lowering therapies with SGLT-2 inhibitors or GLP-1 receptor antagonists lead to cardiovascular benefit. However, it is uncertain whether this is (entirely) attributable to the reduction in glucose.[16]

Markers of the lipid profile that were not selected
Small dense LDL cholesterol was not selected as outcome by the Committee. There are pathophysiological theories that in particular the small particles of total LDL cholesterol are a risk factor for ASCVD. 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 CVD 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 outcomes.[47]

HDL cholesterol was not selected as outcome by the Committee. Although cohort studies have shown that higher HDL cholesterol levels are associated with reduced cardiovascular outcomes,[48] RCTs did not show that HDL cholesterol-raising therapies lower the risk of cardiovascular outcomes.[49] In addition, Mendelian randomisation studies showed no evidence of a causal relationship of HDL cholesterol with cardiovascular outcomes.[50]

Triglycerides were not included as outcome by the Committee. Although cohort studies and genetic epidemiological studies convincingly showed a causal role of triglycerides

in the development of ASCVD,[51,52] evidence that intervening on triglycerides, in particular with fibrates, reduces cardiovascular events is limited.[53]

3 Types of studies included

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 (i.e. prospective cohort studies, nested case-control studies and case-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 derive an overall effect size. Combining findings from several studies creates greater statistical power and yields more precise estimates of the relationship or effect in comparison with the original studies.

The Committee complemented the evidence from SRs and MAs of RCTs with individual reports of RCTs published after the most recent search date of the SR or MA. Pooled analyses of prospective cohort studies were supplemented with individual prospective cohort studies. The Committee searched for such prospective studies by screening the articles that cited the retrieved publications in PubMed and by checking reference lists of included publications.

For a selection of literature evaluations, the Committee pooled the results of all relevant studies itself. The Committee decided to do so in cases where the available MA included one or more studies that did not meet the inclusion criteria of the Committee, hindering the Committee in drawing conclusions based on these MAs. This was also done when both a MA and several supplementary studies were available or when only individual studies were available. The Committee only pooled results if it was considered helpful to draw conclusions on the effects of the dietary factor on health outcomes. A random effects meta-analysis approach was used.

The background documents on the dietary factors 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. In general, 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 for 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 eleven 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 or mortality due to a disease or mortality regardless of the cause of death (all-cause mortality);
- RCTs into effects of dietary factors on surrogate outcomes;
- Prospective cohort studies into associations between dietary factors and morbidity or mortality due to disease or all-cause mortality.

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 the dietary factor on chronic diseases, all-cause mortality or surrogate outcomes. In the case of evidence from prospective cohort studies, the Committee drew conclusions about the associations between the dietary factor and chronic diseases or all-cause mortality. In addition, the Committee judged the strength of the evidence supporting those conclusions.

3.3 Sources and search strategies

For each dietary factor, the Committee performed one or more systematic literature searches, using PubMed and Scopus. The exact search strategy per dietary factor is explained in the corresponding background documents.

In the evaluation of the evidence regarding foods fortified with plant sterols and/or stanols and regarding supplements with monacolin K from red yeast rice, the Committee used reports of the European Food Safety Authority (EFSA) as a starting point.[54-56] These reports describe the evaluation of the efficacy of these products for the benefit of a requested health claim. Where needed, additional systematic literature searches (according to the approach used for the other dietary factors evaluated in the current advisory report) to identify more recent studies or studies that were more specified to the target group of the current advisory report were performed by the Committee itself.

3.4 Study populations

The Committee included studies performed in people with ASCVD or in subgroups thereof. Three groups of people with ASCVD were distinguished: people with CHD, people with cerebrovascular disease (stroke) and people with PAD. Where sufficient literature was available, the Committee evaluated whether or not relationships between dietary factors and health outcomes differed between those groups.

The Committee found studies that included people with a high risk of CVD, but who did not all have ASCVD at baseline. If stratified analyses were available among the group of participants with ASCVD, the Committee included the results from these stratified analyses. If stratified analyses were not available, the Committee only included those studies in which the vast majority (approximately 90% or more) of participants had ASCVD at baseline.

Studies that comprised people with total CVD or total stroke (not further specified) were also included by the Committee, since most of the CVDs are due to atherosclerosis,[57] and because most stroke cases have an ischaemic cause.[28,57]

Studies among people with severe heart failure (New York Heart Association class III or IV) were excluded as the Committee expects that the impact of dietary interventions will be limited due to their poor prognosis. Studies among people with less severe heart failure and ASCVD were included. The Committee also found studies in people with atrial fibrillation and/or an implantable cardioverter defibrillator (ICD), for whom it was unknown if they also suffered from ASCVD. It decided to exclude these studies, because it assumes that atrial fibrillation has an atherosclerotic cause in less than 90% of cases.

The Committee aimed to further distinguish subgroups within the group of people with ASCVD, amongst others according to use of lipid-lowering drugs (such as statins) or blood pressure-lowering drugs. In the past two decades, the use of such cardiovascular medication has increased substantially in the management of people with ASCVD. The risk of a recurrent ASCVD is therefore significantly reduced. This may contribute to findings of less effective dietary interventions in people who use medication as compared to people who do not. Also, it may be more difficult to demonstrate a potential effect of a dietary intervention beyond the effects of adequate medication. The Committee examined whether it saw any indications that the effects or associations would be different in people who use (specific types of) medication compared to those who do not.

There is increasing evidence that the development of CVD and symptoms of the disease are different in men than in women, which may mean that men and women should be treated differently and that the role of diet could be different.[16] Where

possible, the Committee evaluated whether the effects or associations of dietary factors with health outcomes differed between men and women.

3.5 Other requirements regarding the study selection

The Committee specified a number of additional requirements for the studies to be included in its evaluation:

- The Committee only included cohort studies in which the dietary exposure was determined after the index event (i.e. the first occurrence of an ASCVD event). If the dietary factor of interest is determined prior to the event, there is a higher chance of reverse causation.
- With respect to the evaluation of hard, clinical health outcomes in cohort studies, the Committee only included studies in which the follow-up was at least 1 year.

3.6 Risk of bias

The Committee used the risk of bias assessments that were reported in the selected reports of SRs and MAs. For individual RCTs (not included in such a MA) that required a risk of bias assessment, the Committee assessed the risk of bias using the Cochrane collaboration tool 2019.[58] This tool allowed for the evaluation of the following five domains: bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result.

3.7 Public comments

A draft version of the advisory report and all background documents (except the document *Methodology for the evaluation of evidence*) were temporarily put on the Council's website in September and October 2022 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?

The public consultation did not yield additional publications on the dietary factors that were evaluated by the Committee and that fit within the method it used. The comments received and the Committee's responses to them are published on the Health Council's website.

4 Evaluation of the 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 studies) of each dietary factor. Below, the Committee describes how the conclusions regarding effects and associations were established in these documents.

4.1 Evaluation of the literature

The Committee aimed to determine the evidence base for the relationship of each of the selected dietary factors with each of the selected health outcomes. In case the Committee based its evaluation on a MA, the assessment began with a table summarising the number and characteristics of the individual cohorts or RCTs contributing to the MA (Annex C; Table C1) and an additional table presented the pooled results of the MA (Annex C; Table C2). When individual RCTs or (pooled analyses of) cohort studies were evaluated, a table was provided summarising these RCTs (Annex C; Table C3) or cohort studies (Annex C; Table C4). For SRs (without MAs), the relevant individual RCTs listed in the SRs were summarised in a table (similar format as for individual RCTs; Table C3). 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.

4.2 Choice from five options for the conclusion of each evaluation

The Committee's conclusion is given below the summary table in the background document and is chosen from one of five fixed options. The five options and their explanations are listed in Table 1. The formulation of the conclusions 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 1 Formulation of conclusions in the background documents

Option	Formulation of conclusion	Explanation
1	High or low dietary exposure increases or decreases the risk of the health outcome (based on RCTs), or high or low dietary exposure is associated with a higher or lower risk of the health outcome (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 explanatory 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 estimate 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 the 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 or 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.	This conclusion was drawn when one or more of the following situations applied: 1) No more than two original studies were available, or there were more than two studies available but the number of participants and/or cases was insufficient. 2) There were three or four studies available, but these 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 available, but all available studies were from one research group and were therefore not independent.

5	No conclusion can be drawn based on the available studies.	Five or more original studies were available, 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 as a guidance tool to support objectivity and consistency in its judgement of the evidence and to draw conclusions on the certainty of the evidence (Annex D). In doing so, it applied the criteria listed in the decision tree for the required number of studies, the number of participants and the number of cases that contributed to the evaluation. In addition, it took the quality of the studies, in particular the risk of bias, and the heterogeneity between studies into consideration. These aspects were based on experience with the advisory reports *Physical activity guidelines 2017*[59] and *Dietary recommendations for pregnant women* (2021)[60] by the Health Council.

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 and that those studies involved a total of at least 150 participants when it concerns RCTs into surrogate outcomes, at least 100 cases when it concerns RCTs into hard clinical outcomes or at least 500 cases when it concerns 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 at least 60 (RCTs into hard clinical outcomes) or 300 (cohort studies) cases; 1 or 2 studies indicates a conclusion of too little research. The required number of participants in individual RCTs naturally depends on the variation in the 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 Committee based its judgement on heterogeneity on the result of the test for heterogeneity (I^2) presented in MAs and considered an I^2 higher than approximately 50% as substantial heterogeneity. Where no test for heterogeneity was available, the Committee based its judgement on the visual inspection of the forest plots. In case of substantial heterogeneity in the size of the effect or association, the Committee considered drawing a non-quantified conclusion. In case of substantial heterogeneity in the direction of the effect or association, the Committee considered the evidence to be contradictory.

The decision tree was initially developed for evaluating results from MAs and pooled analyses. The Committee also used the decision tree as a basis for the evaluation of

the totality of evidence from multiple individual cohort studies or RCTs (not meta-analysed).

4.4 From conclusions to recommendations

At the end of the background documents, the Committee summarised the conclusions for each dietary factor 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 dietary factor, the totality of the evidence, in line with the approach used by the DDG2015 Committee (explained in the text box below). Only convincing evidence from research among people with ASCVD could give reason to change an existing recommendation of the DDG2015 for people with ASCVD. For dietary factors where no conclusions could be drawn, the Committee advised maintaining the DDG2015 for people with ASCVD.

Convincing and plausible evidence

The following approach was used by the DDG2015 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 dietary 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 strong conclusions from cohort studies are supported by a single RCT in which disease was used as the measure of outcome (*proof of principle*), the Committee also concludes that the effect has been convincingly demonstrated. Where only strong conclusions based on cohort studies were 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 a certain amount); where an effect is merely 'plausible', no quantitative recommendation is normally made.[2]

4.5 Safety

For a selection of dietary factors, the Committee considered, in addition to the effectiveness, the safety when drawing conclusions and formulating recommendations. This concerned products fortified with plant sterols and/or stanols, supplements with monacolin K from red yeast rice and supplements with EPA and DHA. The Committee used safety evaluations of EFSA and the European Commission (further explained in the respective background documents).

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Annexes

Annex A Committee on Nutrition and Cardiovascular disease working group

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- Prof. J.W.J. Beulens, Professor of lifestyle and cardiometabolic disease epidemiology, Amsterdam UMC, *vice chairperson* (since 17 January 2022)
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- Prof. M. Visser, Professor of Healthy Aging, Vrije Universiteit Amsterdam, *chairperson until May 2021*
- Prof. S.J.L. Bakker, Professor of Internal Medicine, University Medical Center Groningen
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- Dr. R.G. Voortman, Associate Professor Nutrition and Lifestyle Epidemiology, Erasmus MC, Rotterdam and Wageningen University, *structurally consulted expert*

Incidentally consulted experts

Consulted because of clinical expertise in the field of cardiovascular diseases:

- T.T. van Loenhout, cardiologist, Gelderse Vallei Hospital, Ede
- Prof. F.L.J. Visseren, Professor in Vascular Medicine, University Medical Center Utrecht

Consulted on the topic of plant sterols and/or stanols, and Mendelian randomisation studies on this matter in particular:

- Prof. J. Plat, professor in physiology of nutrition with special attention for sterol metabolism, Maastricht University
- Dr. S. Burgess, medical statistician, University of Cambridge (United Kingdom)

Observers

- M. Kunst, Ministry of Health, Welfare and Sport, The Hague
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Annex B Overview of dietary factors covered in guidelines for the prevention and/or management of people with (AS)CVD

The tables in this annex give an overview of the dietary factors that are discussed in national and international guidelines for the prevention and/or management of people with (atherosclerotic) cardiovascular disease.[2,15-27] The Committee noted that most dietary recommendations in these guidelines are based on primary prevention studies.

Table B1 Information about energy, carbohydrate, mono- and disaccharides and added sugars provided in existing reports on the prevention and/or management of (AS)CVD

Report	Energy (body weight)	Carbohydrates	Mono- and disaccharides	Added sugars
Dutch dietary guidelines 2015[2]	-	-	-	-
CVRM guideline 2018[27]	In case of healthy BW, maintain BW, eat healthily and exercise; if overweight or obese, exercise sufficiently and reduce BW in a healthy way	-	-	-
AHA Lifestyle management 2013[21]	Achieve and maintain a healthy weight	-	-	-
ESC CVD prevention 2021[16]	Reduce weight when overweight or obese	-	-	≤10 E%; restrict sugar from sugar-sweetened beverages in particular
AHA Cardiovascular health 2021[20]	Achieve and maintain a healthy BW	-	-	Minimise intake
ESC Dyslipidaemia 2019[15]	Reduce excessive body weight[a,b,c,d]	• Reduce CHO intake to 45-55 E%[a,c] • Replace CHO by UFA[b]	Reduce intake[a]	≤10 E% (in addition to the amount present in natural foods such as fruits and dairy)[c]
AHA-ACC Blood cholesterol 2018[25]	*AHA-LM* guideline	-	-	-
ESC Hypertension 2018[19]	Reduce BW in case of overweight and obesity; maintain a healthy BW[e]; avoid obesity	-	-	-
AHA-ACC High blood pressure 2018[26]	Reduce BW in case of overweight/obesity; best goal is ideal BW	-	-	-

Report	Energy (body weight)	Carbohydrates	Mono- and disaccharides	Added sugars
ESC Secondary prevention CCS 2019[18]	Obtain and maintain a healthy BW[f]; if overweight/obese, reduce BW[g]	-	-	-
ESC Secondary prevention ACS 2020[17]	*ESC-SP-CCS* guideline	-	-	-
AHA-ASA Secondary prevention stroke 2014[23]	Usefulness of weight loss among patients with a recent TIA or ischemic stroke and obesity is uncertain.	-	-	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	Maintain/achieve a BMI of 18.5-24.9 kg/m^2; in case of overweight is initial goal to reduce BW by 5-10%	-	-	-
AHA-ACC Management stable IHD 2012[24]	Maintain/achieve a BMI of 18.5-24.9 kg/m^2; in case of overweight is initial goal to reduce BW by 5-10%[h]	-	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; BW: body weight; CCS: chronic coronary syndromes; CHO: carbohydrates; CVRM: cardiovascular risk management; d: days; DDG: Dutch dietary guidelines; E%: percentage of energy; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; total-C: total cholesterol; UFA: unsaturated fatty acids

Footnotes:

[a] To reduce TG-rich lipoprotein levels

[b] To increase HDL-C levels

[c] To improve the overall lipid profile

[d] To reduce total-C and LDL-C levels

[e] Healthy BW was defined as a BMI of approximately 20-25 kg/m^2 for people aged <60 years and is higher in older people.

[f] Healthy BW was defined as a BMI <25 kg/m^2.

[g] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

[h] Recommendations in this report were aligned with the *AHA/ACCF Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update* guideline.[22]

Table B2 Information about saturated fatty acids, unsaturated fatty acids, trans fatty acids and omega-3 polyunsaturated fatty acids provided in existing reports on the prevention and/or management of (AS)CVD

Report	Saturated fatty acids	Unsaturated fatty acids	*Trans* fatty acids	n-3 PUFA supplements
Dutch dietary guidelines 2015[2]	-	-	-	-
CVRM guideline 2018[27]	Max. 10 E%; replace SFA by PUFA, MUFA or CHO from whole grains (based on e.g. [61] and [62])	Results of studies described, but no recommen-dation provided	Max. 1 E% (based on [62])	Not recommended
AHA Lifestyle management 2013[21]	Max. 5-6 E%[a]	-	Reduce intake[a]	-
ESC CVD prevention 2021[16]	Max. 10 E%; replace SFA by PUFA, MUFA or CHO (from whole grains)	-	Minimise intake; none from processed foods	▪ Results of studies were described, but no recommendation was provided. ▪ n-3 PUFAs (IPE 2 x 2 g/d) may be considered in combination with a statin in patients with triglycerides >135 mg/dL despite statin use and lifestyle measures
AHA Cardiovascular health 2021[20]	Adopt a diet low in SFA	-	Adopt a diet low in TFA	-
ESC Dyslipidaemia 2019[15]	• Max. 10 E%, or max. 7 E% in case of hypercholesterol-aemia[d,e] • Replace SFA by MUFA or PUFA[b]	-	Avoid intake[c,d,e]	Recommended[b]
AHA-ACC Blood cholesterol 2018[25]	-	-	-	Recommended in case of persistent severe hyper-triglyceridemia (fasting TG ≥500 mg/dL)
ESC Hypertension 2018[19]	Have a low SFA intake	Increased consumption recommended	-	-
AHA-ACC High blood pressure 2018[26]	Consume a diet low in SFA (as part of a DASH dietary pattern)	-	-	Results of studies described (fish oil may lower BP), but the extent or quality of the evidence is considered less persuasive. No specific recommendation provided.

Report	Saturated fatty acids	Unsaturated fatty acids	*Trans* fatty acids	n-3 PUFA supplements
ESC Secondary prevention CCS 2019[18]	Max. 10 E%; replace SFA by PUFA[f]	-	As little as possible; <1 E%; none from processed foods[f]	-
ESC Secondary prevention ACS 2020[17]	*ESC-SP-CCS* guideline	-	*ESC-SP-CCS* guideline	-
AHA-ASA Secondary prevention stroke 2014[23]	-	-	-	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	Max. 7 E%[d]	-	Max. 1 E%[d]	Recommended (1 g/d)
AHA-ACC Management stable IHD 2012[24]	Max. 7 E%; replace by UFA or CHO[g]	-	Max. 1 E%[h]	Results of studies described (fish oil supplements may reduce CV risk and TG levels), but no specific recommendation provided

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BW: body weight; CCS: chronic coronary syndromes; CHO: carbohydrates; CVRM: cardiovascular risk management; d: days; DDG: Dutch dietary guidelines; E%: percentage of energy; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; IPE: icosapent ethyl; LDL-C: low-density lipoprotein cholesterol; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids; TG: triglycerides; total-C: total cholesterol; UFA: unsaturated fatty acids

Footnotes:

[a] To reduce LDL-C levels

[b] To reduce TG-rich lipoprotein levels

[c] To increase HDL-C levels

[d] To improve the (overall) lipid profile

[e] To reduce total-C and LDL-C levels

[f] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

[g] Recommendations in this report were aligned with the *AHA/ACCF Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update* guideline.[22]

Table B3 Information about dietary cholesterol, protein, dietary fibre and salt provided in existing reports on the prevention and/or management of (AS)CVD

Report	Dietary cholesterol	Protein	Dietary fibre	Salt
Dutch dietary guidelines 2015[2]	-	-	-	Limit to ≤6 g/d
CVRM guideline 2018[27]	Recommendations from existing guidelines described, but no recommenda-tion provided	-	Consume 30-40 g/d (based on [63])	*DDG2015* guideline
AHA Lifestyle management 2013[21]	Evidence was considered insufficient to provide a recommendation	-	-	▪ Limit to ≤6 g/d[a]; ▪ Further reduction to 3.75 g/d can result in greater BP reduction; ▪ Reduction by at least 2.5 g/d already lowers BP
ESC CVD prevention 2021[16]	When guidelines to lower SFA intake are followed, reductions in dietary cholesterol intake follow	-	30-45 g/d, preferably from whole grains	Reduce to <5 g/d
AHA Cardiovascular health 2021[20]	Results of studies are described, but no recommendation was provided	-	Adopt a diet rich in fibre	Choose and prepare foods with little or no salt
ESC Dyslipidaemia 2019[15]	<300 mg/d[a,b]	-	Increase intake[b]	-
AHA-ACC Blood cholesterol 2018[25]	-	-	-	-
ESC Hypertension 2018[19]	-	-	-	Limit to <5 g/d
AHA-ACC High blood pressure 2018[26]	-	Results of studies described (higher protein intake may lower BP), but the extent or quality of the evidence is considered less persuasive. No specific recommendation provided	Results of studies described (fibre may lower BP), but the extent or quality of the evidence is considered less persuasive. No specific recommendation provided	Optimal goal is <3.75 g/d, but aim for at least a 2.5-g/d reduction
ESC Secondary prevention CCS 2019[18]	-	-	35-45 g/d, preferably from whole grains[c]	≤5-6 g/d[c]

Report	Dietary cholesterol	Protein	Dietary fibre	Salt
ESC Secondary prevention ACS 2020[17]	-	-	*ESC-SP-CCS* guideline	*ESC-SP-CCS* guideline
AHA-ASA Secondary prevention stroke 2014[23]	-	-	-	• Limit sodium intake to <6g/d; • Further reduction to <3.75 g/d can result in greater BP reduction
AHA-ACCF Secondary prevention ASCVD 2011[22]	<200 mg/d[a]	-	-	Reduce intake
AHA-ACC Management stable IHD 2012[24]	<200 mg/d[d]	-	-	Reduce intake[d]

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; CCS: chronic coronary syndromes CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol; total-C: total cholesterol

Footnotes:

[a] To improve the (overall) lipid profile

[b] To reduce total-C and LDL-C levels

[c] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

[d] Recommendations in this report were aligned with the *AHA/ACCF Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update* guideline.[22]

Table B4 Information about potassium, vitamins and minerals, fruits and vegetables provided in existing reports on the prevention and/or management of (AS)CVD

Report	Potassium	Vitamin and/or mineral supplements	Fruits	Vegetables
Dutch dietary guidelines 2015[2]	-	Nutrient supplements are not needed, except for people who belong to a group for which supplementation applies	≥200 g/d	≥200 g/d
CVRM guideline 2018[27]	Results of studies described (higher potassium intake may decrease BP), but no recommen-dation provided	Results of studies on vitamin A, B, C, E and B-vitamins described, but no recommendations provided	*DDG2015* guideline	*DDG2015* guideline
AHA Lifestyle management 2013[21]	Results of studies described, but no recommendation provided	-	Consume a diet that emphasises intake of fruits[a,b]	Consume a diet that emphasises intake of vegetables[a,b]

Report	Potassium	Vitamin and/or mineral supplements	Fruits	Vegetables
ESC CVD prevention 2021[16]	Results of studies described (higher potassium intake has favourable effects on BP and stroke risk), but no recommendation provided	Results of studies on vitamin A, C, D, E and B-vitamins described, but no recommendations provided	≥200 g/d	≥200 g/d
AHA Cardiovascular health 2021[20]	It is noted that a healthy dietary pattern is rich in potassium, but no specific recommendation is provided	• Insufficient evidence to support use of high-dose vitamin and mineral supplements • Vitamin and mineral supplementations should not be used as a replacement for a healthy dietary pattern[c]	Eat plenty; choose a wide variety; limit types with added salt or sugar	Eat plenty; choose a wide variety; limit types with added salt or sugar
ESC Dyslipidaemia 2019[15]	-	-	Diet with a focus on fruit is recommended	Diet with a focus on vegetables is recommended
AHA-ACC Blood cholesterol 2018[25]	Results of studies described (increased potassium intake is associated with BP reduction), but no specific recommen-dation provided	-	*AHA-LM* guideline	*AHA-LM* guideline
ESC Hypertension 2018[19]	-	-	Increased consumption of fresh fruits recommended	Increased consumption recommended
AHA-ACC High blood pressure 2018[26]	3500-5000 mg/d[d], preferably by consumption of a diet rich in potassium	Results of studies on calcium supplementation and on magnesium supplementation described (both may lower BP), but the extent or quality of the evidence is considered less persuasive. No specific recommendation provided	Consume a diet rich in fruits (as part of a DASH dietary pattern)	Consume a diet rich in vegetables (as part of a DASH dietary pattern)
ESC Secondary prevention CCS 2019[18]	-	-	≥200 g/d[e]	≥200 g/d[e]

Report	Potassium	Vitamin and/or mineral supplements	Fruits	Vegetables
ESC Secondary prevention ACS 2020[17]	-	-	*ESC-SP-CCS* guideline	*ESC-SP-CCS* guideline
AHA-ASA Secondary prevention stroke 2014[23]	-	Routine supplementation with a single vitamin or a combination of vitamins not recommended	Consumption recommended (as part of a Mediterranean-type diet)	Consumption recommended (as part of a Mediterranean-type diet)
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	Recommended (fresh fruits)	Recommended
AHA-ACC Management stable IHD 2012[24]	-	-	Recommended (fresh fruits)[f]	Recommended[f]

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CKD: chronic kidney disease; CVD: cardiovascular disease; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol

Footnotes:

[a] To reduce LDL-C levels

[b] To reduce BP

[c] Individual nutrient supplements may be needed in cases of inadequacy or for those eating restricted diets (e.g. vegans, certain groups of older adults).

[d] Potassium supplementation (preferably in dietary modification) is recommended unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion.

[e] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

[f] Recommendations in this report were aligned with the *AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update* guideline.[22]

Table B5 Information about nuts, whole grains, refined carbohydrates and sugar-sweetened or sugar-containing beverages provided in existing reports on the prevention and/or management of (AS)CVD

Report	Nuts	Whole grains	Refined carbohydrates	Sugar-sweetened or -containing beverages
Dutch dietary guidelines 2015[2]	≥15 g/d, unsalted	≥90 g/d	Replace refined cereal products by whole grain products	Minimise intake
CVRM guideline 2018[27]	*DDG2015* guideline	*DDG2015* guideline	*DDG2015* guideline	*DDG2015* guideline

Report	Nuts	Whole grains	Refined carbohydrates	Sugar-sweetened or -containing beverages
AHA Lifestyle management 2013[21]	Consume a diet that includes nuts[a,b]	Consume a diet that emphasises intake of whole grains[a,b]	-	Consume a diet that limits intake of sugar-sweetened beverages[a,b]
ESC CVD prevention 2021[16]	30 g/d, unsalted	Consumption recommended (as part of a more plant-based food pattern)	-	Minimise intake
AHA Cardiovascular health 2021[20]	Consumption recommended (as healthy protein source)	Choose foods made from whole grains instead of refined grains	-	Minimise intake
ESC Dyslipidaemia 2019[15]	-	Diet with a focus on whole grains is recommended	-	▪ Use with moderation[c]; ▪ Limit in case of elevated TG levels or visceral adiposity[c]
AHA-ACC Blood cholesterol 2018[25]	*AHA-LM* guideline	*AHA-LM* guideline	Avoid refined carbohydrates in case of persistent severe hypertriglyceridemia (fasting TG ≥500 mg/dL)	*AHA-LM* guideline
ESC Hypertension 2018[19]	Increased consumption recommended	Eat a healthy balanced diet containing whole grains	-	Not recommended
AHA-ACC High blood pressure 2018[26]	-	Consume a diet rich in whole grains (as part of a DASH dietary pattern)	-	-
ESC Secondary prevention CCS 2019[18]	30 g/d, unsalted[d]	Consumption recommended (as part of a Mediterranean dietary pattern)[d]	Avoid or limit refined carbohydrates (as part of a Mediterranean dietary pattern)[d]	Avoid consumption[d]
ESC Secondary prevention ACS 2020[17]	*ESC-SP-CCS* guideline	*ESC-SP-CCS* guideline	*ESC-SP-CCS* guideline	*ESC-SP-CCS* guideline
AHA-ASA Secondary prevention stroke 2014[23]	Consumption recommended (as part of a Mediterranean-type diet)	Consumption recommended (as part of a Mediterranean-type diet)	-	-

Report	Nuts	Whole grains	Refined carbohydrates	Sugar-sweetened or -containing beverages
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	-	-
AHA-ACC Management stable IHD 2012[24]	-	Adopt a diet high in whole grains	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CHO: carbohydrates; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides

Footnotes:

[a] To reduce LDL-C levels

[b] To reduce BP

[c] To improve the overall lipid profile

[d] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

Table B6 Information about sweets, dairy, fish and poultry provided in existing reports on the prevention and/or management of (AS)CVD

Report	Sweets	Dairy	Fish	Poultry
Dutch dietary guidelines 2015[2]	-	A few portions/d, including milk or yogurt	One serving/wk, preferably fatty fish	-
CVRM guideline 2018[27]		*DDG2015* guideline	*DDG2015* guideline	
AHA Lifestyle management 2013[21]	Consume a diet that limits intake of sweets[a,b]	Consume a diet that includes low-fat (instead of full-fat) dairy[a,b]	Consume a diet that includes fish[a,b]	Consume a diet that includes poultry[a,b]
ESC CVD prevention 2021[16]	-	-	1-2 times/wk, preferably fatty fish	-
AHA Cardiovascular health 2021[20]	-	Low-fat or fat-free instead of full-fat dairy recommended (as healthy protein source)	Consumption recommended (as healthy protein source)	Consumption recommended (as healthy protein source), preferably lean cuts and not processed
ESC Dyslipidaemia 2019[15]	-	-	Diet with a focus on fish is recommended	-

Report	Sweets	Dairy	Fish	Poultry
AHA-ACC Blood cholesterol 2018[25]	*AHA-LM* guideline	*AHA-LM* guideline	*AHA-LM* guideline	*AHA-LM* guideline
ESC Hypertension 2018[19]	-	Eat a healthy balanced diet containing low-fat dairy	Increased consumption recommended	-
AHA-ACC High blood pressure 2018[26]	-	Consume a diet rich in low-fat dairy (as part of a DASH dietary pattern)	-	-
ESC Secondary prevention CCS 2019[18]	-	Limited intake of low-fat dairy recommended[c]	1-2 servings/wk, preferably fatty fish[c]	-
ESC Secondary prevention ACS 2020[17]	-	*ESC-SP-CCS* guideline	*ESC-SP-CCS* guideline	-
AHA-ASA Secondary prevention stroke 2014[23]	Consume a (Mediterranean-type) diet that limits intake of sweets	Low-fat dairy recommended (as part of a Mediterranean-type diet)	Consumption recommended (as part of a Mediterranean-type diet)	Consumption recommended (as part of a Mediterranean-type diet)
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	Low-fat dairy recommended	-	-
AHA-ACC Management stable IHD 2012[24]	-	Low-fat dairy recommended[d]	Results of a MA described, but no specific recommendation provided	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CHO: carbohydrates; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol; MA: meta-analysis

Footnotes:

[a] To reduce LDL-C levels

[b] To reduce BP

[c] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

[d] Recommendations in this report were aligned with the *AHA/ACCF Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update* guideline.[22]

Table B7 Information about red meat, processed meat, ultra-processed foods and plant-based meat alternatives provided in existing reports on the prevention and/or management of (AS)CVD

Report	Red meat	Processed meat	Ultra-processed foods	Plant-based meat alternatives
Dutch dietary guidelines 2015[2]	Limit intake, particularly processed meat	Limit intake	-	-
CVRM guideline 2018[27]	*DDG2015* guideline	*DDG2015* guideline	-	-
AHA Lifestyle management 2013[21]	Consume a diet that limits intake of red meat[a,b]	-	-	-
ESC CVD prevention 2021[16]	Max. 350-500 g/wk, restrict processed red meat in particular	Restrict intake	-	-
AHA Cardiovascular health 2021[20]	Results of studies described, but no recommendation provided	Minimise intake	Minimise intake	Insufficient evidence to provide a recommendation
ESC Dyslipidaemia 2019[15]	-	-	-	-
AHA-ACC Blood cholesterol 2018[25]	*AHA-LM* guideline	-	-	-
ESC Hypertension 2018[19]	Have a low consumption of red meat	-	-	-
AHA-ACC High blood pressure 2018[26]	-	-	-	-
ESC Secondary prevention CCS 2019[18]	Limited intake of (lean) red meat recommended[c]	-	-	-
ESC Secondary prevention ACS 2020[17]	*ESC-SP-CCS guideline*	-	-	-
AHA-ASA Secondary prevention stroke 2014[23]	Consume a (Mediterranean-type) diet that limits intake of red meat	-	-	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	-	-
AHA-ACC Management stable IHD 2012[24]	-	-	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CVD: cardiovascular disease; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; EESC: European Society of

Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol;

Footnotes:

[a] To reduce LDL-C levels

[b] To reduce BP

[c] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

Table B8 Information about legumes, soy products, fats and oils and garlic provided in existing reports on the prevention and/or management of (AS)CVD

Report	Legumes	Soy products	Fats and oils	Garlic
Dutch dietary guidelines 2015[2]	Eat weekly	-	Replace hard fats by soft fats and vegetable oils	-
CVRM guideline 2018[27]	*DDG2015* guideline	-	*DDG2015* guideline	-
AHA Lifestyle management 2013[21]	Consume a diet that emphasises intake of legumes[a,b]	-	Consume a diet that includes non-tropical vegetable oils[a,b]	-
ESC CVD prevention 2021[16]	Consumption recommended (as part of a Mediterranean or more plant-based food pattern)	-	Replace animal fats with vegetable sources of fats[a]	-
AHA Cardiovascular health 2021[20]	Consumption recommended (as healthy protein source)	-	Use liquid, non-tropical plant oils instead of animal fats and partially hydrogenated fats	
ESC Dyslipidaemia 2019[15]	-	Results of studies described, but no recommendation provided	-	-
AHA-ACC Blood cholesterol 2018[25]	*AHA-LM* guideline	-	*AHA-LM* guideline	-
ESC Hypertension 2018[19]	Increased consumption recommended	-	Eat a healthy balanced diet containing olive oil (as source of UFA)	-
AHA-ACC High blood pressure 2018[26]	-	-	-	Effects insufficiently proved. No recommendation provided.
ESC Secondary prevention CCS 2019[18]	Consumption recommended (as part of a Mediterranean dietary pattern)[c]	-	Limited intake of liquid vegetable oils recommended[c]	-

Report	Legumes	Soy products	Fats and oils	Garlic
ESC Secondary prevention ACS 2020[17]	*ESC-SP-CCS* guideline	-	*ESC-SP-CCS* guideline	-
AHA-ASA Secondary prevention stroke 2014[23]	Consumption recommended (as part of a Mediterranean-type diet)	-	Olive oil recommended (as part of a Mediterranean-type diet)	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	-	-
AHA-ACC Management stable IHD 2012[24]	-	-	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; AHA-LM: AHA Lifestyle management 2013 guideline; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CVD: cardiovascular disease; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol; UFA: unsaturated fatty acids

Footnotes:

[a] To reduce LDL-C levels

[b] To reduce BP

[c] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

Table B9 Information about alcohol, coffee, tea and probiotics provided in existing reports on the prevention and/or management of (AS)CVD

Report	Alcohol	Coffee	Tea	Probiotics
Dutch dietary guidelines 2015[2]	Do not drink alcohol or ≤1 glass/d	Replace unfiltered by filtered coffee	Drink 3 cups/d	-
CVRM guideline 2018[27]	*DDG2015* guideline	*DDG2015* guideline	*DDG2015* guideline	-
AHA Lifestyle management 2013[21]	-	-	-	-
ESC CVD prevention 2021[16]	Max. 100 g/wk	Results of studies on non-filtered coffee and total coffee described, but no recommendation provided	-	-
AHA Cardiovascular health 2021[20]	If you do not drink alcohol, do not start; if you choose to drink alcohol, limit intake	-	-	-

Report	Alcohol	Coffee	Tea	Probiotics
ESC Dyslipidaemia 2019[15]	Moderate alcohol consumption (≤1 unit/d) is acceptable in those who drink alcohol, if TG levels are not elevated (in that case: reduce intake)[a]	-	-	-
AHA-ACC Blood cholesterol 2018[25]	Avoid alcohol in case of persistent severe hyper-triglyceridaemia (fasting TG ≥500 mg/dL)	-	-	-
ESC Hypertension 2018[19]	If alcohol is consumed, limit to 14 (♂) or 8 (♀) units/wk	Results of studies described (caffeine has an acute pressor effect; coffee intake is associated with CV benefits), but no specific recommendation provided	Results of studies described (green or black tea intake may have a small BP-lowering effect), but no specific recommendation provided	-
AHA-ACC High blood pressure 2018[26]	If alcohol is currently consumed, one should not drink more than 2 (♂) or 1 (♀) standard drinks/d	Effects insufficiently proved. No recommendation provided.	Effects insufficiently proved. No recommendation provided.	Results of studies described (probiotics may lower BP), but the extent or quality of the evidence considered less persuasive. No specific recommendation provided.
ESC Secondary prevention CCS 2019[18]	If alcohol is consumed, limit intake to <100 g/wk or <15 g/d[b]	-	-	-
ESC Secondary prevention ACS 2020[17]	*ESC-SP-CCS* guideline	-	-	-
AHA-ASA Secondary prevention stroke 2014[23]	• Heavy drinkers should eliminate or reduce their alcohol intake; • Light to moderate alcohol consumption (2 (♂) or 1 (♀) drinks/d) may be reasonable;	-	-	-

Report	Alcohol	Coffee	Tea	Probiotics
	• If alcohol is not consumed, one should not start			
AHA-ACCF Secondary prevention ASCVD 2011[22]	Alcohol moderation	-	-	-
AHA-ACC Management stable IHD 2012[24]	Alcohol moderation	-	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; CCS: chronic coronary syndromes; CVD: cardiovascular disease; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; TG: triglycerides

Footnotes:

[a] To improve the overall lipid profile

[b] Lifestyle recommendations were largely based on the *2016 ESC Guidelines on CVD prevention in clinical practice*[32] (an updated version of which was published in 2021[16]).

Table B10 Information about (foods enriched with) phytosterols, red yeast rice, fibre supplements and flaxseed provided in existing reports on the prevention and/or management of (AS)CVD

Report	(Foods enriched with) phytosterols	Red yeast rice	Fibre supplements	Flaxseed
Dutch dietary guidelines 2015[2]	-	-	-	-
CVRM guideline 2018[27]	Results of studies described: functional foods with 2 g/d of phytosterols may reduce LDL-C by 10%; studies with clinical endpoints are missing. Therefore no recommendation could be provided.	Not recommended	-	-
AHA Lifestyle management 2013[21]	-	-	-	-
ESC CVD prevention 2021[16]	Results of studies described (functional foods with phytosterols (2 g/d) are effective in lowering LDL-C by 10%; studies with clinical endpoints are	Not recommended (may even cause side-effects)	-	-

Report	(Foods enriched with) phytosterols	Red yeast rice	Fibre supplements	Flaxseed
	missing). No recommendation provided			
AHA Cardiovascular health 2021[20]	-	-	-	-
ESC Dyslipidaemia 2019[15]	Recommended[d]	Recommended in people with elevated plasma cholesterol who do not qualify for statin therapy[a]	Results of studies described (ß-glucan lowers total-C and LDL-c), but no recommendation provided	-
AHA-ACC Blood cholesterol 2018[25]	-	-	-	-
ESC Hypertension 2018[19]	-	-	-	-
AHA-ACC High blood pressure 2018[26]	-	-	-	Results of studies described (flaxseed may lower BP), but the extent or quality of the evidence considered less persuasive. No specific recommendation provided
ESC Secondary prevention CCS 2019[18]	Results of studies described (dietary supplements with phytosterols may lower LDL-C, but have not been shown to improve clinical outcomes), but no specific recommendation provided	-	-	-
ESC Secondary prevention ACS 2020[17]	May be considered as an adjunct to pharmacological therapy in (very) high-risk patients who fail to achieve LDL-C goals on statins or	-	-	-

Report	(Foods enriched with) phytosterols	Red yeast rice	Fibre supplements	Flaxseed
	who cannot be treated with statins			
AHA-ASA Secondary prevention stroke 2014[23]	-	-	-	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	-	-
AHA-ACC Management stable IHD 2012[24]	Addition of 2 g/d of plant sterols/stanols was referred to as a potentially beneficial dietary intervention	-	Addition of >10 g/d of viscous fibre was referred to as a potentially beneficial dietary intervention	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; IHD: ischemic heart disease; LDL-C: low-density lipoprotein cholesterol; total-C: total cholesterol

Footnotes:

[a] To reduce total-C and LDL-C levels

Table B11 Information about Mediterranean diet, DASH diet, USDA food pattern/AHA diet and more plant-based diets provided in existing reports on the prevention and/or management of (AS)CVD

Report	Mediterranean diet (or similar)	DASH diet	USDA food pattern or AHA diet	More plant-/less animal-based diet
Dutch dietary guidelines 2015[2]	-	-	-	Adopt a more plant-/less animal-based dietary pattern
CVRM guideline 2018[27]	Results of studies were described, but no recommendation was provided.	-	-	*DDG2015* guideline
AHA Lifestyle management 2013[21]	Results of studies were described, but no recommendation was provided.	Recommended (for BP reduction, combine with lower salt intake)	Recommended	-
ESC CVD prevention 2021[16]	Adopt Mediterranean (or similar) diet	-	-	Adopt a more plant-based dietary pattern
AHA Cardiovascular health 2021[20]	Results of studies described, but no recommendation provided	Results of studies described, but no recommendation provided	Results of studies described, but no recommendation provided	-

Report	Mediterranean diet (or similar)	DASH diet	USDA food pattern or AHA diet	More plant-/less animal-based diet
ESC Dyslipidaemia 2019[15]	Results of studies described (Mediterranean diet has proved to be effective in CV risk factors), but no specific recommendation provided	Results of studies described (DASH diet has proved to be effective in CV risk factors), but no specific recommendation provided	-	-
AHA-ACC Blood cholesterol 2018[25]	-	-	-	-
ESC Hypertension 2018[19]	Recommended	-	-	-
AHA-ACC High blood pressure 2018[26]	Results of studies described (Mediterranean diet have been shown to lower BP), but the extent or quality of the evidence is considered less persuasive. No specific recommendation provided	Recommended	-	-
ESC Secondary prevention CCS 2019[18]	Recommended	-	-	-
ESC Secondary prevention ACS 2020[17]	*ESC-SP-CCS* guideline	-	-	-
AHA-ASA Secondary prevention stroke 2014[23]	Recommended	-	-	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	-	-
AHA-ACC Management stable IHD 2012[24]	-	-	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CV: cardiovascular; CVRM: cardiovascular risk management; DASH: Dietary Approaches to Stop Hypertension; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; ESC-SP-CCS: ESC Secondary prevention CCS 2019 guideline; IHD: ischemic heart disease; USDA: United States Department of Agriculture

Table B12 Information about vegetarian diet, low-carbohydrate diet, very low-fat diet and ketogenic diet provided in existing reports on the prevention and/or management of (AS)CVD

Report	Vegetarian diet	Low-carbohydrate diet	Very low-fat diet	Ketogenic diet
Dutch dietary guidelines 2015[2]	-	-	-	-
CVRM guideline 2018[27]	-	-	-	-
AHA Lifestyle management 2013[21]	-	-	-	-
ESC CVD prevention 2021[16]	-	Results of a review described, but no recommendation provided (except that medical or dietetic supervision is needed when adopting such diets)	-	Results of a review described, but no recommendation provided (except that medical or dietetic supervision is needed when adopting such diets)
AHA Cardiovascular health 2021[20]	-	-	-	Insufficient evidence to support this diet
ESC Dyslipidaemia 2019[15]	-	No justification to recommend very low-carbohydrate diets	-	-
AHA-ACC Blood cholesterol 2018[25]	-	-	Recommended in case of persistent severe hyper-triglyceridaemia (fasting TG ≥500 mg/dL)	-
ESC Hypertension 2018[19]	-	-	-	-
AHA-ACC High blood pressure 2018[26]	Results of studies described (vegetarian diet have been shown to lower BP), but the extent or quality of the evidence is considered less persuasive. No specific recommendation provided.	Results of studies described (low-carbohydrate diet have been shown to lower BP), but the extent or quality of the evidence is considered less persuasive. No specific recommendation provided.	-	-
ESC Secondary prevention CCS 2019[18]	-	-	-	-

Report	Vegetarian diet	Low-carbohydrate diet	Very low-fat diet	Ketogenic diet
ESC Secondary prevention ACS 2020[17]	-	-	-	-
AHA-ASA Secondary prevention stroke 2014[23]	-	-	-	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	-	-
AHA-ACC Management stable IHD 2012[24]	-	-	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CCS: chronic coronary syndromes; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; IHD: ischemic heart disease; TG: triglycerides.

Table B13 Information about intermittent fasting, berbine and policosanol provided in existing reports on the prevention and/or management of (AS)CVD

Report	Intermittent fasting	Berbine (plant-based alkaloid)	Policosanol (sugarcane wax)
Dutch dietary guidelines 2015[2]	-	-	-
CVRM guideline 2018[27]	-	-	-
AHA Lifestyle management 2013[21]	-	-	-
ESC CVD prevention 2021[16]	Results of a review described, but no recommendation provided	-	-
AHA Cardiovascular health 2021[20]	Insufficient evidence to support this diet	-	-
ESC Dyslipidaemia 2019[15]	-	Results of studies described, but no specific recommendation provided	Results of studies described, but no specific recommendation provided
AHA-ACC Blood cholesterol 2018[25]	-	-	-
ESC Hypertension 2018[19]	-	-	-
AHA-ACC High blood pressure 2018[26]	-	-	-
ESC Secondary prevention CCS 2019[18]	-	-	-

Report	Intermittent fasting	Berbine (plant-based alkaloid)	Policosanol (sugarcane wax)
ESC Secondary prevention ACS 2020[17]	-	-	-
AHA-ASA Secondary prevention stroke 2014[23]	-	-	-
AHA-ACCF Secondary prevention ASCVD 2011[22]	-	-	-
AHA-ACC Management stable IHD 2012[24]	-	-	-

Abbreviations: ACC(F): American College of Cardiology (Foundation); ACS: acute coronary syndrome; AHA: American Heart Association; ASA: American Stroke Association; ASCVD: atherosclerotic cardiovascular disease; CCS: chronic coronary syndromes; CVRM: cardiovascular risk management; DDG: Dutch dietary guidelines; ESC: European Society of Cardiology; IHD: ischemic heart disease

Annex C Summary tables for the evaluation of the results from meta-analyses, pooled analyses, individual RCTs and cohort studies

Table C1 Summary table for the effects or associations evaluated in the background documents: pooled analyses

Aspect	Explanation
Number of studies	Specification, per health outcome, of the total number of studies on which the pooled analysis is based.
Number of participants and cases	Specification, per health outcome, of the total number of participants in the analysis and the total number of participants that developed the health outcome during follow-up (in case of RCTs specified for the intervention group and the control group).
Study durations	Specification of the follow-up periods of the included studies.
Dietary exposure	Specification of the dietary factor under study.
Dietary assessment method	Specification of the method of dietary assessments used in the included studies.
Strength of the effect or association	Refers to a specific table in which the pooled results are presented.
Study population	Specification of the participant characteristics, such as body weight status, use of medications and sex (men, women or both), and specification of the continent or country where the research took place.

Table C2 Summary table for the effects or associations evaluated in the background documents: results of pooled analyses

Aspect	Explanation
Outcome	Specification of the health outcome for which the results are presented.
Result	Specification of the pooled effect or risk estimate with a 95% confidence interval, where possible, in relation to (the change in) the dietary factor*; level of heterogeneity (expressed as I^2)**; and number of studies contributing to the pooled result. * In case results were obtained from an existing meta-analysis and that meta-analysis presented effects based on both 'fixed effects' and 'random effects', the Committee used the results of the 'random effects' model. In case the Committee pooled results itself, it used a random effects approach. ** An I^2 less than approximately 25% was considered little or no heterogeneity, an I^2 between approximately 25% and 50% was considered moderate heterogeneity and an I^2 higher than approximately 50% was considered substantial heterogeneity. In case of moderate or substantial heterogeneity, the heterogeneity was explained in the accompanying text. 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 estimates. 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.

Table C3 Summary table for each study evaluated in the background documents: individual randomised controlled trials

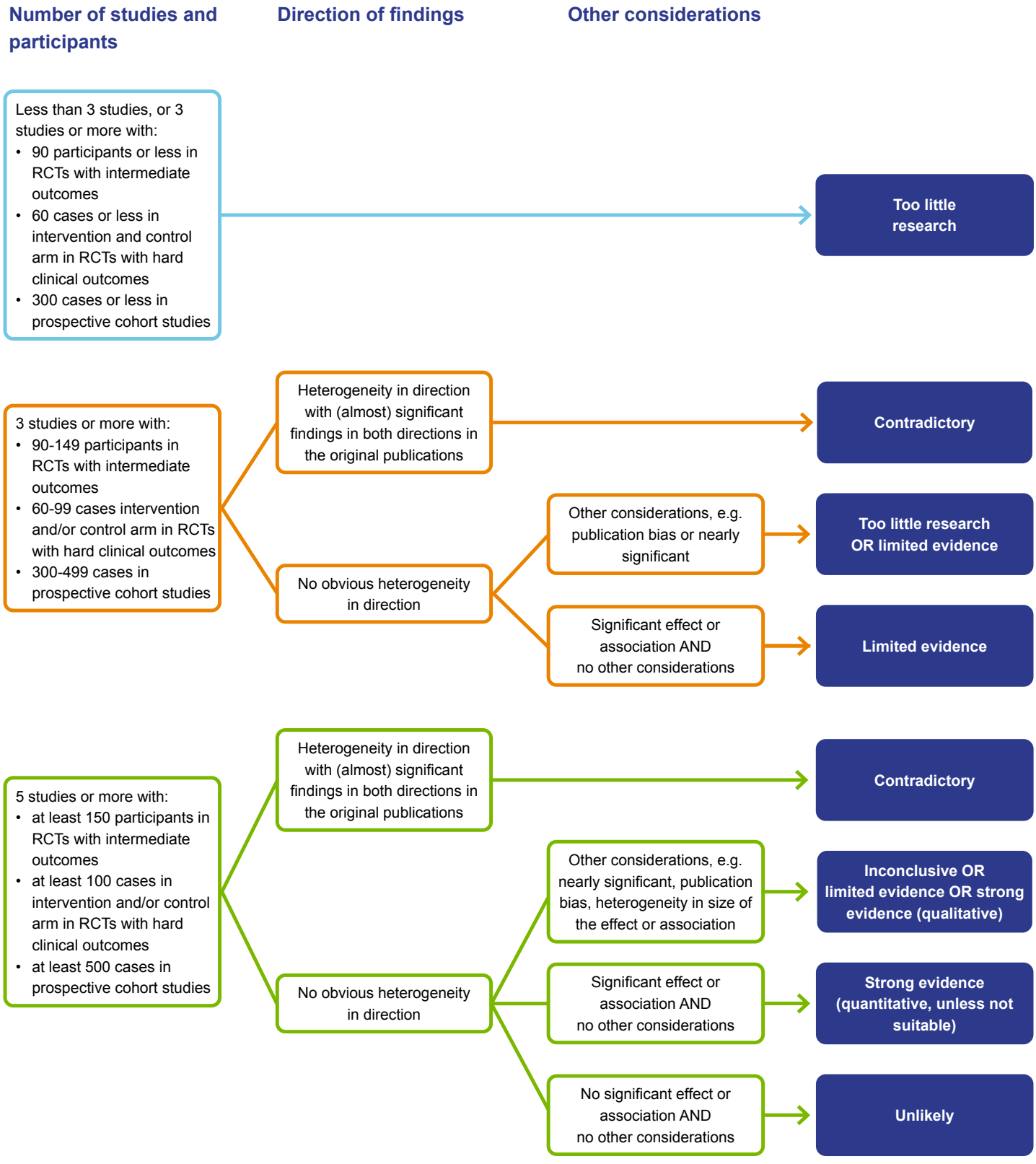
Aspect	
Trial name	Specification of the name of the randomised controlled trial.
Study duration	Specification of the follow-up periods of the included studies.
Primary disease	Specification of the first cardiovascular event that the participant experienced (i.e. the index event).
Study design	Specification of the design of the study.
Diet of intervention (i) and control (c) group	Specification of the composition of the study diets.
Number of participants in intervention (i) and control (c) group; number of cases	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 (the change in) the dietary factor.
Study population	Specification of the participant characteristics, such as body weight status, use of medications and sex (men, women or both), and specification of the continent or country where the research took place.

Table C4 Summary table for each study evaluated in the background documents: individual or pooled cohort studies

Aspect	Explanation
Study duration	Specification of the follow-up periods of the included studies.
Primary disease	Specification of the first cardiovascular event that the participant experienced (i.e. the index event).
Study design	Specification of whether the description refers to one individual cohort study or to a combination of cohort studies (pooled analyses).
Cohort name	Specification of the name of the cohort(s).
Dietary 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 (long-term) health outcome during follow-up.
Strength of the association	Specification of the risk estimate with a 95% confidence interval in relation to (the change in) the dietary factor.
Study population	Specification of the participant characteristics, such as body weight status, use of medications and sex (men, women or both), and specification of the continent or country where the research took place.

Annex D Decision tree

Figure 1 Decision tree for evaluating the available scientific evidence



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