Health Council of the Netherlands

Methodology for the evaluation of the evidence for the Dutch dietary guidelines 2015

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to:

the Minister of Health, Welfare and Sport

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Foreword

This background document describes the methodology for the evaluation of the evidence used by the Committee that prepared the Dutch dietary guidelines 2015. During the production process of the guidelines, the President of the Health Council of the Netherlands offered the opportunity to comment on draft versions of background documents concerning nutrients, foods and dietary patterns. The Committee finalized the background documents taking into account the comments, provided that these were in agreement with the procedure described in this document. The background documents, comments and the Committee's reaction to the comments are only in Dutch.

Contents

1 Introduction

In this document, Methodology for the evaluation of the evidence for the Dutch dietary guidelines 2015, the Committee (Annex A) describes how it evaluates the evidence in the background documents. In this introductory chapter, the Committee explores the domain covered by this advisory report. In Chapter 2, the Committee substantiates its reasons for basing the "Dutch dietary guidelines 2015" advisory report on studies in which exposure was measured before the outcome was determined. Chapter 3 describes the background documents' topics: nutrients, foods and dietary patterns. It also addresses points of special interest with regard to estimating intake. In Chapter 4, the Committee outlines the 10 pivotal chronic diseases in preparing the guidelines and how this translates into specific measures of outcome per type of study. The Committee has carried out a literature review to evaluate the evidence. In Chapter 5 it describes the approach used. In Chapter 6, the Committee indicates how it formulates conclusions in the background documents. In Chapter 7, the Committee provides details of the information that is integrated into the "Dutch dietary guidelines 2015" advisory report.

Annex B is a glossary.

1.1 The domain of the advisory report: prevention of chronic diseases

The dietary guidelines focus on the prevention of chronic diseases in the general population. These guidelines describe the nutrients, foods and dietary patterns needed to achieve health gain in the Netherlands. The description of the evidence is based on the international scientific literature. Yet, dietary guidelines are country-specific, so this advisory report is focused on the Dutch situation. Differences between Western countries mainly reflect differences in dietary patterns. The extent to which the average consumption of a nutrient or food (or food group) deviates from the optimal level of consumption determines the health gain that can be achieved by changes in intake. For instance, information about the optimal consumption of fruit and vegetables is less important in countries where people already eat sufficient amounts of fruit and vegetables. Dietary guidelines may also differ from one country to another due to differences in the prevalence of chronic diseases and the associated risk factors. For example, due to the high prevalence of overweight and obesity in the United States, the Dietary guidelines for the Americans place substantial emphasis on the prevention of obesity and on the health gain that obese individuals can achieve by dieting.[1]

Guidelines for patients with diseases are outside the domain covered by this advisory report

Although the dietary guidelines are aimed at the general population, they are also important for patient groups. Some patient groups, however, need specific dietary

recommendations. This advisory report does not address such disease-specific dietary guidelines. This is the responsibility of the medical profession.

The diet of children up to the age of two is outside the domain covered by this advisory report

The Committee considers the guidelines to be generally applicable to individuals aged two and above, even though the type of study that underpins this advisory report rarely involves children. Children up to the age of two are outside the scope of this advisory report. There is, indeed, a growing body of evidence that nutrition before birth and in infants and toddlers has an effect on health, including the measures of outcome addressed by this advisory report. However, the diets of infants and toddlers differ significantly from those of older children and adults. In the run of 2016, the Health Council will launch an advisory process on healthy nutrition during pregnancy and lactation and for toddlers.[2]

2 Types of study on which the advisory report is based

In this chapter, the Committee substantiates its reasons for basing the advisory report and the background documents on studies in which exposure was measured before the outcome was determined. It identifies the types of study on which its work is based, showing how they complement one another.

2.1 Scope limited to studies in which exposure was measured before the outcome was determined

The Committee bases these dietary guidelines on the results of studies in human subjects in which exposure was measured before the outcome was determined. Intake data collected after the diagnosis of a disease are less reliable than prospectively collected data. If someone is told that he has a particular disorder or disease that is (or may be) affected by diet, this may be sufficient reason for him to change his dietary pattern. If that is indeed the case, then the post-diagnostic diet will no longer be an accurate reflection of the pre-diagnostic diet. Accordingly, it will no longer be possible to obtain a reliable impression of the role of dietary factors in the aetiology of the disease. It may also be that participants' reports of their past dietary pattern are, consciously or unconsciously, coloured by the disease from which they are suffering. This recall bias can be a substantial factor in nutritional research.[3] Thus the results of studies in which food consumption data are only collected once a disease has been diagnosed have limited validity (for example, cross-sectional studies, case reports and most case-control studies). Accordingly, these have been excluded from this advisory report. The Committee notes that recall bias is less important in other types of case-control study, such as drug research.

Partly for reasons of feasibility, the Committee excludes evidence from experimental animal studies and *in vitro* research. The value of these types of study lies in the generation and testing of hypotheses regarding possible mechanisms of action. While such studies can lead to conclusions about the *in vitro* situation or about effects in experimental animals, the same cannot be said of effects in human subjects. Of course, such findings could well serve as a springboard for studies to determine whether the effect also occurs in human subjects. When drawing up the dietary guidelines, however, *in vitro* research and experimental animal studies provide insufficient guidance.

The Committee includes all types of observational studies in which exposure is determined before the disease is diagnosed. To improve readability, studies of this type are referred to as "cohort studies" in the remainder of this advisory report. Some prime examples are prospective cohort studies, "nested" case-control studies and case-cohort studies.

2.2 The results of randomised controlled trials and prospective cohort studies complement each other

Studies in which nutritional data are collected prior to the onset of disease can be either experimental or observational in nature. A debate is currently taking place in scientific journals concerning the value of randomised controlled intervention trials (RCTs) compared to cohort studies. Table 1 summarises the pros and cons of RCTs and cohort studies. This shows that cohort studies can provide information that supplements the data obtained from RCTs, and vice versa. With regard to the relationships between diet and chronic diseases, the value of cohort studies lies in their (potentially) long follow-up period, the (potentially) large number of participants and the representativeness of the participants to the general population or the relevant population group. The strength of RCTs lies in the fact that, by eliminating bias and confounding, studies of this type can provide strong evidence for causal relationships.

2.2.1 Experimental research (RCTs)

Experimental research involves an investigation of what happens when the researcher changes the level of exposure. In describing experimental research, the Committee has primarily focused on RCTs. The Committee has excluded all experiments that lack a control group.

In RCTs, the participants are divided into groups on the basis of chance (for example, by throwing dice). One or more groups are given a treatment whose effect the researchers wish to determine, while another group (that, aside from the intervention, is completely comparable to the group being treated) serves as a control. Ideally, neither the participants, the researchers nor those administering/performing the treatments will know which participants belong to which groups. Such studies are described as “blinded”. This approach can only be used if a treatment (placebo) is available for the control group that can not be distinguished from the experimental treatment.

2.2.2 Effective RCTs deliver evidence about the causality of a relationship

Based on good quality RCTs, it is possible to determine whether or not there is a causal relationship between the intervention and the effect. It is important to bear in mind that coincidental circumstances can cause any study, regardless of its quality and type (i.e. even a high-quality RCT), to generate outcomes that give a false impression. The statistical significance level (p-value) indicates the size of the risk of a false-positive outcome. For that reason, the evidence for a causal relationship is stronger if the effect is found in several RCTs, rather than in just one.

RCTs provide evidence about the causal chain. If an intervention is effective somewhere in the causal chain, this is not necessarily the specific cause of the effect in question. For example, although draining swamps (intervention) results in less malaria (effect), it would be incorrect to conclude that swamps cause malaria. Malaria is caused by a parasite that is transmitted to humans by mosquitoes.[4]

Table 1 Pros and cons of RCTs and prospective cohort studies.[5]

	RCTs	Cohort studies
Confounding	No	Can not be ruled out
Strength of the evidence regarding causality	Strong	Less strong
Representativeness for general population	Often limited	Generally good
Measure of outcome	Often risk factor, occasionally morbidity/mortality	Usually morbidity/mortality
Levels of exposure	One or a few; often relatively high	All levels present in the study population
Number of participants	Limited	Large
Duration of study relative to time for chronic diseases to develop	Short or limited	Long
Effects that occur (or mainly occur) in specific stages of life and to a lesser extent (or not at all) in other stages.	More likely to be missed due to limited duration of study	More likely to be observed due to extensive duration of study

2.2.3 Observational studies (cohort studies)

The goal of observational studies is to collect study data in a way that has the minimum possible impact – or none at all – on the existing situation. Accordingly, the relationship between diet and chronic disease is studied in the same context that occurs in practice. In cohort studies follow-up observations can be carried out after periods without research activity. Therefore, cohort studies can last for many years or even several decades. For the purposes of research into the aetiology of chronic diseases – which arise gradually over long periods of time – that is a major asset.

Some cohort studies collect food consumption data on several occasions, to give a better picture of the long-term consumption. Dietary data collected after the occurrence of the disease in question is not included in the analysis.

2.2.4 Cohort studies provide less strong evidence for causality than RCTs

Like RCTs, cohort studies into the association of diet with chronic disease aim to provide evidence of causality. Such evidence is less strong, however, as confounding (or residual confounding) can never be ruled out in studies of this type. Nevertheless, in some specific cases, causality has been convincingly demonstrated on the basis of results obtained in cohort studies.[*] Within the domain of the dietary guidelines,

[*] Uncovering the relationship between smoking and lung cancer is the classic example of the use of observational studies to deduce a causal relationship.[6,7] This involves a very strong dose-response relationship, in which people who smoke more than one pack of cigarettes per day are 10 times more likely

however, cohort studies do not provide sufficiently strong evidence to support definitive conclusions about causality. Take the following cases, for example. Here, the findings from cohort studies were both consistent and convincing, yet these were negated once RCTs became available:

- In the case of beta carotene, cohort studies yielded strong evidence for a protective effect against lung cancer. However, RCTs demonstrated that, among smokers, supplements containing high doses of beta carotene actually increased the risk of this disease.[8,9]
- Based on cohort studies, folate had a preventive effect on cardiovascular diseases. However, when results from RCTs became available, supplements containing high doses of folic acid did not have an effect among heart patients.[10,11]

2.3 The background documents separately evaluate the evidence from RCTs and cohort studies

In view of the differences between RCTs and cohort studies, the Committee evaluates the evidence from RCTs and cohort studies separately in the background documents.[*] Based on evidence from RCTs, the Committee draws conclusions about the *effects* of food consumption on chronic diseases and on the strength of the evidence supporting those conclusions. In the case of evidence from cohort studies, the Committee draws conclusions about the *relationships (associations)* between food consumption and chronic diseases and on the strength of the evidence supporting those conclusions.

to develop lung cancer than non-smokers. Annex C contains further details about conclusions derived from observational studies into the probability of a causal relationship.

[*] The Committee has, therefore, opted to take a different approach to that used by the Dietary Guidelines for Americans[1], the World Cancer Research Fund[12] and the Nordic Nutrition Recommendations (NNR). In those reports, the highest level of evidence is not attached solely to good-quality RCTs. In the absence of RCTs, it is also ascribed to a few good cohort studies.

3 Aspects of nutrition that are evaluated

In this chapter, the Committee describes the three levels at which they evaluate the relationship between diet and the risk of chronic diseases: nutrients, foods and dietary patterns. It also addresses points of special interest with regard to estimating the associated intake.

3.1 Background documents on nutrients

A series of background documents deals with the effects of nutrients on chronic diseases:

- proteins
- fatty acids
- digestible carbohydrates
- dietary fibre
- dietary cholesterol
- sodium
- potassium
- alcohol
- micronutrient supplements.

No background documents on micronutrients from normal diets have been drawn up as the evidence has been described in a series of advisory reports dating from 2008-2009 and 2012:

- Evaluation of the dietary reference values for vitamin D (2012).[13]
- Towards an adequate intake of vitamins and minerals (2009).[14]
- Towards an adequate intake of vitamin A (2008).[15]
- Towards an adequate intake of vitamin D (2008).[16]
- Towards maintaining an optimum iodine intake (2008).[17]
- Towards an optimal use of folic acid (2008).[18]

The Committee used these advisory reports when drafting the Dutch dietary guidelines 2015.

3.2 Background documents on foods, beverages and dietary patterns

Another series of background documents describe the evidence regarding the effects of the following foods on chronic diseases:

- fish
- vegetables
- fruit
- cereals and cereal products
- legumes

- nuts and seeds
- dairy products
- meat
- eggs
- potatoes
- fats and oils

and the effects of the following beverages:

- tea
- coffee
- water
- beverages with added sugar
- alcoholic beverages (beer, wine and spirits).

There is also a background document describing the relationship between dietary patterns and chronic diseases.

3.3 Quality aspects of exposure data

There are various methods for estimating the intake of foods and nutrients. The methods used in food consumption studies include questionnaires (some very detailed, others less so), food frequency questionnaires, methods involving dietary records (in which foods may or may not be weighed) and interview methods. Some methods are related to the total diet, others to a selection of major foods or food groups. Some methods are designed to accurately record the diet on a specific day or a few days, while others focus on the average consumption over the past month (or the past few months).

Identifying the best method for determining the intake of a dietary factor involves considerations such as the frequency of consumption, the variation in the quantity used, and the accuracy with which people are able to estimate quantities. A 24-hour recall method gives a reasonable picture of bread intake, as people's bread consumption varies little from day-to-day. However, a 24-hour time window is too short for the purpose of estimating fish consumption, as most Dutch people eat fish no more than once a week and many only eat it sporadically.

Biomarkers of intake are objectively measurable characteristics that give an indication of the intake of a certain nutrient. These are useful if they give a good quality picture of intake. Biomarkers of intake are only available for a few nutrients. For instance, the preferred method for estimating sodium intake involves determining the excretion of sodium in one or more 24-hour urine samples.

The background documents explore problems specifically affecting the estimation of exposure to the dietary factor in question.

4 Measures of outcome evaluated

In this chapter, the Committee explains how it selected the measures of outcome. Morbidity and mortality are addressed first, then the following risk factors: blood pressure, LDL cholesterol and body weight.

4.1 Diseases pivotal to the dietary guidelines

The dietary guidelines are based on the evidence concerning the effects of diet on the aetiology of diseases. The top-10 Dutch diseases in terms of mortality, years of potential life lost, or burden of disease according to the 2007 Public Health Status and Forecasts were used as a starting point (Table 2).[19] In the case of four disorders listed in Table 2, there is little or no evidence of a relationship with diet: anxiety disorders, self-inflicted injuries, pneumonia and osteoarthritis. Accordingly, the Committee has excluded these disorders from this advisory report. Dental caries was included in the 2006 Dietary guidelines, but has now been excluded from the background documents as it is not one of the top-10 diseases in the Netherlands.

Table 2 Top10 diseases in the Netherlands: mortality, years of potential life lost and burden of disease in 2007.[19]

	Mortality	Years of potential life lost	Burden of disease (DALYs)
1	Coronary heart disease	Lung cancer	Coronary heart disease
2	Lung cancer	Coronary heart disease	Depression
3	Stroke	Stroke	Stroke
4	Dementia	Colorectal cancer	Anxiety disorders
5	Heart failure	Chronic obstructive pulmonary diseases	Diabetes mellitus
6	Chronic obstructive pulmonary diseases	Breast cancer	Lung cancer
7	Pneumonia	Heart failure	Chronic obstructive pulmonary diseases
8	Colorectal cancer	Dementia	Osteoarthritis
9	Diabetes mellitus	Self-inflicted injuries	Injuries resulting from accidents in the home
10	Breast cancer	Pneumonia	Dementia

Accordingly, the Committee has based the background documents for the dietary guidelines on the relationship between food consumption and the occurrence of the following disorders and diseases:

- coronary heart disease
- stroke
- heart failure
- diabetes mellitus type 2

- chronic obstructive pulmonary diseases
- breast cancer
- colorectal cancer
- lung cancer
- dementia
- depression.

In the context of the advisory report, the Committee focuses on dementia, due to the great public interest in this topic. However, very few studies have been carried out into the relationship between dietary factors and clinically diagnosed dementia. Yet research has been conducted into the relationship with cognition and cognitive decline. People who develop dementia experience a decline in cognitive functions. For that reason, the Committee also addresses the issue of cognitive decline. In order to establish cognitive decline, cognitive performance must be assessed repeatedly over a period of years. The measure of outcome is the change in cognitive functioning. The Committee disregards studies in which cognitive functions were only determined on a single occasion (the measure of outcome here is cognitive performance rather than cognitive decline) as they do not provide sufficient information. Studies into the validity of cognitive tests generally involve a single determination of cognitive function, they seldom include a determination of cognitive decline.[20]

Similarly, very few studies have been carried out into the relationship between dietary factors and the development of clinical depression. Accordingly, the Committee also examines relationships with the onset of depressive symptoms. Depressive symptoms are generally temporary. They arise, fade away after a while, and may eventually return. Accordingly, the Committee studies the relationship between dietary factors and the onset of depressive symptoms (and not - as in cognition - the relationship with the change in depressive symptoms).

There are a wide range of tests both for cognition and for depressive symptoms. In general, if studies are based on different tests, their results can not be combined. Such combination is only possible if a number of studies all use a similar test.

In the case of a few dietary factors, the Committee evaluates diseases that do not occur in the aforementioned selection. Thus, prostate cancer is discussed in the background document on alpha linolenic acid and stomach cancer in the background document on sodium.

4.2 Morbidity and mortality as measures of outcome

There are various ways of exploring the effects on, or relationships with chronic diseases. Ideally, the researchers will determine which participants develop the disease in question. This will enable the study to directly provide information about the effects on, or relationships with the risk of disease. However, the use of these outcome measures place high demands on the number of participants and on the duration of the study. This is because the study will only provide useful results if enough participants develop the disease in question or die from it.

The Committee examines both the incidence of disease and the associated death rates. These measures of outcome provide different types of information, and both have their own value. Mortality is a more concrete measure of outcome than morbidity, yet the former is not solely determined by the aetiology of disease, but also by the disease prognosis and by the effectiveness of the associated treatment. Disorders that do not lead to death can generate a major burden of disease (for example, non-fatal strokes with residual symptoms or severe depressions).

With reference to specific dietary factors: restriction to specific diseases

Although mortality regardless of cause of death is an important endpoint, this measure of outcome only provides an initial (and very nonspecific) step in the search for relationships between diet and health. Causes or influencing factors vary greatly from one disease to another. Mortality regardless of cause of death conveys nothing about the aetiology of individual diseases. Accordingly, the Committee does not incorporate this measure of outcome into the background documents on specific dietary factors. For the same reason, neither the total incidence of cancer nor total cancer mortality are included. There are marked differences in aetiology from one type of cancer to another. The Committee only reports on the total incidence of – and mortality from – cardiovascular disease if this is the primary measure of outcome of an RCT and if published cohort studies contain little or no details of coronary heart disease, stroke and heart failure.

Mortality regardless of cause of death (total mortality) is, however, evaluated in the background document on alcohol and dietary patterns. Alcohol is related to a large number of diseases, both favourable and unfavourable. Dietary patterns relate to various aspects of nutrition. Therefore, alcohol and dietary patterns are also evaluated in relation to total mortality.

4.3 Causal risk factors: blood pressure, LDL cholesterol and body weight

A risk factor is a predictor of the risk of disease. Risk factors are of interest because they involve significantly fewer participants and shorter study durations than the outcomes morbidity or mortality. For instance, dietary effects on blood pressure and LDL cholesterol can be identified in just a few weeks, while clarifying the effect of diet on coronary heart disease requires an intervention period of several years. This is a major advantage in experimental research, as RCTs that use morbidity or mortality as a measure of outcome are difficult to implement and expensive and therefore few in number (see section 4.2).

Although interventions with a favourable effect on a risk factor often have the assumed and favourable health effect, that is not always the case. Yudkin et al[21] argue that risk factors cannot replace morbidity or mortality as measures of outcome. They substantiated this view with a number of examples[*] from the field of pharmacology, in

[*] The examples given by Yudkin et al[21], in which pharmacological interventions with a favourable effect on a risk factor were actually found to be unfavourable in terms of health. Rosiglitazone reduces blood

which interventions with a favourable effect on a risk factor were actually found to be unfavourable in terms of health.

The Committee accepts a risk factor when (in addition to evidence from cohort studies that it predicts the risk of disease) RCT results convincingly demonstrate that a change in the risk factor leads to a change in the risk of disease. Blood pressure, LDL cholesterol and body weight are the only causal risk factors that pass this test.

The Committee assesses the evidence from RCTs with blood pressure, LDL cholesterol or body weight as measures of outcome, while disregarding cohort studies that use these intermediate measures of outcome. The Committee disregards RCTs into the effects of those causal risk factors if these took place in the context of an energy-restricted diet. This is because the dietary guidelines are based on a normal diet. In the background documents, the Committee does not translate any conclusions about the effects of dietary factors on causal risk factors into conclusions about their effects on morbidity. Ultimately, dietary guidelines are drawn up on the basis of the overall evidence. In its advisory report, the Committee gives details of the weight attached to each of the various types of study.

Blood Pressure

In cohort studies, blood pressure is associated with the risk of cardiovascular disease. The strongest association is with stroke.[25,26] RCTs have shown that a wide range of blood-pressure lowering interventions (such as medications), lead to a reduction in the risk of cardiovascular disease, both in patients and in individuals without cardiovascular disease.[27,28]

The Committee focuses primarily on systolic blood pressure, because it is more reliably measured than diastolic blood pressure. In comparison to diastolic blood pressure, the effects on systolic blood pressure are generally greater and more likely to achieve statistical significance, while the estimated effects for systolic and diastolic blood pressure usually point in the same direction. The Committee specifies situations in which there is no evidence for an effect on systolic blood pressure, but where there are indications of an effect on diastolic blood pressure.

Details of the effects on both systolic and diastolic blood pressure are only given in the background document on dietary patterns. Section 4.2 indicates that a broader perspective is adopted for dietary patterns than is the case with nutrients or foods.

A four-week intervention period is preferred, as this can reliably indicate whether a given intervention has an effect on blood pressure.

glucose levels, but leads to an increased risk of cardiovascular disease.[22] Torcetrapib reduces LDL cholesterol levels and raises HDL cholesterol levels, but causes increased morbidity and mortality.[23] In diabetic patients, combination therapy with ramipril and telmisartan leads to reduced albuminuria, but it is nevertheless associated with a higher risk of severe kidney damage.[24]

LDL cholesterol

In support of the use of LDL cholesterol as an intermediate measure of outcome, the Committee refers to a report by the US Institute of Medicine (IOM) entitled "Evaluation of biomarkers and surrogate endpoints in chronic disease"* and to two recently published meta-analyses.[29-31] This showed that cohort studies (risk factor predicts risk of disease) and RCTs (interventions that affect the risk factor lead to a changed risk of disease) both provide support for the use of LDL cholesterol as a causal risk factor for cardiovascular disease.

An intervention period of at least 2 weeks is required to determine the effect of an intervention on LDL cholesterol. [32,33]

Body weight

In cohort studies, a high body mass index is associated with a higher mortality[34,35] and morbidity[36,37] and with a higher risk of cardiovascular disease[38,39], diabetes[40] and cancer (including cancers of the oesophagus, thyroid, colon, kidney, gall bladder and endometrium)[41]. Based on these associations, it seems likely that weight loss is beneficial to health. Undesirable weight loss, however, is actually associated with a greater mortality.[42] The reason for this is that some diseases cause weight loss and result in a higher mortality risk.

Intervention studies have provided evidence that desirable weight loss is beneficial for obese individuals. The main body of evidence relates to severely obese individuals who have undergone bariatric surgery†. In the case of such high-risk operations, however, randomised allocation is ethically unacceptable. Accordingly, their effects have not been studies in the context of RCTs. Non-randomised studies have shown

* The IOM describes a procedure for assessing whether a given biomarker can be used as an intermediate measure of outcome. It also assesses this process on the basis of six examples. [29] The IOM procedure consists of three stages. *Stage 1:* Assessment of the quality of the biomarker test: the validity, the reproducibility between different laboratories and clinical settings, as well as sensitivity and specificity. *Stage 2:* Establishing the biomarker as a risk factor for disease requires support both from cohort studies (intermediate predicts risk of disease) and from RCTs (interventions that affect the risk factor lead to a changed risk of disease). *Stage 3:* The IOM only considers the risk factor to be applicable in those settings to which the test results from stages 1 and 2 relate. *Assessment on the basis of six examples:* Of the six examples used to assess this procedure (tumour size, C-reactive protein (CRP), troponin, LDL cholesterol, HDL cholesterol and beta carotene), IOM only considers LDL cholesterol to be suitable as outcome causal risk factor. Since the support is based on RCTs into the effects of lipid-affecting drugs on cardiovascular disease, the IOM believes that the intermediate can only be applied in the setting of drug research. Unlike the IOM, the Committee also accepts LDL cholesterol also as a causal risk factor for research on nutrition and health.

† Bariatric surgery is the collective term for operative procedures aimed at achieving weight loss, such as fitting a gastric band, gastric reduction, or connecting the oesophagus directly to the intestine so that food no longer passes through the stomach.

that, compared to matched controls, individuals who have undergone bariatric surgery have a lower mortality risk[43], and lower risks of developing diabetes[44-46] and cardiovascular diseases[47]. The improvement in glycaemic control is (at least in part) a direct result of reduced food consumption. Between 30 and 100 percent of diabetic patients can stop taking their diabetes medication a few days after bariatric surgery, when energy intake has been drastically reduced, but body weight is still virtually unchanged.[48] Compared to bariatric surgery, trials involving lifestyle interventions achieve substantially less weight loss. The effects of lifestyle-intervention mediated weight loss on disease risks have not been conclusively demonstrated[49,50], but a systematic review suggests that it may have a preventive effect on diabetes[51].

By preference, an intervention period of several months is needed to determine whether a given intervention has an effect on body weight.

4.4 Primary and secondary measures of outcome and post hoc analyses

Intervention studies are set up to investigate one or more specific research questions. On this basis, researchers define their primary measures of outcome and, often, several secondary measures of outcome as well. In addition – once the results have become available – analyses are often carried out that were not previously planned and for which the study was not designed. These are referred to as *post hoc* analyses.

The risk of obtaining results that are solely due to coincidence and that lead to erroneous conclusions is smallest in the case of measures of outcome that are specifically targeted by the study design (primary and secondary measures of outcome) and greatest in the case of *post hoc* analyses. For that reason, the Committee assigns the greatest value to an intervention study's primary and secondary measures of outcome. Although the Committee attaches great importance to the matter, in practice it is often impossible to distinguish between the primary, secondary and *post hoc* analyses of RCTs. The Committee bases the background documents on systematic reviews and meta-analyses wherever possible, certainly in the case of RCTs with causal risk factors (see section 3.4.4). Although published meta-analyses often give details of the primary and secondary measures of outcome used in the meta-analysis itself, they rarely specify whether the results in the original studies involved primary, secondary or *post hoc* analyses.

Cohort studies are subject to the same type of problems as the *post hoc* analyses of RCTs. Cohort studies are used to perform a wide range of analyses within the potential scope of these datasets. Accordingly, in the case of cohort studies, it is especially important that a number of different studies present similar results.

5 Literature search for the background documents

In this chapter, the Committee gives details of the procedure it follows when conducting literature searches, starting with types of publication, the sequence continues with populations studied, types of study, and sources.

5.1 Pooled analyses, meta-analyses and systematic reviews

In principle, the Committee limits its literature review to a critical evaluation of pooled analyses, meta-analyses and systematic reviews published in peer-reviewed journals. In pooled analyses and meta-analysis, the findings from several original studies that used similar research questions and approaches are combined to create a new risk assessment. In a pooled analysis, the individual person data are analyzed and adjustment for confounders in each original study are carried out using a standard procedure. The results are then combined. In a meta (regression) analysis, the published risk assessments are combined. Combining findings from several studies creates greater statistical power and yields more accurate estimates of the relationship or effect in comparison with the original studies. Focusing on pooled analyses, meta-analyses and systematic reviews helps the Committee to ensure that the amount of work involved remains manageable.

The background documents give details of which pooled analyses and meta-analyses have been found. If certain publications have been disregarded, the reasons behind this decision are explained. Such reasons may concern methodological caveats or a lack of detail concerning the methods used, characteristics or outcomes. Older publications that include only a fraction of the published studies are excluded if more recent, good-quality publications are available.

5.2 General population, high-risk groups and patient groups

In general, literature searches focus on research that falls within the domain of the advisory report (see section1.1) and which, therefore, relates to the general population. The Committee makes an exception in the case of RCTs that use the incidence of disease or the associated mortality as a measure of outcome. Studies of this type are scarce and the participants in published RCTs are generally patients or individuals who are at high risk with regard to the measure of outcome under investigation. Due to their importance in terms of assessing the causality of the relationship, such RCTs are also taken into consideration if they are implemented in groups of patients or in high-risk groups.

5.3 Study types

Sections 2.2, 4.2 and 4.3 show that, in the background documents, the Committee draws conclusions based on the evidence from the following study types:

- RCTs into effects on the incidence of – or mortality from – diseases
- RCTs into the effects on three causal risk factors
- Cohort studies into associations with disease, in which food consumption was established prior to diagnosis of the disease in question.

Very few published RCTs use incidence of disease or mortality as a measure of outcome. However, these provide crucial information about the causality of the relationship between dietary factors and disease. In the absence of good-quality meta-analyses of this type of study, the Committee describes the original RCTs and uses them as 'proof-of-principle'.

A different procedure is used for RCTs with causal risk factors and for cohort studies. For these types of study, the Committee restricts itself to pooled analyses, meta-analyses, and systematic reviews. This information is then supplemented with research published subsequent to the literature search of the most recent meta-analysis. Any topics for which there are no published meta-analysis or systematic review are disregarded. The search strategy approach is depicted in Figure 1.

5.4 Sources

The published studies listed in the background documents are mainly derived from literature searches in the PubMed database. Those searches feature the following basic format: "dietary factor"[Mesh] AND ("systematic review"[Publication Type] OR "meta analysis"[Publication Type]). The literature review covers articles published up to the end of July 2014. The Committee also used existing reports to find relevant publications. These documents included the former Dutch dietary guidelines[10], and the dietary guidelines from the US[1,52], Australia[53] and the Nordic Countries[54], the 2007 report by the World Cancer Research Foundation (WCRF)[12] and updates thereof, and European Food Safety Authority reports on dietary reference intakes[55]. These existing reports are based on a wider range of study types than those targeted by the Committee.

After July 2014 until September 2015 the committee searched for new meta-analyses, that were only included if they provided additional information.

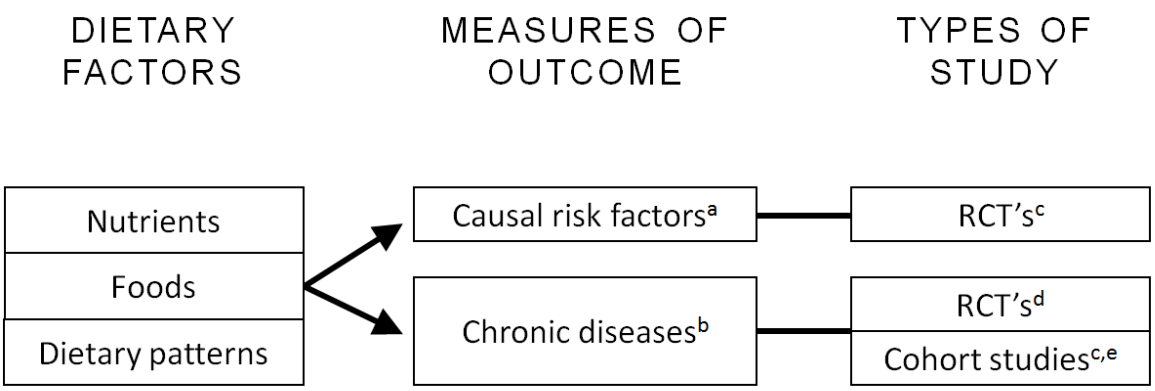

Figure 1: Search strategy.

[a] The Committee takes into consideration effects on three causal risk factors: blood pressure, LDL cholesterol, and body weight (see section 4.3).

[b] The Committee evaluates the relationship with 10 diet-related diseases: coronary heart disease, stroke, heart failure, type 2 diabetes mellitus, chronic obstructive pulmonary disease, breast cancer, colorectal cancer, lung cancer, dementia and depression (see section 4.1).

[c] The Committee focuses primarily on pooled analyses, meta-analyses and systematic reviews (see section 5.1).

[d] There are only a few published RCTs into effects on diseases. Due to these studies' importance in terms of conclusions about causality, the Committee describes all published RCTs relating to these measures of outcome, regardless of whether any published meta-analyses and systematic reviews are available (see section 5.3).

[e] In this advisory report, the term "cohort study" refers to all types of prospective observational study (see section 2.1).

6 Conclusions in the background documents

In the background documents, the Committee evaluates the evidence with regard to effects (in the case of RCTs) or associations (in case of cohort studies). Below, it gives details of the way in which conclusions about these effects and relationships are reached.

6.1 Summary of findings in standardised tables

The Committee describes findings in terms of the greatest contrast (highest versus lowest intake categories) and the results of dose-response analyses. Each individual evaluation begins with a summary, in the form of a table with a standardised layout (Table 3).

Table 3 Summary table for each effect or relationship in the background documents.

Executive summary	Explanatory notes
Published studies	Here the Committee specifies the number of meta-analyses and the number of cohort studies or RCTs.
Heterogeneity	Yes/No; if "Yes", then the Committee will provide an explanation, where possible. Meta-analyses involve tests for heterogeneity between the original studies. If such tests indicate that there is little or no heterogeneity (I^2 <0.25) then "No" is entered in the summary table. Where there is moderate (I^2 0.25-0.50, p <0.10) or significant (I^2 >0.50 and p <0.10) heterogeneity, "Yes" appears in the summary table. Where no heterogeneity test is available, the Committee assesses the degree of overlap between the confidence intervals of the original studies or meta-analyses and the direction of the risk estimates.
Strength of the effect/relationship	If it is possible to draw a conclusion about an association or effect, the Committee specifies the effect estimate or risk assessment here, if possible in relation to intake (or to changes in intake).
Study population	Here, in the case of cohort studies, the Committee gives details of the continent in which the study took place (Europe, North America, Australia & New Zealand, Asia). Gender is specified if the published studies were restricted solely to men or solely to women. In the case of RCTs, the Committee gives details of the patient group or high-risk group, gender and age.

6.2 Choice of four options for the conclusion per evaluation

Immediately below this summary table is the conclusion, in which the Committee selects one of four options (Table 4). Intervention studies and cohort studies address different issues, which is reflected in the wording of the conclusion. Accordingly, conclusions based on RCTs are phrased in terms of effects (causality), whereas conclusions based on cohort studies are phrased in terms of associations and relationships. Wherever conclusions point to the existence of a relationship or effect,

the Committee indicates whether it considers the evidence involved to be limited or strong.

Table 4 Formulation of conclusions in the background documents.

Option	Formulation of the conclusion	Explanatory notes
1	*High or low intake increases or decreases the risk of disease (based on RCTs), or* *High or low intake is associated with a greater or smaller risk of disease (based on cohort studies).* *The evidence involved is limited or strong.*	In conclusions of this type, the Committee specifies the strength of the evidence based on the availability of published studies, the presence or absence of heterogeneity, the strength of the relationship, and any additional considerations that are specified in the explanatory notes. If the conclusion relates to a specific population or a specific level of exposure, then the requisite specification is given. If the evidence is strong, the Committee quantifies the effect or relationship in question, but if it is limited then the conclusion is qualitative in nature.
2	*A given effect or relationship is unlikely.*	This applies where there is a sufficiently large number of studies that failed to find any evidence of a given effect or relationship. In the case of causal risk factors, the effect estimator is around zero; in the case of studies that use morbidity or mortality as a measure of outcome, the relative risk is close to 1.00.
3	*The effect or relationship is ambiguous.*	One or more of the following conditions is true: 1) A meta-analysis has revealed a substantial and unexplained level of heterogeneity. 2) There are substantial differences in the direction of effects or relationships between individual intervention studies or cohort studies.
4	*There are too few studies to support conclusions about a given effect or relationship.*	One or more of the following conditions is true: 1) Just a single original study was published 2) All published studies derive from a single research group, so they are not independent 3) The published studies are of insufficient quality to support a conclusion about the relationship or effect. 4) The published studies provide an insufficient basis to support the conclusion that a given relationship or effect exists, yet, by the same token, they cannot support the conclusion that a given relationship or effect is unlikely.

The conclusion is followed by the explanatory notes, in which the Committee presents details of the assessed study. In that text and the accompanying table (or tables), the Committee presents details of the study data that underpin the summary table.

At the end of every background document, the Committee summarises the main findings regarding the dietary factor in question, per relationship and per study type.

7 The Dutch dietary guidelines 2015 advisory report

The Dutch dietary guidelines 2015 advisory report integrates the information from the background documents and from various past Health Council advisory reports, and interprets them as a coherent whole.[56] With regard to the background documents, this mainly concerns findings supported by strong evidence. RCT's with disease as endpoint are scarce. The results of these trials are presented as 'proof of principle'. Previous Health Council advisory reports included in the Dutch dietary guidelines 2015 advisory report are those on micronutrients cited in section 3.1 (2008-2012)[13-18], and the advisory report entitled Guidelines for a Healthy Diet: the ecological perspective (2011)[57].

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A The Committee

- Prof. D Kromhout, Vice President of the Health Council (*until 1 January 2015*), The Hague, *chairperson*
- Prof. J. Brug, Professor of Epidemiology, VU Medical Center, Amsterdam
- Prof. A.W. Hoes, Professor of Clinical Epidemiology and General Practice, University Medical Center Utrecht
- Dr. J.A. Iestra, nutritionist, University Medical Center Utrecht
- Prof. H. Pijl, Professor of Diabetology, Leiden University Medical Center, *member (until 1 April 2015), advisor (from 1 April 2015 onwards)*
- Prof. J.A. Romijn, Professor of Internal Medicine, Academic Medical Center, Amsterdam
- Prof. J.C. Seidell, Professor of Nutrition and Health, VU University Amsterdam
- Prof. P. van 't Veer, Professor of Nutrition, Public Health and Sustainability, Wageningen University and Research Centre, *member (until 1 June 2015), advisor (from 1 June 2015 onwards)*
- Prof. M. Visser, Professor of Healthy Aging, VU University Amsterdam and VU University Medical Center, Amsterdam
- Prof. J.M. Geleijnse, Professor of Nutrition and Cardiovascular Diseases, Wageningen University and Research Centre, *advisor*
- Prof. J.B. van Goudoever, Professor of Paediatrics, VU University Medical Center Amsterdam and Academic Medical Center, Amsterdam, *advisor*
- Prof. M.T.E. Hopman, Professor of Integrative Physiology, Radboud University Medical Center, Nijmegen, *advisor*
- Prof. R.P. Mensink, Professor of Molecular Nutrition, Maastricht University, *advisor*
- Prof. A.M.W.J. Schols, Professor of Nutrition and Metabolism in Chronic Diseases, Maastricht University, *advisor*
- Prof. M.H. Zwietering, Professor of Food Microbiology, Wageningen University and Research Centre, *advisor*
- C.A. Boot, M.Sc., Ministry of Health, Welfare and Sport, The Hague, *observer*
- Dr. J. de Goede, Health Council of the Netherlands, The Hague, *scientific secretary*
- Dr. C.J.K. Spaaij, Health Council of the Netherlands, The Hague, *scientific secretary*
- Dr. R.M. Weggemans, Health Council of the Netherlands, The Hague, *scientific secretary*

B Glossary

Biomarker
A biomarker is an objectively measurable characteristic that gives an indication of a normal biological process (e.g. nutrient status), of a disease process (e.g. LDL cholesterol) or of the pharmacological response to treatment.[29]

Body mass index
An individual's Body Mass Index (BMI) is their body weight (in kilograms) divided by the square of their height (in metres). It is also referred to as the Quetelet Index.

Cohort study
In this advisory report, the term cohort study is used as a collective term for the various types of observational studies in which food consumption is determined before the disease is diagnosed. Such studies include prospective cohort studies, nested case-control studies, and case-cohort studies.

Confounder
A confounder is a factor that is correlated both with exposure (in this advisory report, intake of the dietary factor under investigation) and with the measure of outcome (disease). Confounding (or residual confounding) can result in an incorrect assessment of the strength of the relationship between exposure and disease. It can even suggest that such a relationship exists when this is not, in fact, the case.

Disability-Adjusted Life Years (DALYs)
The DALY (Disability-Adjusted Life Year) is an index determined both by the number of people dying prematurely from disease and by the number of years that people live with limitations as a result of disease. The weight assigned to years of life with disease is determined by the severity of the disease in question. The number of years of life is multiplied by a factor whose value lies between 0 and 1.[58]

Post hoc analyses
Analyses that were not planned prior to the intervention study, that were not targeted by the study and for which the study was not designed.

Primary and secondary measures of outcome
Measures of outcome targeted by the intervention study. These are described by the researchers involved prior to the implementation of the study. The primary measures of outcome determine the design of the study.

Primary and secondary prevention
Primary prevention involves the prevention of a given disease in individuals who are free of the disease in question. Secondary prevention involves the prevention of a recurrence or an aggravation of a given disease in individuals who have had the disease in question.

Risk factor
An intermediate measure of outcome is a measure which, based on both observational and experimental studies, has been shown to be predictive of disease risk.

Statistical power
In high-quality studies, the number of participants is determined based on the statistical power required. A statistical power of 80 percent means that the study in question contains sufficient participants to establish the existence of an intended effect on the relevant measure of outcome with a probability of 80 percent.

C Evidence of causality from observational studies: the Bradford Hill criteria

In 1965, Sir Austin Bradford Hill published a set of nine criteria to assess the likelihood of a causal relationship between factors such as smoking and lung cancer, on the basis of findings from observational studies (Table 5).[59] These "Bradford Hill criteria" are still frequently used today, even though some caveats (most of which Bradford Hill had already pointed out in 1965) have become increasingly emphasised over the years.[4,60]

In this advisory report, the Committee has used four of the nine Bradford Hill criteria (1, 2, 4 and 5).

The Committee attaches the greatest weight to criterion 4 (cause precedes effect), due to the major problem posed by recall bias in nutritional research (see section 3.1). Accordingly, this advisory report is based solely on studies in which exposure was measured before the outcome (disease) was determined.

In this advisory report, criteria 1, 2 and 5 are taken into account when assessing the strength of the evidence. Causal relationships are more likely where there is a strong relationship, consistent findings, and a dose-response relationship. However, this does not mean that the option of a causal relationship can be rejected if there is a weak relationship, inconsistent results, and no dose-response relationship. Suppose, for instance, that no dose-response relationship has been found. There are a range of possibilities that might account for this. Firstly, there is no causal relationship and no dose-response relationship. Secondly, there is a causal relationship, but no dose-response relationship, possibly due to a threshold-value effect. Thirdly, there is a causal relationship with a dose-response relationship, but it was not possible to demonstrate the existence of the latter relationship as the variation in exposure is too small. Therefore, the option of a causal relationship cannot be rejected in the absence of a dose-response relationship. Nor, indeed, does finding a dose-response relationship provide conclusive evidence of a causal relationship, as the dose-response relationship can also be the result of a misleading variable (confounder).

With regard to criterion 3 (the specificity of the effect), Bradford Hill pointed out that this should not be overly emphasised. Meanwhile, this criterion is no longer considered relevant, as exposures may be related to several diseases.
The criteria for plausibility (6), coherence (7) and analogy (9) have limited value because they are heavily dependent on knowledge level and because it is indeed possible to derive explanations for many relationships. Causal relationships may still be possible in cases where findings do not appear to be plausible or coherent. After all, the evidence may be deficient.

Table 5 The nine criteria drawn up by Bradford Hill in 1965 to enable views to be formed about the possible causality of a relationship even in the absence of RCTs.

Nine criteria that, according to Bradford Hill (1965), provide evidence for causality.[60]		
1	A strong relationship	Bradford Hill gave examples in which specific risks are greatly increased, in some cases by several orders of magnitude. While a relationship of this strength is indicative of a causal relationship, Bradford Hill emphasised that the hypothesis of a causal relationship should not be too readily dismissed in the case of apparently weak relationships.
2	Consistency	If the relationship repeatedly emerges under a range of conditions and using a range of research techniques then the existence of a causal relationship is more likely than when the relationship only occurs in a limited number of published studies. However, Bradford Hill pointed out that inconsistent results are no reason to reject the hypothesis of a causal relationship as there may be a logical explanation for differences in study outcomes.
3	Specificity	If a relationship is found between a specific group or location and a specific disease while that same group or location is not associated with an increased risk of other diseases, then that is an indication of a causal relationship. Bradford Hill warned that this point should not be overly emphasised, giving examples of cases in which the risks of two and even several diseases are increased, and noting that diseases often have multiple causes.
4	Cause comes before effect	One issue in connection with the supposed cause and the supposed effect is: Which came first, the chicken or the egg? Bradford Hill suggested that this question is particularly relevant to diseases that develop slowly. One of the examples he cited in this connection is the relationship between dietary pattern and health. Does a given dietary pattern result in the disease or does the disease result in a given dietary pattern?
5	Dose-response relationship	There is more likely to be a causal relationship in cases where increased exposure is associated with a more pronounced effect. According to Bradford Hill, however, causality cannot be excluded even if the most pronounced effect is found at low levels of exposure. The nature of a relationship can be too complex or measurement errors may be too large to reveal a dose-response relationship. Bradford Hill concluded this topic by stating that researchers should actively seek out potential dose-response relationships.
6	Plausibility	Biological plausibility can support a causal hypothesis. However, Bradford Hill also stated that plausibility cannot be made a requirement for causality, as this criterion is too dependent on the evidence at the time in question. A relationship that is being investigated may involve a new – or as yet unknown – mechanism of action.
7	Coherence	According to Bradford Hill, problems can arise when a relationship contradicts generally accepted knowledge about biology and about the aetiology of diseases.
8	Quasi-experiment	Bradford Hill developed his criteria for situations in which experimental research is not feasible. He noted, however, that quasi-experimental evidence may be available in some cases. For instance, it is possible to determine whether the termination of exposure (by giving up smoking, for example) has the effect of reducing the risk of disease. According to Bradford Hill, evidence of this type is a strong indication of causality.
9	Analogy	In some situations, an analogy can be an indication of causality. The case of Thalidomide, for example, has led to a more rigorous assessment of the potential dangers posed by medication use during pregnancy to the unborn child.

Criterion 8, the availability of quasi-experimental evidence, plays no part in this advisory report. This is partly because such data is rarely available within the domain of the Dutch dietary guidelines 2015 and partly because results from studies of this type carry a high risk of confounding.

During the 1960s, the development of views in the United States concerning causality and observational research largely reflected that seen in Great Britain.[61]

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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