

# Nuts and seeds and chronic diseases

No. 2025/19A2e, The Hague, 4 December 2025

Background document to:

Dutch dietary guidelines: dietary protein sources and dietary patterns 2025.

No. 2025/19e, The Hague, 4 December 2025



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# 1 Introduction

This background document belongs to the advisory report *Dutch dietary guidelines: dietary protein sources and dietary patterns 2025 (DDG2025)*.<sup>1</sup> It describes the methodology for the search, selection and evaluation of the literature regarding the effects and associations of nuts and seeds consumption with health outcomes. It also describes the scientific evidence on this topic and the conclusions that have been drawn by the council's committee on Nutrition. These conclusions form the basis for the derivation of the 2025 dietary recommendation on nuts and seeds.

The committee on Nutrition has set up a working group to prepare this background document. The committee takes final responsibility for the content of the background document. A list of the committee members can be found in the advisory report.<sup>1</sup> A list of the working group members can be found in Annex A of this background document.

## 1.1 Definition of nuts and seeds

In the context of this advisory report, the committee uses the word nuts to describe the products that consumers and nutrition researchers generally consider to be nuts and seeds; the word is not used in its botanical sense. The most familiar types are walnuts, almonds, hazelnuts, cashews, pistachios, macadamia nuts, Brazil nuts, pecans, pine nuts, flax seeds, sesame seeds, sunflower seeds, pumpkin seeds, poppy seeds and chia seeds. Peanuts are legumes but are more similar to nuts than legumes in terms of oil content. Therefore, in the context of this advisory report, peanuts are also considered to be nuts. Quinoa seeds are seeds in its botanical sense but are in nutrient composition more similar to grains and in food practice mostly used as grains. Therefore, quinoa seeds are not considered to be seeds for this advisory report. Betel nuts, coconuts or soy nuts (roasted soybeans) are not considered to be nuts in the context of this advisory report.

## 1.2 Intake of nuts in the Netherlands

According to the most recent Dutch National Food Consumption Survey (DNFCS; 2019-2021), the mean consumption of nuts and seeds, including nut spreads, is 14.6 g/d for Dutch adults, of which 5 g/d unsalted. Women eat less nuts and seeds compared to men (11.9 and 17.4 g/d, respectively), but almost as much unsalted nuts and seeds (5 and 6 g/d, respectively). Half of the Dutch adults consume little or no nuts and seeds (less than 2 g/d on average). People that do consume nuts and seeds, consume this on 2 to 3 days a week. On such consumption days, the median consumption is 30 g.<sup>2,3</sup> The intake of unsalted nuts and seeds increased compared to the DNFCS of 2012-2016.<sup>4</sup>

## 2 Methodology

Below, the methodology used for the evaluation of the evidence is presented. In addition, a description is given of the selection of literature on the topic of nuts and seeds in relation to health outcomes.

### 2.1 Health outcomes

The committee focused on the health outcomes described below.

#### *Chronic diseases:*

Similar to the approach used for the Dutch dietary guidelines 2015 (DDG2015),<sup>5</sup> the committee focused on the most common chronic diseases (that are potentially nutrition related) in the Netherlands.<sup>6,7</sup> These include: coronary heart disease (CHD), stroke, heart failure, type 2 diabetes, cancer subtypes (colorectal cancer and breast cancer), obesity (in some evaluations combined with overweight), depression, chronic obstructive pulmonary disease (COPD) and dementia. Furthermore, evidence for total cardiovascular disease (CVD) and total cancer was included, but only in case the committee expected (based on the quick scans, described below) that such evidence would provide additional insights (on top of the evidence focused on the afore and below listed outcomes) that could be of added value for drawing up or changing a dietary guideline. The committee preferred to use evidence for CVD subtypes and cancer subtypes because these may have different aetiologic pathways related to different dietary exposures. Total CVD and total cancer comprise different subtypes and therefore provide less specific insights in the aetiology underlying the relationships between dietary factors and chronic diseases.

The committee focused on studies that addressed primary prevention of chronic diseases. This means that the relationship between a dietary factor and development of a chronic disease was investigated in people who did not have the disease at the start of the study. Moreover, in general, the committee preferred to base its evaluation on studies that addressed non-fatal events or the combined outcome of fatal and non-fatal events (thus: not solely focused on fatal events) because the availability and quality of care may play a larger role in the outcome of fatal, compared to non-fatal events. Exceptions to this were made in case there were aetiological reasons to specifically address fatal events (e.g. for fish and fatal cardiovascular outcomes).

#### *Causal risk factors and other short-term outcomes:*

These include the following: blood pressure (systolic and diastolic), low-density lipoprotein (LDL) cholesterol, body weight, glycated haemoglobin (HbA1c) and estimated glomerular filtration rate (eGFR).

Causal risk factors are thought to capture the causal pathway that leads to the disease outcome and can be seen as replacement endpoints for the disease of interest.<sup>8</sup> Because of this, the committee considers that an effect on a causal risk factor will also lead to an effect on chronic disease risk. An example is LDL cholesterol as causal risk factor for CHD and stroke. The advantage of using causal risk factors (and other short-term outcomes) in experimental studies is that they usually need considerably fewer participants and shorter study durations (usually several weeks to months) than studies investigating morbidity or mortality outcomes. For instance, dietary effects on LDL cholesterol can be identified in just a few weeks, compared to several years for CHD. Similar to the approach used in 2015, blood pressure, LDL cholesterol and body weight were selected as causal risk factors. As explained in the DDG2015 background document on methodology,<sup>5</sup> these factors 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. More recent evidence confirms the causality, presented below.

Blood pressure: A meta-analysis of 48 randomised controlled trials (RCTs) confirmed that multiple blood pressure lowering treatments, including more versus less intensive treatments, reduce the risk of cardiovascular events, including CHD and stroke. This was found in people with and without CVD.<sup>9</sup> Moreover, Mendelian randomisation studies support that blood pressure is causally associated with the risk of CHD and stroke.<sup>10,11</sup>

LDL cholesterol: Recent reports confirmed that numerous and different types of studies, including prospective cohort studies, RCTs and Mendelian randomisation studies, have convincingly shown that higher LDL cholesterol causes cardiovascular events, such as CHD.<sup>12</sup> The evidence from RCTs is based on various interventions performed among both primary and secondary prevention trials: A meta-analysis of 49 RCTs showed that the use of statin and various non-statin therapies, including diet, that reduce LDL cholesterol, reduce the risk of cardiovascular events.<sup>13</sup> In line with the committee, the European Food Safety Authority (EFSA) also acknowledges that reducing blood LDL cholesterol (by dietary modification and drugs) would generally reduce the risk of development of CHD.<sup>14</sup>

Body weight: Recent reports confirmed the importance of weight loss via various interventions for the prevention of type 2 diabetes, based on RCTs.<sup>15,16</sup> Moreover, the causal role of both general and central adiposity, indicated by body mass index and waist-to-hip ratio respectively, in the development of type 2 diabetes and other chronic diseases has been confirmed in Mendelian randomisation studies.<sup>17</sup> Besides body weight, the committee also searched for literature with waist circumference as outcome, because this may also reflect the causal pathway from adiposity to type 2

diabetes. However, very few relevant studies with this endpoint were found, and that evidence did not contribute to the guidelines.

HbA1c and eGFR: These factors were not yet included in 2015, and were added for the 2025 advisory report because these are important diagnostic indicators of chronic diseases (elevated HbA1c for type 2 diabetes and long-term decline in eGFR for chronic kidney disease).<sup>18-20</sup> The committee considered evidence based on such outcomes as potentially supportive for the guidelines. However, in practice, insufficient research focused on these factors was found to include in the committee's evaluations.

*Other outcomes:*

These include the following: all-cause mortality, quality of life, perceived health and fertility.

The committee additionally searched for evidence focused on quality of life, perceived health and fertility, which could be considered as supportive evidence for the guidelines. However, in practice, insufficient evidence on these outcomes, which fulfilled the inclusion criteria of the committee, was found.

Evidence focused on the all-cause mortality outcome was additionally evaluated, but only in case the committee expected (based on the quick scans, described below) that such evidence would provide additional insights that could be of added value for drawing up or changing a dietary guideline. The reason for this is similar to that described above, for the total CVD and total cancer outcomes.

## **2.2 Type of studies**

The committee evaluated the state of science for each dietary factor – health outcome combination, based on meta-analyses (MAs) and pooled analyses. In MAs, reported results of multiple individual studies are combined and analysed. In pooled analyses, individual participant data of multiple studies are combined and analysed.

The committee selected MAs and pooled analyses of the following type of studies:

- Randomised controlled trials (RCTs) into effects of dietary factors on the incidence of morbidity/mortality due to a disease;
- RCTs into effects of dietary factors on causal risk factors;
- Prospective cohort studies into associations of dietary factors with morbidity or mortality due to disease.

*Substitution analyses*

In some of the background documents, substitution analyses were also included as a part of the evaluation. In RCTs, substitution was based on comparisons of the effects of consumption of two diets, each with another dietary protein source (keeping the rest of the diet as similar as possible). In observational cohort studies, substitution was hypothetically investigated by statistical modelling based on (baseline) dietary intake

data. Because substitution did not actually take place in observational cohort studies, the committee interpreted the evidence as associations for dietary protein source 1 versus dietary protein source 2 with disease outcomes.

#### *Mendelian randomisation studies*

The committee additionally considered evidence from Mendelian randomisation studies, to serve as potential supportive evidence for certain guidelines. In Mendelian randomisation studies, genetic variants are used to investigate causal associations between dietary intake and risk of chronic diseases.<sup>21</sup> Only for the topic of dairy products, relevant Mendelian randomisation studies were found, as further explained in the background document on dairy products and chronic diseases.<sup>22</sup>

### **2.3 Quick scans**

For efficiency reasons, the committee decided to make use of recent reports of other organisations where possible. To this end, quick scans were performed at the start of the advisory trajectory (2023). These quick scans were aimed at summarising the state of science in an efficient way and to identify aspects on which the dietary guidelines may need to be updated.

To identify differences and similarities compared to the DDG2015, the guidelines for each specific dietary factor (e.g. fruits and vegetables, fats and oils or dairy products) were compared to the recent advices on these dietary factors of the *Nordic Nutrition Recommendations 2023* (NNR2023),<sup>23</sup> and the *Dietary Guidelines for Americans 2020-2025* (DGA2020).<sup>24</sup> Moreover, the conclusions and findings regarding the relationships of dietary factors with health outcomes reported in the DDG2015 were compared to conclusions and findings reported in the background documents of the NNR2023 and of the DGA2020. In addition, and based on the above referred documents, the committee identified topics for which there may now be sufficient evidence to draw conclusions on, where this was not yet possible in 2015.

Based on the quick scans, the committee decided to focus its evaluation of nuts and seeds in particular on the following:

- The committee noted that the NNR2023 advised a larger amount of nuts than the DDG2015. Since there is now more research on the consumption of nuts and seeds and its association with chronic disease risk, the committee decided to evaluate whether the quantification of the guideline on nuts and seeds needs to be updated. The committee additionally aimed to evaluate whether there are differences in health effects between different types of nuts and seeds.
- In addition, the committee noted that for the following health outcomes, there is new and relevant literature that may be leading or supportive for the dietary guideline on nuts and seeds: CHD, stroke, type 2 diabetes, total cancer, LDL

cholesterol, blood pressure and body weight. Therefore, the committee focused its evaluation of nuts and seeds on these health outcomes.

## **2.4 Consulted literature**

For the evaluation of nuts and seeds consumption and its effects or associations with the selected health outcomes, the committee used the following sources of literature:

- The committee used MAs addressed in the NNR2023 advisory report,<sup>23</sup> and in the NNR2023 background documents on nuts and seeds,<sup>25,26</sup> that include studies published until 13 September 2021 (PubMed) and 29 October 2021 (Web of Science).
- The committee additionally used pooled analyses of cohorts that contributed to the European Prospective Investigation into Cancer and nutrition (EPIC). EPIC publications were searched by the committee via a systematic literature search (search last updated on 8 July 2024). The committee used such pooled analyses in case these were not included in the above referred MAs, which was not the case for studies on nuts and seeds consumption and health outcomes.
- For a selection of dietary factors, the committee additionally performed systematic literature searches in PubMed and Scopus to search for more recent literature (than NNR). This was only done in case the committee expected such a search would yield additional information that could potentially impact the conclusions drawn by the committee. This was applicable to the following situations:
  - For dietary factors on which, after publication of the recent reports (referred to above), there are scientific advances that could impact the dietary guidelines.
  - For dietary factors on which there is relatively much scientific discussion and/or no consensus on the health effects/associations in the field.

For the topic of nuts and seeds consumption, the committee decided that a search for more recent literature was not required.

From all MAs and pooled analyses retrieved via aforementioned sources, the most recent and complete MAs and pooled analyses that fit within the inclusion criteria of the committee (i.e. based on selected study designs and health outcomes) and which together gave the most comprehensive overview of the studies available on each dietary factor – health outcome combination were selected for the committee's evaluation.

## **2.5 Evaluation of evidence**

For each dietary factor – health outcome combination, an evaluation of the state of science was performed, further explained below.

### **2.5.1 Drawing conclusions based on a decision tree**

The findings from prospective cohort studies and RCTs were separately evaluated by the committee. Per dietary factor – health outcome combination, a table summarising the main characteristics and results of the major MA(s) and/or pooled analyse(s) that contributed to the evaluation was presented. Below the summary table, the committee gave the conclusion, for which there are six fixed options:

- There is an association/effect with a strong level of evidence;
- There is an association/effect with a limited level of evidence;
- An association/effect is unlikely;
- The evidence is inconclusive;
- The evidence is contradictory;
- There is too little research.

The conclusions on (the certainty of) the evidence regarding the effect or association between nuts and seeds consumption and health outcomes were based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, the committee took the quality of the studies, in particular the risk of bias, and the heterogeneity in findings between studies, into account. The committee used the decision tree (presented in Annex B) as a guidance tool to support consistency in drawing conclusions. This decision tree was also applied by previous committees of the Health Council,<sup>27-29</sup> and includes elements that are also present in other evaluation methods for determining the quality and certainty of scientific evidence, such as GRADE (for example: heterogeneity and risk of bias).<sup>30</sup>

The formulation of conclusions was different for RCTs than for cohort studies: RCTs allowed statements about effects (causality) to be made, whereas cohort studies only allowed statements about associations to be made.

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. This text was accompanied by a table that showed relevant details related to the included studies.

### **2.5.2 Extensiveness of evaluation**

Per dietary factor – health outcome combination, the committee decided on the level of detail of its evaluation. Extensive evaluations were performed for dietary factor – health outcome combinations of which conclusions could potentially be leading for drawing up a new guideline or changing an existing guideline. Remaining dietary factor – health outcome combinations, of which conclusions unlikely changed compared to 2015 or could only be supportive to a guideline, were evaluated less extensively.

The differences between conclusions that are leading and those that are supportive for drawing up a guideline are described in Chapter 2 of the advisory report.<sup>1</sup> In extensive

evaluations, the committee drew formal conclusions based on the decision tree, and presented the evaluation according to the format described in Section 2.5.1. In less extensive evaluations, the committee did not draw such formal conclusions. Instead, the state of science was briefly (with less details) summarised in text with an accompanying table. Such a less extensive evaluation was in particular done to check whether potential effects or associations with remaining subtypes of exposures and remaining health outcomes were indeed in a supportive direction, or at least not in an opposite direction as compared to the conclusions on the exposure subtypes and outcomes that were extensively evaluated.

The committee performed, in principle, only (extensive and less extensive) evaluations of dietary factor – health outcome relationships when at least 5 individual studies of a specific study type were included in the selected MAs and/or pooled analyses. This was done because at least 5 studies are needed to qualify the evidence as strong, and because only conclusions with a strong level of evidence are considered for drawing up the dietary guideline (see Chapter 2 of the advisory report<sup>1</sup>). The committee could decide to make exceptions in this approach, based on expert judgement of the evidential value, public interest and extent of scientific discussion.

For the topic of nuts and seeds consumption, the committee noted, based on the quick scans and selected recent literature, that the evidence could potentially be (new and) leading for drawing up a nuts and seeds guideline for the following topics, which were therefore extensively evaluated:

- Based on prospective cohort studies:
  - Consumption of nuts and seeds and the risk of CHD;
  - Consumption of nuts and seeds and the risk of stroke;
  - Consumption of nuts and seeds and the risk of type 2 diabetes.
- Based on RCTs:
  - Consumption of nuts and effects on LDL cholesterol;
  - Consumption of flax seeds and effects on LDL cholesterol;
  - Consumption of flax seeds and effects on blood pressure;
  - Consumption of flax seeds and effects on body weight.

Remaining topics were less extensively evaluated.

## **2.6 Deriving a dietary guideline on nuts and seeds**

Effects and associations of nuts and seeds with chronic disease risk are described in Chapter 3 of this background document. The committee used the totality of conclusions with strong evidence described in this document, together with conclusions based on substitution of dietary protein sources,<sup>31</sup> environmental and chemical food safety aspects,<sup>32,33</sup> for drawing up the guideline on nuts and seeds. The (methodology used

for the) translation of the totality of evidence into dietary guidelines and recommendations is described in the advisory report.<sup>1</sup>

### 3 Evaluation of the evidence

This chapter describes the scientific evidence on the associations or effects of nuts and seeds consumption and subtypes thereof on or with risks of chronic diseases or causal risk factors. Evaluations are grouped according to health outcome.

#### 3.1 Coronary heart disease

The DDG2015 concluded there is strong evidence that consumption of 15 g/d of nuts is associated with a 20% lower risk of CHD.<sup>34</sup> This was based on 2 MAs, each including 6 prospective cohort studies. There are now more studies available on this topic.<sup>25</sup> The committee performed an extensive evaluation, in particular to evaluate whether the quantification of the conclusion needs to be updated.

Summary of evidence for the association between nuts and seeds consumption and risk of coronary heart disease

Aspect	Explanation
Available studies	1 meta-analysis of 39 cohorts <sup>25</sup>
Heterogeneity	Yes, in magnitude of the association <sup>25</sup>
Strength of the association	RR (95% CI) for highest versus lowest category: 0.82 (0.76, 0.89) <sup>25</sup> Dose-response analysis: evidence for a non-linear dose-response curve (p-value 0.009) <sup>25</sup>
Consumption level examined	Highest – lowest category: 5 to 100 g/d – none <sup>25</sup> Interquartile ranges (P25 to P75) in g/d: ♂ 0.1 to 4.3; ♀ 0.0 to 4.3 <sup>35</sup>
Study population	Europe, United States of America, Middle East, Australia, multinational cohorts <sup>25</sup>

**Conclusion: The combined consumption of 15 to 30 grammes of nuts, peanuts and seeds per day is associated with a 20% lower risk of coronary heart disease.**

**Evidence level: Strong**

**Additional remarks: Based on the non-linear dose-response curve, the risk appeared to level off between 15 and 30 grammes per day. For intakes above 30 grammes per day there was too little research.**

#### *Explanation*

The committee used the MA of Arnesen et al.<sup>25</sup> for its evaluation, including 13 reports that together included 39 prospective cohort studies. Of these cohort studies, 13 were European (including the publication of Perez-Cornago et al.,<sup>35</sup> a pooled analysis of data from 10 countries that contributed to EPIC, counted as 10 cohorts by the committee). The MA focused on studies into total, fatal and non-fatal CHD. The follow-up time of the included studies varied from 3.5 to 32 years.

In this MA, the exposure was defined as overall consumption of nuts and seeds, including peanuts and nut spreads. Categories of nut consumption that were compared in the studies that contributed to this MA varied, for instance: 5 to 100 versus 0 g/d (a relatively large difference in exposure) and  $\geq 5.3$  versus 0 g/d (a relatively small difference in exposure). However, in most reports, the highest consumption level was between  $\geq 2$  servings and  $\geq 5$  servings per week, corresponding to, approximately  $\geq 8$  to  $\geq 20$  g/d (on average approximately  $\geq 15$  g/d), assuming a portion (serving) size is 28 g.

In the highest versus lowest category of intake analysis, an 18% lower CHD risk was found by Arnesen et al (Table 1). The dose-response analysis showed evidence for a non-linear association. The risk of CHD especially decreased with increasing intakes of nuts and seeds up till 15 g/d, and the extent of risk reduction levelled off between 15 and 30 g/d, up to approximately 20%.

For fatal CHD, the non-linear dose-response analysis showed no further risk reduction at intakes  $\geq 15$  g/d, while for non-fatal CHD, the dose-response association tended to be more linear, with slight further reductions in CHD risk also above intakes of 15 g/d. However, these findings must be interpreted cautiously due to relatively fewer datapoints in these separate analyses, especially for intakes above 15 g/d. There were no datapoints for intakes higher than 30 g/d.

There was substantial heterogeneity between studies for the highest versus lowest category of intake analysis. Visual inspection of the forest plot showed no heterogeneity in direction but only in magnitude of the association. The heterogeneity could be partly explained by the authors based on subgroup analyses. Compared to the overall associations between nuts and seeds consumption and CHD risk, associations were stronger in studies from the USA and in studies with less than 10 years of follow-up. Another explanation could be that the highest and lowest comparison categories between studies varied markedly. This may also explain why associations in studies from the USA were stronger than in studies from European countries, as the findings for European countries were mainly driven by the pooled EPIC analysis (10 out of 13 cohorts) in which the intake level of nuts was relatively low.

In total, 18 out of the 39 cohorts adjusted the associations for hypercholesterolaemia, likely including or reflecting elevated LDL cholesterol, which is an established CHD risk factor that may well be on the causal pathway from nuts and seeds consumption to CHD. Such adjustment may therefore lead to overadjustment and attenuation of associations with CHD. Subgroup analyses showed that RRs were stronger in studies without adjustment for hypercholesterolaemia (RR: 0.78, 95% CI: 0.69 to 0.88) compared to studies with adjustment for hypercholesterolaemia (RR: 0.86, 95% CI: 0.78 to 0.94), although this difference was not statistically significant.

Seven reports were judged to have moderate risk of bias and seven to have serious risk of bias, based on the Risk of Bias for Nutrition Observational Studies tool (the pooled EPIC analysis,<sup>35</sup> pooled analysis of the Nurses' Health Study (NHS) I and II and Health Professionals Follow-Up Study (HPFS),<sup>36</sup> and studies of Albert et al.,<sup>37</sup> Blomhoff et al.,<sup>38</sup> Fraser et al.,<sup>39</sup> Gopinath et al.,<sup>40</sup> and Ivey et al.<sup>41</sup>). Subgroup analyses showed that associations were not different between studies with moderate and serious risk of bias.

The committee noted that the Risk of Bias tool selected by Arnesen et al. uses a target trial framework, assessing cohort studies against a hypothetical high-quality, randomised trial, with little confounding and other sources of bias. In the working method of the committee, such judgements may be too strict, because the committee evaluates the evidence from cohort studies and RCTs separately, and an integration of evidence from RCTs and cohort studies is made in a later phase (see Chapter 2 of the advisory report<sup>1</sup>), considering the evidential value and pros and cons of cohort studies and RCTs.

Most other MAs evaluated for the DDG2025 used Risk of Bias tools that are more specific for cohort studies, such as the Newcastle-Ottawa scale. Pooled analyses of EPIC and NHS I, II and HPFS studies were generally classified to have low or moderate risk of bias in other MAs used for the committee's evaluation, based on the Newcastle-Ottawa scale.<sup>42-46</sup> Moreover, the studies of Albert et al., Blomhoff et al., and Fraser et al. were also included in the MAs used for the DDG2015, and these were scored to have a high quality in these MAs.<sup>47,48</sup> Taking into account these risk of bias judgements, and the committee's working method, the committee sees no major concerns with respect to risk of bias for the studies included in the MA of Arnesen et al.

Arnesen et al. reported that the MA-work was partly funded by several non-commercial organisations. No information was given on the remaining funding sources.

The authors that contributed to the MA reported no potential conflicts of interest. One of the reports included in the MA was partly funded by industry (de Souza et al.<sup>49</sup>). Based on visual inspection of the forest plot, the committee judged that excluding this study from the MA would not substantially impact the MA findings.

With respect to different types of nuts and seeds, Arnesen et al. reported that there were insufficient data to conclude on the association between specific types of nuts or seeds and CHD risk. The committee was aware of another MA, of Aune et al.,<sup>50</sup> which reported, based on 5 cohort studies, that risk reductions for CHD mortality were similar for peanuts as for total nuts.

Based on the above and taking into account the decision tree, the committee concluded that there is strong evidence that the consumption of 15 to 30 g/d of nuts, peanuts and seeds is associated with approximately 20% lower CHD risk.

This conclusion was based on the observations that intakes of approximately 8 to 20

g/d (on average approximately  $\geq 15$  g/d) of nuts and seeds were associated with an 18% CHD risk reduction, that the largest risk reduction was achieved at intakes of 15 g/d, and that slight further reductions in risk were observed between 15 and 30 g/d, up to approximately 20%. The number of studies and cases included in the evaluation is sufficient for drawing a conclusion with a strong evidence level, findings remained to a large extent robust in sensitivity analyses, and there were no major considerations that may downgrade the certainty of the evidence. For intakes above 30 g/d, the committee concluded that there is too little research to base conclusions on.

**Table 1** Characteristics and results of meta-analyses on the association between nuts and seeds consumption and risk of coronary heart disease

Author, year, study design	Nuts and seeds consumption level examined	Type of analysis	N PCS	N participants; N cases	Strength of the association: RR (95% CI)	I <sup>2</sup>	Study population (n)	Risk of bias (n reports)
Arnesen, 2023, MA	Highest: 5 to 100 g/d; Lowest: none.	High vs. low	39 (13 reports)	1186541; 40549	0.82 (0.76, 0.89)	64%	USA (8), Europe (13), Middle East (1), Australia (1), multinational (16)	Moderate (6), Serious (7)
Arnesen, 2023, MA	Highest: 5 to 100 g/d. Lowest: none.	Per +30 g/d	NR (14 reports)	NR; 40904	0.79 (0.70, 0.89); Evidence for a non-linear dose-response curve (p-value 0.009)	NR	NR	NR

Abbreviations: CI: confidence interval; MA: meta-analysis; NR: not reported; PCS: prospective cohort studies; RR: relative risk; USA: United States of America; vs.: versus.

### 3.2 LDL cholesterol

In the DDG2015, it was concluded there is strong evidence that the intake of 35 g/d of nuts or flax seeds lowers LDL cholesterol by approximately 0.15 mmol/L.<sup>34</sup> This was based on a pooled analysis of 25 RCTs into nuts, 1 MAs including 11 RCT into walnuts, 1 MA including 11 RCTs into flax seeds, and 6 individual RCTs. More recent MAs suggest that the quantification of the conclusion may need to be updated, and to be separated for nuts and flax seeds. The committee therefore performed separate evaluations for total nuts, and different types of nuts and seeds.

### 3.2.1 Total nuts

Summary of evidence for the effect of total nuts compared to various controls on LDL cholesterol

Aspect	Explanation
Available studies	1 meta-analysis of 17 randomised controlled trials <sup>25</sup> and 1 meta-analysis of 37 randomised controlled trials <sup>51</sup>
Heterogeneity	Yes, in magnitude <sup>25,51</sup>
Strength of the association	<ul style="list-style-type: none"> <li>• Mean difference (95% CI) for intervention versus control group: -0.13 (-0.21, -0.05) mmol/L;<sup>25</sup></li> <li>• Effect (95% CI) per +28 g/d: -0.10 (-0.13, -0.09) mmol/L.<sup>51</sup></li> </ul>
Consumption level examined	<ul style="list-style-type: none"> <li>• Median: 54 g/d; range: 28 to 84 g/d;<sup>25</sup></li> <li>• Range: 15 to 100 g/d.<sup>51</sup></li> </ul>
Population	Europe, United States of America, Australia, New Zealand, Asia <sup>25</sup> or NR <sup>51</sup>

**Conclusion: Consumption in the range of 15 to 85 grammes of nuts per day lowers LDL cholesterol with approximately 0.10 mmol per liter.**

**Evidence level: Strong**

#### *Explanation*

The committee selected the MAs of Arnesen et al.<sup>25</sup> (n RCTs=17) and Del Gobbo et al.<sup>51</sup> (n RCTs=37) for its evaluation of the effect of total nut consumption on LDL cholesterol. The two MAs included only three overlapping RCTs, and thus largely different RCTs, mainly because Arnesen et al. included a number of more recent trials and also applied other, more strict inclusion criteria than Del Gobbo et al.

The committee noted that both these MAs mainly included RCTs that addressed effects of specific nut types (e.g. almonds, walnuts or peanuts) and only few RCTs that investigated mixed nuts consumption. The RCT durations varied between 12 and 24 weeks in Arnesen et al., and between 3 and 26 weeks in Del Gobbo et al. Both MAs included a mixture of RCTs performed in apparently healthy individuals and in people at higher risk for cardiovascular diseases.

Arnesen et al. showed that the consumption of 28 to 84 g/d (median approximately 54 g/d) of nuts decreases LDL cholesterol with on average 0.13 mmol/l, compared to various controls (Table 2). Subgroup analyses showed no differences in LDL cholesterol-lowering effects between doses of nuts of <54 g/day and of ≥54 g/day, suggesting that the LDL cholesterol lowering effect may be similar over the range of intake (28 to 84 g/d).

Del Gobbo et al. showed an 0.10 mmol/l decrease in LDL cholesterol per 28.4 g/d of nuts compared to various controls (Table 2). For this MA, the range of intake in individual RCTs was 15 to 100 g/day. The effect sizes and corresponding variances were standardised to 28.4 g/d of nuts. In addition, del Gobbo et al. showed a dose-response curve, without such standardisation. At nut intakes between 15 and 85 g/d,

the LDL reduction seemed fairly similar across this intake range. Above 85 g/d, there were very few datapoints.

In both MAs, there was substantial or moderate heterogeneity between RCTs, which was mainly in magnitude of the effect. As reported by the MA-authors, the heterogeneity was likely explained by differences in effects by types of nuts<sup>25</sup> or in differences between participants (larger risk reductions were seen in people with dyslipidaemia or prediabetes; these RCTs also had a higher risk of bias, see subgroup analyses by risk of bias below).<sup>25</sup> Also, differences in other study aspects such as type of control may have contributed to the heterogeneity.

The committee noted that one of the included RCTs, of Casas-Agustench et al.,<sup>52</sup> was reported to have an LDL lowering effect in the MA of Del Gobbo et al., and to have an increasing effect in the MA of Arnesen et al., the latter being in line with the original RCT report. The committee saw no apparent reason for this difference. Excluding this RCT in the MA of Arnesen et al. did not substantially change the overall MA result.

The effect estimates for the effects of nuts on LDL cholesterol slightly differed between the MAs of Arnesen et al. and de Gobbo et al. This may be due to the differences in study selection and in doses of nut intake examined in the included RCTs.

After exclusion of studies at high risk of bias, the differences in effect sizes between the MAs became more similar. Arnesen et al. used the Cochrane Risk of bias 2.0 tool to judge the risk of bias, and judged 5 out of the 17 RCTs as high risk of bias. Excluding the studies at high risk of bias attenuated the effect estimate to -0.09 (95% CI: -0.11, -0.07) mmol/L. Del Gobbo et al. assessed study quality using the American Dietetic Association Evidence Analysis Process, and judged 1 out of the 37 RCTs as low quality. In studies that were judged as high quality, the effect estimate was -0.10 (95% CI: -0.12, -0.08) mmol/L. In studies with moderate quality, the effect estimate was and -0.13 (95% CI: -0.16, -0.10) mmol/L.

Del Gobbo et al. reported indirect funding for MA-authors by the industry and International Tree Nut Council. Arnesen et al. reported no conflicts of interest. Del Gobbo et al. did not report on the funding sources of the individual RCTs included in the MA. In the MA of Arnesen et al., 14 out of the 17 RCTs were entirely or partially funded by industry. For 2 RCTs, there was no information on the funding sources, and 1 RCTs was funded by a non-industry agency. Based on this information, the committee was unable to judge whether industry funded studies differed in results compared to non-industry funded studies.

Based on the above and taking into account the decision tree, the committee concluded that there is strong evidence that consumption between 15 and 85 g/d of nuts lowers LDL cholesterol with approximately 0.10 mmol/l. The quantification of this conclusion was based on the observation that both MAs found approximately

0.10 mmol/L reduction in LDL cholesterol, and that this effect was observed at different levels of nut consumption within the observed consumption range of 15 to 85 g/d. The number of studies and participants included in the evaluation is sufficient for drawing a conclusion with a strong evidence level, findings remained largely robust in sensitivity analyses, and there were no major considerations that may downgrade the certainty of the evidence.

**Table 2** Characteristics and results of meta-analyses of randomised controlled trials on the effect of total nuts consumption compared to various controls on LDL cholesterol

Author, year, study design	Intervention; comparison	N RCTs; N participants	Strength of the effect: MD (95% CI), mmol/L	I <sup>2</sup>	Study populations (n)	Risk of bias (n)
Arnesen, 2023, MA	i: 28 to 84 g/d (median 54 g/d) tree nuts and peanuts; c: various controls such as no nuts, diets similar to dietary guidelines, habitual diet or savoury snacks.	In total: 17; 1602. Of these, 6 RCTs were performed in healthy populations.	Overall: -0.13 (-0.21, -0.05); In healthy populations: -0.09 (-0.12, -0.07)	69%  NR	Europe (2), USA (3), Australia (2), New Zealand (1), Asia (4), India (3), Turkey (1) <sup>a</sup>	Low (2), Some concerns (10), High (5)
Del Gobbo, 2015, MA	i: 15 to 100 g/d tree nuts; c: various controls, such as isoenergetic diets or common background diets (with or without nuts), including a habitual diet, low-fat diet or, Mediterranean diet.	In total: 37; 1980. Of these, 17 RCTs were performed in healthy populations.	Overall, effect per +28 g/d: -0.10 (-0.13, -0.09); In healthy populations, effect per +28 g/d: -0.11 (-0.14, -0.07)	38%  NR	Continent: NR <sup>b</sup>	High quality (23), Neutral (13), Low quality (1)

Abbreviations: c: comparison; CI: confidence interval; i: intervention; MD: mean difference; mmol/L: millimol per liter; NR: not reported; RCT: randomised controlled trial, USA: United States of America.

<sup>a</sup> In terms of health status, the following populations were included: generally healthy people (n=6), populations with dyslipidaemia (n=2), populations with metabolic syndrome (n=7), populations with prediabetes (n=2).

<sup>b</sup> In terms of health status, the following populations were included: apparently healthy people (n=17), populations with overweight/obesity (n=4), populations with metabolic syndrome (n=4), populations with high cholesterol (n=6), populations with type 2 diabetes (n=5), a population with prostate disease (n=1).

### 3.2.2 Different types of nuts and seeds

Regarding different types of nuts, the network MA of Liu et al.,<sup>53</sup> directly comparing different types of nuts, and the findings from MAs on specific types of nuts (walnuts,<sup>25,54</sup> almonds,<sup>25,55</sup> pistachios,<sup>25,56</sup> hazelnuts,<sup>57</sup> cashew nuts,<sup>58</sup> peanuts<sup>59</sup>) are in line with the conclusion that the overall consumption of nuts lowers LDL cholesterol (addressed in Section 3.2.1). The majority of RCTs were focused on almonds, walnuts and pistachios, and the general observation is that LDL cholesterol is lowered with consumption each of these types of nuts (Table 3). Effect estimates and levels of statistical significance for these types of nuts differed by MA, and, where reported, there was a large extent of heterogeneity (in magnitude of effect) between the RCTs on

almonds and pistachios. Likely, reasons for heterogeneity are similar to the reasons described above (for total nuts; Section 3.2.1). For other types of nuts, including hazelnuts, cashew nuts and peanuts, there were relatively few studies available, which limits the certainty of the study findings. Nevertheless, the findings for these types of nuts generally also pointed towards reducing effects on LDL cholesterol.

A MA on chia-seeds suggested no evidence for an effect on LDL cholesterol.<sup>60</sup>

**Table 3** Characteristics and results of meta-analyses of randomised controlled trials on the effect of the consumption of different types of nuts and seeds compared to various controls on LDL cholesterol

Author, year	Intervention; comparison	N RCTs; <sup>a</sup> N participants	Strength of the effect: MD (95% CI), mmol/L	I <sup>2</sup>
Asbaghi, 2021	i: <b>Almonds:</b> 10 to 100 g/d; c: various controls, such as no nuts, placebo capsule, (isocaloric) substitution food (e.g. muffin or olive oil), low fat diet or hypocaloric diet/	26; 2028	-0.15 ( -0.23, -0.07)	83%
Arnesen, 2023	i: <b>Almonds:</b> 30 to 57 g/d (median 54 g/d); <sup>b</sup> c: various controls, such as no nuts, habitual diet or savoury snacks.	4; NR	-0.22 (-0.33, -0.12)	NR
Liu, 2020	i: <b>Almonds:</b> 20 to 168 g/d; <sup>b</sup> c: various controls, such as habitual diet without almonds, and with control foods.	8; 552	-0.12 (-0.23, -0.01)	NR
Guasch-Ferré, 2018	i: <b>Walnuts:</b> 15 to 108 g/d; c: various controls, such as ad libitum control diet, Mediterranean diet, habitual diet, low-fat diets or provided control meals.	24; 1020	-0.14 (-0.20, -0.09)	0%
Arnesen, 2023	i: <b>Walnuts:</b> 30 to 57 g/d (median 54 g/d); <sup>b</sup> c: various controls, such as no nuts, similar to dietary guidelines or savoury snacks.	5; NR	-0.15 (-0.30, -0.00)	NR
Liu, 2020	i: <b>Walnuts:</b> 20 to 168 g/d; <sup>b</sup> c: various controls, such as habitual diet without walnuts, and with control foods.	14; 1279	-0.09 (-0.12, -0.07)	NR
Ghanavati, 2020	i: <b>Pistachios:</b> 42 to 80 g/d or 10 to 20% of energy; c: various controls, such as standard diet, diet according to guidelines of the AHS.	8; 404	-0.06 (-0.15, 0.02)	92%

Author, year	Intervention; comparison	N RCTs; <sup>a</sup> N participants	Strength of the effect: MD (95% CI), mmol/L	I <sup>2</sup>
Arnesen, 2023	i: <b>Pistachios</b> : 30 to 57 g/d (median 54 g/d); <sup>b</sup> c: various controls, such as no nuts, similar dietary guidelines, other fatty foods.	4; NR	-0.17 (-0.28, -0.05)	NR
Liu, 2020	i: <b>Pistachios</b> : 20 to 168 g/d; <sup>b</sup> c: various controls, such as habitual diet without pistachios, and with control foods.	4; 250	-0.17 (-0.28, -0.06)	NR
Perna, 2016	i: <b>Hazelnuts</b> : 29 to 60 g/d (i) c: various controls, such as no nuts, self-selected diet or no additional food (c)	3; 216	Median difference: -0.15 (95% HPD: -0.31, -0.003)	NR
Liu, 2020	i: <b>Hazelnuts</b> : 20 to 168 g/d; <sup>b</sup> c: various controls, such as habitual diet without hazelnuts, and with control foods.	3; 222	-0.09 (-0.23, 0.04)	NR
Jalali, 2020	i: <b>Cashew nuts</b> : 30 to 42 g/d; c: control, not further specified.	3; 352	-0.02 (-0.12, 0.08)	33%
Liu, 2020	i: <b>Cashew nuts</b> : 20 to 168 g/d; <sup>b</sup> c: various controls, such as habitual diet without cashew nuts, and with control foods.	3; 207	-0.09 (-0.22, 0.03)	NR
Jafari, 2020	i: <b>Peanuts</b> : approximately 46 to 77 g/d; c: various control diets, including habitual diet, hypocaloric diet and American Diabetes association meal plan.	3; 164	-0.23 (-0.41, -0.06)	96%
Teoh, 2018	i: <b>Chia seeds</b> : 4 to 50 g/d, whole or grounded and added to a food (n=4), or a dehydrated mixture (n=1); c: various controls, such as wheat or oat bran, placebo flour including soy, calcium caseinate mixture.	5; 258	-0.01 (-0.24, 0.21)	0%

Abbreviations: AHS: American Heart Association; c: comparison; CI: confidence interval; HPD: highest posterior density; max: maximum of; i: intervention; MD, mean difference; NR: not reported; mmol/L: millimol per liter; RCT, randomised controlled trial.

<sup>a</sup> For subgroup analyses based on type of nuts, only subgroups including 3 or more studies are reported.

<sup>b</sup> This intake range applies to all types of nuts addressed in the MA. The range of intake of this specific type of nut falls within this intake range.

### 3.2.3 Flax seeds

Summary of evidence for the effect of flax seeds compared to various controls on LDL cholesterol

Aspect	Explanation
Available studies	1 meta-analysis of 23 randomised controlled trials <sup>61</sup>
Heterogeneity	Yes, in magnitude <sup>61</sup>
Strength of the association	Mean difference (95% CI): -0.26 (-0.37, -0.14) mmol/L <sup>61</sup>
Consumption level examined	Range: 10 to 60 g/d <sup>61</sup>
Population	Europe, United States of America, Canada, South-America, Asia <sup>61</sup>

**Conclusion: Consumption of flax seeds lowers LDL cholesterol.**

**Evidence level: Limited**

**Additional remark: Flax seed consumption in the range between 10 and 60 grammes per day was investigated in studies underlying this conclusion.**

#### *Explanation*

The MA of Hadi et al.,<sup>61</sup> including 23 RCTs (24 comparisons), was selected for the committee's evaluation of whole flax seeds and its effect on LDL cholesterol. The analysis of whole flax seeds was performed as a subgroup analysis by Hadi et al, with the main MA also including RCTs on flax seed lignans and oils. The subgroup analysis selected for the committee's evaluation investigated the effects of whole flax seeds, including grounded (n=6) and defatted (n=1) flax seeds. A consumption level between 10 and 60 g/d was addressed. The durations of the interventions ranged between 4 and 54 weeks.

Hadi et al., found that consumption of flax seeds decreased LDL cholesterol with 0.26 mmol/L, compared to various controls (Table 4). There was substantial heterogeneity between RCTs. Visual inspection of the forest plot showed that the heterogeneity was mainly in the magnitude of the effect, and not in the direction. As the category of whole flax seeds was already a subgroup, Hadi et al. did not perform further subgroup analyses that might explain the heterogeneity. However, subgroup analyses for the main MA (including a maximum of 71 RCTs, also including RCTs into flax seed lignans and oils) were performed. These showed that the effect of flax seed interventions on LDL cholesterol was only visible in populations with reported elevated baseline LDL cholesterol levels (n=48 RCTs; as compared to 8 RCTs in people without elevated LDL cholesterol), and in populations with reported dyslipidemia and postmenopausal women (n=15 and 6 RCTs, respectively). In contrast, no effects were found in healthy populations (n=17 RCTs) and populations with reported metabolic syndrome and diabetes (n=18 RCTs) and cardiovascular diseases (n=7 RCTs). In the majority of these subgroups, heterogeneity between studies remained present.

The MA-authors evaluated the risk of bias using the Cochrane’s Collaboration tool, and judged 9 out of the 23 RCTs to have a high risk of bias (in particular on the items blinding of participants, personnel and outcome assessment). Furthermore, for all RCTs there were unknown risks of bias on at least one to five items, in particular with respect to the randomisation procedure. The MA-authors did not further investigate the potential differences in effects between studies based on risk of bias.

Hadi et al. reported evidence for funnel plot asymmetry based on visual inspection of a funnel plot for the main MA (also including flax seed lignans and oils). This might be the result of publication bias but might also be due to other causes (e.g. heterogeneity between larger and smaller studies).

The authors of this MA reported no conflicts of interest. The funding sources for individual RCTs that contributed to the MA were not reported.

Based on the above, and taking into account the decision tree, the committee concluded that there is limited evidence that consumption in the range of 10 to 60 g/d of flax seeds lowers LDL cholesterol. The evidence was judged limited due to the substantial level of heterogeneity between RCT-findings. The heterogeneity was not directly explained by the authors, but only via subgroup analyses in the main analysis, that included a broader definition of the intervention of flax seeds. In these subgroup analyses, there were large differences in effects between different types of study populations, such as between people with elevated LDL cholesterol levels and apparently healthy people. Moreover, it was uncertain whether and to what extent the RCTs with a high risk of bias impacted the MA findings.

**Table 4** Characteristics and results of meta-analyses of randomised controlled trials on the effect of flax seeds compared to various controls on LDL cholesterol

Author, year, study design	Intervention; comparison	N RCTs; N participants	Strength of the effect: MD (95% CI), mmol/L	I <sup>2</sup>	Study populations (n)	Risk of bias (n)
Hadi, 2019, MA	i: 10 to 60 g/d of whole (n=17), grounded (n=6) or defatted (n=1) flax seeds; <sup>a</sup> c: various controls, such as no flax seeds, sunflower seeds, wheat bran/germ/flour or raw rice.	23 (24 comparisons); NR (>90) <sup>a</sup>	-0.26 (-0.37, -0.14)	77%	Europe (1), USA (5), Canada (4), South-America (5), Asia (9) <sup>b</sup>	High (9); Low or unknown (15)

Abbreviations: c: comparison; CI: confidence interval; i: intervention; MD: mean difference; mmol/L: millimol per liter; NR: not reported; RCT: randomised controlled trial; USA: United States of America.

<sup>a</sup> This applies to the number of participants in the intervention group. The total number of participants is thus higher.

<sup>b</sup> In terms of health status, the following populations were included: healthy people (n=3), populations with hypercholesterolemia (n=8), a population with cardiovascular diseases (n=1), populations with prostate cancer (n=2), a population with peripheral arterial disease (n=1), populations with obesity (n=2), haemodialysis patients (n=1), populations with type 2 diabetes (n=2), populations with metabolic syndrome (n=2), a population with non-alcoholic fatty liver disease (n=1), not reported (n=1).

### 3.3 Stroke

The DDG2015 concluded there is too little research to draw conclusions on the association between nuts and seeds consumption and stroke risk.<sup>34</sup> There are now more studies available on this topic. The committee performed an extensive evaluation on the association between nuts and seeds consumption and risk of stroke.

Summary of evidence for the association between nuts and seeds consumption and risk of stroke

Aspect	Explanation
Available studies	1 meta-analysis of 34 cohorts <sup>25</sup>
Heterogeneity	No <sup>25</sup>
Strength of the association	<ul style="list-style-type: none"><li>RR (95% CI) for highest versus lowest category: 0.91 (0.85, 0.97);<sup>25</sup></li><li>Dose-response analysis: evidence for a non-linear dose-response curve (p-value 0.03).<sup>25</sup></li></ul>
Consumption level examined	<ul style="list-style-type: none"><li>Highest – lowest category: 5 to 100 g/d – none;<sup>25</sup></li><li>Interquartile ranges (P25 to P75) in g/d: ♂ 0.1 to 4.3; ♀ 0.0 to 3.5.<sup>43</sup></li></ul>
Study population	Europe, United States of America, Middle East, Australia, multinational cohorts <sup>25</sup>

**Conclusion: The combined consumption of approximately 10 to 20 grammes of nuts, peanuts and seeds per day is associated with a 10% lower risk of stroke. Evidence level: strong**

**Additional remarks: For intakes between 20 and 30 grammes per day, the association is inconclusive. For intakes above 30 grammes per day, there is too little research.**

#### *Explanation*

The committee used the MA of Arnesen et al.<sup>25</sup> for its evaluation, including 10 publications that together included 34 prospective cohort studies. Of these cohort studies, 10 were European (including the publication of Tong et al.,<sup>35</sup> with data from 9 European countries that contributed to EPIC, counted as 9 cohorts by the committee). The MA focused on studies into total, fatal and non-fatal stroke and ischemic stroke. The follow-up time of the included studies varied from 3.5 to 32 years.

In this MA, the exposure was defined as overall consumption of nuts and seeds, including peanuts and nut spreads. Categories of nut consumption that were compared in the cohorts that contributed to this MA varied, for instance: 5 to 100 versus 0 g/d (a relatively large difference in exposure) and 10.2 versus 0 g/d (a relatively small difference in exposure). However, in most reports, the highest consumption level was between  $\geq 2.5$  servings and  $\geq 7$  servings per week, corresponding to, approximately  $\geq 10$  to 28 g/d (on average approximately  $\geq 20$  g/d), assuming a portion (serving) size is 28 g.

In the highest versus lowest category of intake analysis, a 9% lower stroke risk was found by Arnesen et al., without substantial heterogeneity between studies (Table 5).

The dose-response analysis showed that there was evidence for a non-linear association. Stroke risk especially decreased with increasing nut and seed intakes up till 10 to 15 g/d. With higher intakes, the dose-response curve progressed towards no significant association (with broad confidence intervals) at 30 g/d. However, most datapoints were of intakes below 20 g/d, and there were few datapoints above 20 g/d and no datapoints for intakes above 30 g/d. Therefore, the findings for intake levels above 20 g/d should be interpreted with caution. In the highest versus lowest analysis, the association was more protective (13% lower risk) in studies investigating only fatal stroke.

In total, 17 out of 34 cohorts adjusted the associations for baseline presence of hypertension, reflecting elevated blood pressure. Blood pressure might be on the causal pathway from nuts and seeds consumption to stroke. Such adjustment may therefore lead to overadjustment and attenuation of associations with stroke. However, subgroup analyses of studies with adjustment for hypertension compared to studies without such adjustment for hypertension showed that risk estimates were similar.

Five reports were judged as having moderate risk of bias and five as having serious risk of bias, based on the Risk of Bias for Nutrition Observational Studies tool (the pooled analysis of EPIC studies,<sup>35</sup> pooled analysis of NHS I, II and HPFS,<sup>36</sup> and studies of Djoussé et al.,<sup>62</sup> Gopinath et al.,<sup>40</sup> and Ivey et al.<sup>41</sup>). Subgroup analyses suggested that associations were stronger in studies with serious risk of bias (11% lower stroke risk in highest versus lowest MA), compared to moderate risk of bias (5% lower stroke risk), although the difference was not statistically significant.

The committee noted that the Risk of Bias tool selected by Arnesen et al. uses a target trial framework, assessing cohort studies against a hypothetical high-quality, randomised trial, with little confounding and other sources of bias. In the working method of the committee, such judgements may be too strict, because the committee evaluates the evidence from cohort studies and RCTs separately, and an integration of evidence from RCTs and cohort studies is made in a later phase (see Chapter 2 of the advisory report<sup>1</sup>), considering the evidential value and pros and cons of cohort studies and RCTs.

Most other MAs evaluated for the DDG2025 used Risk of Bias tools that are more specific for cohort studies, such as the Newcastle-Ottawa scale. Pooled analyses of EPIC, including the study by Tong et al., and pooled analyses of NHS I, II and HPFS studies were generally classified as low or moderate risk of bias in other MAs used for the committees evaluation, based on the Newcastle-Ottawa scale.<sup>42-46</sup> Moreover, the study by Djoussé et al. and an older version of the pooled analysis of NHS I, II and PHFS<sup>63</sup> were also included in the MAs used for the DDG2015, and these were scored as having a high quality in these MAs.<sup>47,48</sup> Taking into account these risk of bias

judgements, and the committees working method, the committee sees no major concerns with respect to risk of bias for the studies included in the MA of Arnesen et al.

Arnesen et al. reported that the MA-work was partly funded by several non-commercial organisations. No information was given on the remaining funding sources.

The authors that contributed to the MA reported no potential conflicts of interest. One of the reports included in the MA was partly funded by industry (de Souza et al.<sup>49</sup>).

Based on visual inspection of the forest plot, the committee judged that excluding this study from the MA would not substantially impact the MA findings.

With respect to different types of nuts and seeds, Arnesen et al. reported that there was insufficient data to conclude on the associations between specific types of nuts or seeds and stroke risk.

Based on the above and taking into account the decision tree, the committee concluded there is strong evidence that the consumption of approximately 10 to 20 g/d of nuts, peanuts and seeds is associated with approximately 10% lower stroke risk. This was based on the observations that an intake of approximately 10 to 28 g/d (on average approximately 20 g/d) of nuts and seeds was associated with a 10% stroke risk reduction, that the largest risk reduction was achieved at intakes of 10 to 15 g/d, and that the dose-response curve progressed towards no association at higher intakes, up to 30 g/d. Most datapoints included in the MA were of intakes below 20 g/d, suggesting that the protective association of the highest versus lowest analyses is likely mostly driven by studies with relatively lower intakes in this range (<20 g/d). The number of studies and cases included in the evaluation is sufficient for drawing a conclusion with a strong evidence level, findings remained to a large extent robust in sensitivity analyses, and there were no major considerations that may downgrade the certainty of the evidence. The committee furthermore concluded that the association between nuts and seeds intakes of 20 to 30 g/d and stroke risk is inconclusive because there were relatively few datapoints within this intake range and confidence intervals in the dose-response analysis were broad. For intakes above 30 g/d, there is too little research to base conclusions on.

**Table 5** Characteristics and results of meta-analyses of prospective cohort studies on the association between nuts and seeds consumption and risk of stroke

Author, year, study design	Nuts and seeds consumption level examined	Type of analysis	N PCS	N participants; N cases	Strength of the association: RR (95% CI)	I <sup>2</sup>	Study population (n)	Risk of bias (n reports)
Arnesen, 2023, MA	Highest: 5 to 100 g/d; Lowest: 0 g/day.	High vs. low	34 (10 reports)	981166; 22635	Total stroke: 0.91 (0.85, 0.97)	25%	Europe (10), USA (6), Middle East (1), Australia (1), multinational (16)	Moderate (5), Serious (5)
Arnesen, 2023, MA	Highest: 5 to 100 g/d; Lowest: 0 g/day.	High vs. low	17 (7 reports)	944799; 15421	Ischaemic stroke: 0.94 (0.85, 1.03)	37%	Europe (11), USA (6)	Moderate (4), Serious (3)
Arnesen, 2023, MA	Highest: 5 to 100 g/d; Lowest: 0 g/day.	Per +30 g/d	NR (11 reports)	NR; NR	Total stroke: 0.99 (0.91, 1.08); Evidence for a non-linear dose-response curve (p-value 0.03)	NR	NR	NR
Arnesen, 2023, MA	Highest: 5 to 100 g/d; Lowest: 0 g/day.	Per +30 g/d	NR (8 reports)	NR; NR	Ischaemic stroke: 0.96 (0.82, 1.13); No evidence for non-linearity (p-value 0.71)	NR	NR	NR

Abbreviations: CI: confidence interval; MA: meta-analysis; NR: not reported; PCS: prospective cohort studies; RR: relative risk; USA: United States of America; vs.: versus.

### 3.4 Blood pressure

The DDG2015 committee concluded that an effect of nuts on systolic blood pressure is unlikely.<sup>34</sup> This was based on a MA with 20 RCTs. More recent evidence supports this conclusion and extends this conclusion to diastolic blood pressure, as described below. For seeds, no separate evaluation could be performed in the DDG2015. There are now sufficient studies on seeds to perform such an evaluation. The committee performed separate evaluations for total nuts, and different types of nuts and seeds.

#### 3.4.1 Total nuts

The committee selected the MAs of Arnesen et al.,<sup>25</sup> del Gobbo et al.,<sup>51</sup> and Mohammadifard et al.,<sup>64</sup> including 11 to 21 RCTs, for its evaluation of the effect of total nut consumption on systolic and diastolic blood pressure. The committee noted that these MAs mainly included RCTs that addressed effects on specific nut types (such as walnuts, almonds or peanuts) and only few RCTs that investigated mixed nuts consumption. The selected MAs suggested that there is no effect of overall nut consumption on systolic and diastolic blood pressure (Table 6). These findings are in line with the conclusions drawn in the DDG2015 on systolic blood pressure. Mohammadifard et al. included two RCTs that investigated soy nuts. Exclusion of these

RCTs from the main MA did not change the findings. Del Gobbo et al. showed a statistically significant increase in systolic blood pressure per 28.4 g/d of nuts. However, this significant increase seemed attributable to the inclusion of one single RCT with a large weight.<sup>65</sup> Del Gobbo et al. reported a strong increasing effect on systolic blood pressure for this RCT, which compared cocoa cream (control) with cocoa plus hazelnut cream (intervention, dose: 30 g/d of hazelnuts). All other included RCTs (n=15) found no significant effect on systolic blood pressure. This specific RCT was not included in the other MAs.

**Table 6** Characteristics and results of meta-analyses of randomised controlled trials on the effects of overall nuts consumption compared to various controls on blood pressure

Author, year	Intervention; comparison	N RCTs; N participants	Strength of the effect: MD (95% CI), mmHg	I <sup>2</sup>
Arnesen, 2023	i: 30 to 57 g/d (median 54 g/d) tree nuts and peanuts; c: various controls, such as no nuts, diets similar to dietary guidelines, habitual diet or savoury snacks.	11; 1,568	SBP: -0.89 (-2.10, 0.32); DBP: -0.33 (-1.16, 0.50)	0%  1%
Mohammadifard, 2015	i: 30 to 108 g/d tree nuts, peanuts and soy nuts; c: various controls, such as low-fat or low-calorie diet, healthy diet, traditional diet.	21; 1652	SBP: -0.91 (-2.18, 0.36); DBP: 0.21 (-0.54, 0.97)	74%  53%
Del Gobbo, 2015	i: 10 to 100 g/d tree nuts; c: various controls, such as isoenergetic diets or common background diets (with or without nuts), including a habitual diet.	16; NR	SBP, effect per +28.4 g/d: 1.29 (0.03, 2.56); DBP, effect per +28.4 g/d: 0.58 (-0.69, 1.84)	0%  0%

Abbreviations: c: comparison; CI: confidence interval; DBP: diastolic blood pressure; i: intervention; MD: mean difference; mmHg: millimeters of mercury; RCT: randomised controlled trial; SBP: systolic blood pressure.

### 3.4.2 Different types of nuts and seeds

Regarding specific types of nuts, the findings of MAs,<sup>25,64,66-69</sup> were generally in line with the overall conclusions that the consumption of nuts does not affect blood pressure (Table 7). Effect estimates for walnuts, almonds and pistachios, and levels of statistical significance for these types of nuts differed slightly by MA, with some, but not consistent, indications for protective effects. Moreover, these subgroup analyses were mostly based on only a few studies and showed high heterogeneity. A MA on chia-seeds suggested no evidence for an effect on blood pressure.<sup>60</sup>

**Table 7** Characteristics and results of meta-analyses of randomised controlled trials on the effects of specific types of nuts and seeds consumption compared to various controls on blood pressure

Author, year	Intervention; comparison	N RCTs; <sup>a</sup> N participants	Strength of the effect: MD (95% CI), mmHg	I <sup>2</sup>
Li, 2020	i: <b>Walnuts:</b> 6 to 108 g/d; c: NR.	18; 1799	SBP: 0.08 (-0.69, 0.85); DBP: 0.08 (-0.25, 0.42)	85% 35%
Arnesen, 2023	i: <b>Walnuts:</b> 30 to 57 g/d (median 54 g/d); <sup>b</sup> c: various controls, such as no walnut, white bread.	4; NR	SBP: -0.67 (-2.86, 1.52); DBP: -0.79 (-2.03, 0.45)	NR NR
Mohammadifard, 2015	i: <b>Walnuts:</b> 30 to 108 g/d; <sup>b</sup> c: various controls, such as low-fat diet, traditional diet.	6; NR	SBP: 0.58 (-2.99, 4.15); DBP: 1.76 (-0.16, 3.68)	85% 79%
Blanco Mejia, 2014	i: <b>Walnuts:</b> 30 to 86 g/d (median 56 g/d); <sup>b</sup> c: various controls, such as habitual diet, low-fat diet.	6; 341	SBP: 1.42 (-2.81, 5.65); DBP: 0.67 (-1.16, 2.50)	NR NR
Eslampour, 2020	i: <b>Almonds:</b> 10 to 73 g/d; c: various controls, such as other snack, healthy diet.	16; 1128	SBP: -0.83 (-2.25, 0.89); DBP: -1.30 (-2.31, -0.30)	59% 0%
Mohammadifard, 2015	i: <b>Almonds:</b> 30 to 108 g/d; <sup>b</sup> c: various controls, such as low-calorie diet, other snack	5; NR	SBP: -2.90 (-5.98, 0.18); DBP: -0.05 (-1.14, 1.05)	69% 0%
Blanco Mejia, 2014	i: <b>Almonds:</b> 30 to 86 g/d (median 56 g/d); <sup>b</sup> c: various controls, such as healthy diet, other snack.	6; 437	SBP: -2.87 (-6.87, 1.14); DBP: 0.57 (-1.20, 2.33)	NR NR
Asbaghi, 2021	i: <b>Pistachios:</b> 25 to 57 g/d or 10 to 20% of energy; c: various controls, such as no pistachio, low-fat diet.	6; 416	SBP: -2.12 (-3.65, -0.59); DBP: 0.33 (-1.38, 2.03)	30% 65%
Mohammadifard, 2015	i: <b>Pistachios:</b> 30 to 108 g/d; <sup>b</sup> c: various controls, such as low-fat diet, regular diet.	3; NR	SBP: -1.82 (-2.97, -0.67); DBP: -0.80 (-1.43, -0.17)	5% 0%
Blanco Mejia, 2014	i: <b>Pistachios:</b> 30 to 86 g/d (median 56 g/d); <sup>b</sup> c: various controls, such as healthy diet, other snack.	6; 341	SBP: -0.35 (-5.08, 4.37); DBP: 0.37 (-1.93, 2.66)	NR NR

Author, year	Intervention; comparison	N RCTs; <sup>a</sup> N participants	Strength of the effect: MD (95% CI), mmHg	I <sup>2</sup>
Teoh, 2018	i: <b>Chia seeds:</b> 4 to 50 g/d, whole or grounded and added to a food (n=3 to 5), or a dehydrated mixture (n=1); c: various controls, such as wheat or oat bran, placebo flour including soy, calcium caseinate mixture.	6; 300 (for SBP) 4; 182 (for DBP)	SBP: -2.57 (-6.70, 1.55); DBP: -3.37 (-7.43, 0.70)	38% 65%

Abbreviations: c: comparison; CI: confidence interval; DBP: diastolic blood pressure; i: intervention; MD: mean difference; mmHg: millimeters of mercury; NR: not reported; RCT: randomised controlled trial; SBP: systolic blood pressure.

<sup>a</sup> For subgroup analyses based on type of nuts, only subgroups including 3 or more studies are reported.

<sup>b</sup> This intake range applies to all types of nuts addressed in the MA. The range of intake of this specific type of nut falls within this intake range.

### 3.4.3 Flax seeds

Summary of evidence for the effect of flax seeds compared to various controls on blood pressure

Aspect	Explanation
Available studies	1 meta-analysis of 8 randomised controlled trials <sup>70</sup>
Heterogeneity	Not reported <sup>70</sup>
Strength of the association	Mean difference (95% CI) for intervention versus control group: <ul style="list-style-type: none"> <li>Systolic blood pressure : -1.81 (-2.03, -1.59) mmHg;<sup>70</sup></li> <li>Diastolic blood pressure: -1.28 (-2.45, -0.11) mmHg.<sup>70</sup></li> </ul>
Consumption level examined	Range: 28 to 60 g/d <sup>70</sup>
Population	South-America, Canada, Asia; <sup>70</sup>

**Conclusion: Consumption of flax seeds lowers systolic and diastolic blood pressure.**

**Evidence level: Limited**

**Additional remark: Flax seed consumption in the range between 28 and 60 grammes per day was investigated in studies underlying this conclusion.**

#### *Explanation*

The MA of Ursoniu et al.,<sup>70</sup> including 7 RCTs (8 comparisons) that addressed whole flax seeds, was included in the committee's evaluation. The effect of whole flax was assessed in a subgroup analysis by Ursoniu et al., with the main MA also including RCTs on flax seed lignans and oils. The category of whole flax seeds also included flax seeds powder. The committee noted that one of the RCTs included flax seed germs, which differ in dietary composition from whole flax seeds, and may therefore be not

entirely representative of whole flax seeds. The consumption levels examined in the RCTs varied between 28 and 60 g/d. The durations of the interventions ranged between 6 and 52 weeks.

Ursoniu et al. showed that the consumption of 28 to 60 g/d of flax seeds statistically significantly decreased systolic blood pressure with 1.81 mmHg and diastolic blood pressure with 1.28 mmHg, compared to various controls (Table 8). The extent of heterogeneity between RCTs was not reported, but visual inspection of the forest plots suggested heterogeneity in magnitude of the effects for both systolic and diastolic blood pressure. As the category of whole flaxseeds was already a subgroup, the MA-authors did not perform further subgroup analyses that might explain possible heterogeneity. However, subgroup analyses for all interventions (also including flax seed lignans and oils) were performed by intervention duration. These analyses showed that the effects were stronger in RCTs with longer intervention durations. No further subgroup analyses were performed, such as by type of study population.

Risk of bias was assessed with the Cochrane quality assessment tool for RCTs. All but one RCTs were judged to have high or unclear risk of bias. More specifically, 3 RCTs were judged to have high risk of bias (in particular for the items blinding of participants, personnel and outcome assessment) and 3 RCTs scored unclear risk of bias for at least two items (in particular because the randomisation procedure and/or blinding procedure were not clear). The authors did not investigate whether there were differences in effects between studies based on risks of bias. The committee noted that, when leaving out one of the RCTs with a high risk of bias (Wu et al.<sup>71</sup>), the effect of all flax seed interventions on systolic blood pressure was not statistically significant anymore in the main analysis (also including flax seed lignans and oils). Ursoniu et al. reported evidence for funnel plot asymmetry for systolic blood pressure, for the main analysis (including flax seed lignans and oils), although this was not significant according to a Begg's rank correlation test and an Egger's linear regression test. For diastolic blood pressure, the Egger's linear regression test was significant. These observations might be the result of publication bias, but might also be due to other causes (e.g. heterogeneity between larger and smaller studies). The authors of this MA reported no conflicts of interest. The type of funding for individual RCTs (e.g. non-industry agency or industry) was not reported.

Based on the above, and taking into account the decision tree, the committee concluded that there is limited evidence that consumption in the range of 28 to 60 g/d of flax seeds lowers systolic and diastolic blood pressure. The evidence was judged limited because subgroup and sensitivity analyses were only available for the main analyses, that included a broader definition of the intervention than only (whole) flax seeds. Moreover, all but one RCTs were judged to have high or unclear risk of bias,

and the impact of RCTs at high risk of bias on the MA findings remained partly uncertain. Also, one of the interventions involved flax seed germs, that may not be entirely representative for whole flax seeds.

**Table 8** Characteristics and results of meta-analyses of randomised controlled trials on the effect of flax seeds consumption compared to various controls on blood pressure

Author, year, study design	Intervention; comparison	N RCTs; N participants	Strength of the effect: MD (95% CI), mmHg	<i>I</i> <sup>2</sup>	Study populations (n)	Risk of bias (n)
Ursoniu, 2016, MA	i: 28 to 60 g/d of whole flaxseed or powder (e.g. milled flaxseed, flaxseed germ, roasted flaxseed chutney powder, flaxseed in bread); c: NR.	7 (8 comparisons); 666	SBP: -1.81 (-2.03, -1.59); DBP: -1.28 (-2.45, -0.11)	NR NR	South-America (2), Canada (2), Asia (3) <sup>a</sup>	Low (1), High (3), Unknown (3)

Abbreviations: c: comparison; CI: confidence interval; DBP: diastolic blood pressure; i: intervention; MD: mean difference; mmHg: millimeters of mercury; NR: not reported RCT: randomised controlled trial, SBP: systolic blood pressure.

<sup>a</sup> In terms of health status, the following populations were included: a population with high risk of cardiovascular disease (n=1), a population with peripheral arterial disease (n=1), populations with dyslipidaemia (n=2), a population with overweight (n=1), a population with metabolic syndrome (n=1), menopausal women (1).

### 3.5 Type 2 diabetes

In the DDG2015, 1 MA including 5 prospective cohort studies was used for the evaluation of the association between nuts and seeds consumption and risk of type 2 diabetes.<sup>34</sup> Based on that MA,<sup>47</sup> the 2015-committee concluded that the study findings were too heterogeneous to draw a conclusion, and that overadjustment for BMI in some of the included cohort studies may have contributed to the heterogeneous findings. The 2015-committee noted that BMI is an established risk factor for type 2 diabetes, and that frequent consumption of nuts has been associated with less strong weight gain with age in cohort studies. Therefore, adjustment for BMI could attenuate a potential beneficial association between nut consumption and type 2 diabetes risk. Two cohort studies included in the MA used by the 2015-committee (NHS I and II by Pan et al.<sup>72</sup>) showed there was an inverse association between consumption of nuts and risk of type 2 diabetes without adjustment for BMI. With adjustment for BMI, however, there was no evidence for an association. The other 3 cohort studies included in the MA only provided estimates with BMI adjustment.

Since 2015, there are substantially more cohort studies available that addressed the association between nuts and seeds consumption and type 2 diabetes risk. Therefore, the committee performed an extensive evaluation.

Summary of evidence for the association between nuts and seeds consumption and risk of type 2 diabetes

Aspect	Explanation
Available studies	1 meta-analysis of 13 cohorts <sup>25</sup>
Heterogeneity	Yes, in direction <sup>25</sup>
Strength of the association	<ul style="list-style-type: none"> <li>RR (95% CI) for highest versus lowest category: 0.95 (0.75, 1.21);<sup>25</sup></li> <li>Dose-response analysis: No evidence for a dose-response relationship (p-value for linearity: 0.98).<sup>25</sup></li> </ul>
Consumption level examined	<ul style="list-style-type: none"> <li>Highest-lowest category: 5 to 100 g/d - 0 g/d;<sup>25</sup></li> <li>Interquartile ranges (P25 to P75) in g/d: ♂ 0 to 16.7; ♀ 0 to 15.0.<sup>73</sup></li> </ul>
Study population	Europe, United States of America, Middle-East <sup>25</sup>

**Conclusion: Results from prospective cohort studies on the association between the combined consumption of nuts, peanuts and seeds and risk of type 2 diabetes are contradictory.**

**Evidence level: not applicable**

*Explanation*

The committee used the MA of Arnesen et al.<sup>25</sup> for its evaluation, including 5 reports that together included 13 prospective cohort studies. Of these cohort studies, 8 were European (i.e. the publication of Buijsse et al.,<sup>73</sup> including data of 8 European countries that contributed to EPIC, counted as 8 cohorts by the committee), and 4 were from the USA (including the analysis of Pan et al.,<sup>72</sup> that combined results from the NHS I and II). The follow-up time of the included studies varied from 6 to 12 years.

In this MA, the exposure was defined as overall nuts and seeds consumption, including peanuts and nut spreads. Categories of nut consumption that were compared in the cohorts that contributed to this MA varied, for instance:  $\geq 7$  servings/wk versus 0, rarely or never (a relatively large difference in exposure), and  $\geq 4$  servings/wk versus  $< 1$  serving/wk (a relatively smaller difference in exposure). In 4 of the 12 cohorts, the highest category of consumption was between  $\geq 4$  servings/wk and  $\geq 7$  servings/wk. This corresponds to approximately  $\geq 8$  to  $\geq 28$  g/d (mean approximately  $\geq 18$  g/d), assuming that one portion (serving) size is 28 g. In a subsample of participants that contributed to the pooled analysis of EPIC cohorts, the mean intake in the highest category of nut consumption was 8.0 g/d (2 servings/wk).

Both the dose-response analysis and the highest versus lowest category of intake analysis showed no statistically significant association between consumption of nuts and seeds and risk of type 2 diabetes (Table 9). There was substantial heterogeneity between studies for the highest versus lowest category of intake analysis, which was not explained. No subgroup analyses were performed due to the limited number of reports included in this MA. Visual inspection of the forest plot showed heterogeneity in

direction, with 9 cohorts (2 reports) showing tendencies towards beneficial associations, 2 cohorts suggesting no association and 1 cohort suggesting a harmful association.

All studies included in the MA of Arnesen et al. adjusted the associations for BMI. BMI could be on the causal pathway between nuts and seeds consumption and occurrence of type 2 diabetes. Therefore, the associations found in the MA may be, to some extent, over-adjusted. As was already noted in the DDG2015, the study by Pan et al.,<sup>72</sup> that was also included in the MA of Arnesen et al., indeed found inverse associations for nut consumption and risk of type 2 diabetes, only in analyses without adjustment for BMI (Table 9). In line with this, the committee noted that another report included in Arnesen et al., of Buijsse et al.,<sup>73</sup> (including 8 cohorts contributing to EPIC), found that non-consumers of nuts (compared to the middle tertile of consumers) had an 11% higher risk of type 2 diabetes in the analysis not adjusted for BMI, whereas there was no association in the analysis with adjustment for BMI (Table 9). For the remaining analyses performed by Buijsse et al. (comparisons of the first and third tertile of nut consumers versus the middle tertile of consumers), no such pattern was observed (Table 9). However, consumption levels of nuts were relatively low and the differences in nut consumption levels between the three consumption-tertiles was small, what may have limited the authors to detect associations. For the remaining studies that contributed to the MA of Arnesen et al., it was unknown whether and to what extent the adjustments for BMI impacted the study findings. These remaining studies showed heterogeneous results with both neutral, protective and harmful associations.

All five reports included in the MA were judged to have serious risk of bias by Arnesen et al., based on the Risk of Bias for Nutrition Observational Studies tool. The committee noted that the Risk of Bias tool selected by Arnesen et al. uses a target trial framework, assessing cohort studies against a hypothetical high-quality, randomised trial, with little confounding and other sources of bias. In the working method of the committee, such judgements may be too strict, because the committee evaluates the evidence from cohort studies and RCTs separately, and an integration of evidence from RCTs and cohort studies is made in a later phase (see Chapter 2 of the advisory report<sup>1</sup>), considering the evidential value and pros and cons of cohort studies and RCTs.

Most other MAs evaluated for the DDG2025 used Risk of Bias tools that are more specific for cohort studies, such as the Newcastle-Ottawa scale. Pooled analyses of EPIC studies were generally classified to have low or moderate risk of bias in other MAs used for the committees evaluation, based on the Newcastle-Ottawa scale.<sup>42-46</sup> Moreover, the studies by Kochar et al.,<sup>74</sup> and Pan et al.<sup>72</sup> (combined analysis of NHS I and NHS II) were also included in one of the MAs used for the DDG2015, and were scored as having a high quality in this MA.<sup>47</sup> Taking into account these risk of bias

judgements, and the committees working method, the committee sees no major concerns with respect to risk of bias for the studies included in the MA of Arnesen et al.

Based on the above and taking into account the decision tree, the committee concluded that findings from prospective cohort studies on the association between the combined consumption of nuts, peanuts and seeds and risk of type 2 diabetes are contradictory because there were suggestions for protective, harmful and neutral associations. Some of the studies included in the MA suggested that over-adjustment for BMI may have contributed to the heterogeneous findings. However, for part of the studies included in the MA, it was unknown whether their findings may have been obscured by BMI adjustments. Since the heterogeneity in directions of associations was also present in these studies for which the impact of BMI adjustment was unknown, the committee drew the overall conclusion that the association is contradictory.

**Table 9** Characteristics and results of meta-analyses of prospective cohort studies on the association between nuts and seeds consumption and risk of type 2 diabetes

Author, year, study design	Nuts and seeds consumption level examined	Type of analysis	N PCS	N participants; N cases	Strength of the association: RR (95% CI)	I <sup>2</sup>	Study population (n)	Risk of bias (n)
Arnesen, 2023, MA	Highest: 5 to 100 g/d; Lowest: 0 g/d.	High vs. low	5; 13	211091; 24389	0.95 (0.75, 1.21)	82%	Europe (8), USA (4), Middle East (1) <sup>c</sup>	Serious (5)
Arnesen, 2023, MA	Highest: 5 to 100 g/d; Lowest: 0 g/d.	Per +30 g/d	NR	NR	No dose-response relationship (p-value: 0.98)	NR	NR	NR
Buijsse, 2015, pooled analysis <sup>a</sup>	P5 to P95: ♂ 0.0 to 16.7 g/d; ♀ 0.0 to 15.0 g/d.	Comparing categories of intake <sup>b</sup>	8	14939 (subcohort members); 12403	Not adjusted for BMI: Non-c.: 1.11 (1.01, 1.22); Tertile 1: 1.01 (0.92, 1.11); Tertile 2: reference group; Tertile 3: 0.93 (0.79, 1.10)  Adjusted for BMI: Non-c.: 1.01 (0.91, 1.13); Tertile 1: 0.93 (0.83, 1.04); Tertile 2: reference; Tertile 3: 0.88 (0.75, 1.03)	0% 0% 49%	Europe (8)	NR
Pan, 2013, pooled analysis <sup>a</sup>	Mean in lowest - highest consumption category: 2.0-28.0 g/d	Comparing categories of intake, and per +2 servings/wk	2	137956; 5930	Not adjusted for BMI: Never/rarely: reference <1 s/wk: 0.99 (0.94, 1.06) 1 s/wk: 0.93 (0.83, 1.04) ≥2 s/wk: 0.88 (0.77, 0.99) Per +2 s/wk: 0.94 (0.90, 0.99)  Adjusted for BMI: Never/rarely: reference <1 s/wk: 1.01 (0.95, 1.08) 1 s/wk: 1.01 (0.90, 1.13) ≥2 s/wk: 1.04 (0.92, 1.18) Per +2 s/wk: 1.02 (0.97, 1.07)	NR	USA (2)	NR

Abbreviations: CI: confidence interval; Non-c.: non-consumers of nuts and seeds; NR: not reported; MA: meta-analysis; PCS: prospective cohort studies; RR: relative risk; s/wk: servings per week, one serving reflecting 28 g; USA: United States of America; vs.: versus.

<sup>a</sup> These pooled analyses were also included in the MA of Arnesen et al. For the MA of Arnesen et al., the analyses with adjustment for BMI were used.

<sup>b</sup> Mean intake values based on a 24-h dietary recall in 1261 members of the sub cohort were: non-consumers: 2.8 g/d, tertile 1: 2.5 g/d, tertile 2: 3.3 g/d, tertile 3: 8.0 g/d.

### 3.6 Body weight

The DDG2015 committee concluded that an effect of nuts on body weight is unlikely.<sup>34</sup> More recent evidence supports this conclusion, as described below. For seeds, no separate evaluation could be performed in the DDG2015. There are now sufficient studies to perform an evaluation on the effect of flax seeds on body weight.

The committee performed separate evaluations for total nuts, different types of nuts and flax seeds.

### 3.6.1 Total and different types of nuts

In the DDG2015, it was concluded that, under ad libitum conditions, an effect of consumption of extra nuts on body weight is unlikely.<sup>34</sup> This was based on the MA of Flores-Mateo et al.,<sup>75</sup> that included 26 RCTs. Findings from the more recent MA of Guarneiri et al.,<sup>76</sup> including 38 RCTs, seem to support this conclusion, because no effect on body weight was found (Table 10). The MA of Guarneiri et al. included only 12 overlapping RCTs with Flores-Mateo et al., due to differences in inclusion criteria apart from a later search date. Moreover, the committee noted that both the MAs of Flores-Mateo et al. and Guarneiri et al. mainly included RCTs that addressed effects of specific nut types and only few RCTs that investigated mixed nuts consumption. Guarneiri et al. did not clearly report whether the RCTs were performed under ad libitum conditions or isocaloric conditions. However, given there was no effect found, this more recent MA did not give reason to reconsider the 2015 conclusion. Recent MAs addressing specific types of nuts (walnuts,<sup>75,77</sup> almonds,<sup>75,78</sup> pistachios,<sup>79</sup> cashew nuts<sup>80</sup>) also suggested there is no effect on body weight (Table 10).

**Table 10** Characteristics and results of meta-analyses of randomised controlled trials on the effects of overall and different types of nuts consumption compared to various controls on body weight

Author, year	Intervention; comparison	N RCTs; <sup>a</sup> N participants	Strength of the effect: MD (95% CI), kg	I <sup>2</sup>
Flores-Mateo, 2013	i: <b>Overall nuts or peanuts:</b> 28 to 120 g/d;	In total: 26; 1650.	Total: -0.18 (-0.70, 0.37);	65%
	c: various controls, such as low-fat, habitual or healthy diet.	Of these, 4 RCTs were performed with combined nuts.	Combined nuts: -0.15 (-0.80, 0.49)	0%
Guarneiri 2021	i: <b>Overall nuts or peanuts:</b> 10 to 100 g/d;	29 without substitution restrictions;	RCTs without substitution instructions: 0.01 (-0.07, 0.08);	0%
	c: various controls, such as habitual or healthy diet, other snacks.	2353;  23 with substitution restrictions; 1383	RCTs with substitution instructions: -0.01 (-0.11, 0.09)	0%
Fang 2020	i: <b>Walnuts:</b> 15 to 108 g/d; <sup>b</sup> c: control, not further specified.	24; 2035	0.08 (-0.03, 0.20) <sup>c</sup>	41%

Author, year	Intervention; comparison	N RCTs; <sup>a</sup> N participants	Strength of the effect: MD (95% CI), kg	I <sup>2</sup>
Flores-Mateo, 2013	i: <b>Walnuts:</b> 28 to 120 g/d; <sup>b</sup> c: various controls, such as low-fat, habitual or healthy diet.	9; 376	-0.34 (-1.66, 0.97)	78%
Eslampour 2020	i: <b>Almonds:</b> 10 to 100 g/d; c: various controls, such as usual or reference diet, other snacks.	28 studies; 35 comparisons; 1688	-0.38 (-0.65, -0.10)	31%
Flores-Mateo, 2013	i: <b>Almonds:</b> 28 to 120 g/d; <sup>b</sup> c: various controls, such as low-fat, habitual or healthy diet.	9; 394	-0.58 (-3.86, 2.70)	68%
Xia 2020	i: <b>Pistachios:</b> 40 to 70 g/d or 10 to 20% of energy; c: various controls, such as no pistachios, low-fat diet, other snacks.	9; 1461	0.22 (-0.50, 0.07)	0%
Jamshidi 2021	i: <b>Cashew nuts:</b> 28 to 42 g/d; c: control, not further specified.	5; 478	0.02 (-1.04, 1.09)	0%

Abbreviations: c: comparison; CI: confidence interval; i: intervention; MD, mean difference; kg: kilogrammes; NR: not reported; RCT, randomised controlled trial.

<sup>a</sup> For subgroup analyses based on type of nuts, only subgroups including 3 or more studies are reported.

<sup>b</sup> This intake range applies to all types of nuts addressed in the MA. The range of intake of this specific type of nut falls within this intake range.

<sup>c</sup> Additionally, the authors reported that there was evidence for a non-linear dose-response curve, with walnut intake reducing body weight (-1.62 kg) in dosages up till 35 g/d.

### 3.6.2 Flax seeds

Summary of evidence for the effect of flax seeds consumption compared to various controls on body weight

Aspect	Explanation
Available studies	One meta-analysis of 18 randomised controlled trials <sup>81</sup>
Heterogeneity	Yes, in magnitude <sup>81</sup>
Strength of the association	Mean differences (95% CI) for intervention versus control group: -1.75 (-2.87, -0.63) kg <sup>81</sup>
Consumption level examined	Range: 25 to 90 g/d <sup>81</sup>
Population	United States of America, Canada, South-America, Asia; <sup>81</sup>

**Conclusion: Consumption of flax seeds lowers body weight.**

**Evidence level: Limited**

**Additional remark: Flax seed consumption in the range between 25 and 90 grammes per day was investigated in studies underlying this conclusion.**

### *Explanation*

The MA of Mohammadi-Sartang et al.,<sup>81</sup> including 18 RCTs, was included in the committee's evaluation. The effect of whole flax was assessed in a subgroup analysis by Mohammadi-Sartang et al., with the main MA also including RCTs on flax seed lignans and oils. The subgroup analysis selected for the committee's evaluation investigated the effects of whole flax seeds, including grounded and defatted flax seeds. Consumption levels varying between 25 and 90 g/d were investigated. The authors did not report whether the included RCTs were performed in ad libitum or isocaloric settings. Also, the authors did not report whether studies with participants following an energy restricted diet were included. The durations of the interventions varied between 3 and 48 weeks.

The MA of Mohammadi-Sartang et al. showed that the consumption of flax seeds decreased body weight with 1.75 kg (Table 11). There was substantial heterogeneity between RCT-findings. Visual inspection of the forest plot showed that the heterogeneity was mainly in magnitude of the effect, and not in direction. As the category of whole flaxseeds was already a subgroup, the authors did not perform further subgroup analyses that might explain this heterogeneity. However, the authors performed subgroup analyses for the main analysis (also including flax seed lignans and oils). These showed that the effect of flax seed interventions on body weight was stronger in RCTs with higher doses of flax seeds (>30 g/d), of lower quality (further described below), with longer follow-up durations ( $\geq 12$  weeks), and in participants with higher baseline BMI ( $\geq 27$  kg/m<sup>2</sup>).

The risk of bias was judged as low in 8 RCTs (high quality) and as high in 10 RCTs (low quality) by Mohammadi-Sartang et al., based on the Jadad scale. The authors reported that a large proportion of the included RCTs did not adequately explain the randomisation and/or blinding procedure, but no detailed descriptions of the potential sources of bias per study were given. For the main analysis (also including flax seed lignans and oils), the effect of flax seed interventions on body weight was stronger in RCTs with a high risk of bias (n=14, -2.19 kg) than in RCTs with a low risk of bias (n=16, -0.15 kg). The reduction in BMI was statistically significant only in the RCTs with high risk of bias

Mohammadi-Sartang et al. reported evidence for funnel plot asymmetry based on visual inspection of funnel plots for the main analysis (also including flax seed lignans and oils). However, this was not statistically significant according to a Begg's rank correlation test and an Egger's linear regression test. The funnel plot asymmetry might be the result of publication bias, but might also be due to other causes (e.g. heterogeneity between larger and smaller studies).

The authors of this MA reported no conflicts of interest. The type of funding for individual RCTs (e.g. agency or industry) was not reported.

Based on the above, and taking into account the decision tree, the committee concluded that there is limited evidence that consumption in the range of 25 to 90 g/d of flax seeds lowers body weight. The evidence was judged limited because it was unknown whether the RCTs were performed under ad libitum or isocaloric conditions, and as part of energy restricted or regular diets. There was substantial heterogeneity in effects, which the authors did not directly explain for studies on whole flax seed. Subgroup analyses of the main analysis, which also included RCTs on flax seed lignans and oils, suggested differences in results between

**Table 11** Characteristics and results of meta-analyses of randomised controlled trials on the effect of flax seed consumption compared to various controls on body weight

Author, year, study design	Intervention; comparison	N RCTs; N participants	Strength of the effect: MD (95% CI), kg	<i>I</i> <sup>2</sup>	Study populations (n)	Risk of bias (n)
Mohammadi-Sartang, 2017, MA	i: 25 to 90 g/d of whole flax seeds (n=13), grounded flax seeds (n=4), or defatted flax seeds (n=1); c: various controls, such as unspecified control, sunflower seeds, raw rice, collagen, moniac flour, wheat germ/ bran, lifestyle counselling	18; 1169	-1.75 (-2.87, -0.63)	62%	USA (4), Canada (4), South-America (3), Asia (7) <sup>a</sup>	High quality (8), low quality (10)

Abbreviations: c: comparison; CI: confidence interval; i: intervention; kg: kilogrammes; MA: meta-analysis; MD: mean difference; RCT: randomised controlled trial; USA: United States of America.

<sup>a</sup> In terms of health status, the following populations were included: healthy people (n=1), populations with hypercholesterolemia (n=4), a population with cardiovascular disease (n=1), populations with obesity (n=2), a population with dyslipidaemia (n=1), a population with peripheral arterial disease (n=1), a population with non-alcoholic fatty liver disease (n=1), populations with metabolic syndrome (n=2), a population with type 2 diabetes (n=1), haemodialysis patients (n=1), postmenopausal women (n=3).

### 3.7 Total cancer

In the DDG2015, total cancer was not addressed as health outcome in relation to nuts and seeds consumption.<sup>34</sup> The MA of Aune et al.<sup>50</sup> suggested, based on 8 prospective cohort studies, that a relatively higher overall consumption of nuts is associated with a lower risk of total cancer, with moderate heterogeneity between studies (Table 12). The heterogeneity was mainly due to differences in the magnitude of the associations, and not in the directions of associations.

The MA of Aune et al. also included analyses on the associations between peanut consumption and risk of total cancer, based on 5 cohort studies. These also suggested beneficial associations, but the associations with peanuts were somewhat weaker than with total nuts, and only statistically significant in the analysis of the highest versus lowest intake category (Table 12).

**Table 12** Characteristics and results of meta-analyses of prospective cohort studies on the association between nuts consumption and risk of total cancer

Author, year	Type of analysis	N PCS; N cases	Strength of the association: RR (95% CI)	I <sup>2</sup>
Aune, 2016	Highest versus lowest	Total nuts: 8; 17603.	Total nuts: 0.82 (0.74, 0.89);	28%
		Peanuts: 5 cohorts.	Peanuts: 0.93 (0.87, 0.99)	19%
Aune, 2016	Per +28 g/d for total nuts; Per +10 g/d for peanuts	Total nuts: 8; 17603.	Total nuts: 0.85 (0.76, 0.94);	42%
		Peanuts: 5 cohorts.	Peanuts: 0.92 (0.82, 1.03)	30%

Abbreviations: CI: confidence interval; NR, not reported; PCS, prospective cohort studies; RR, relative risk.

### 3.8 Cardiovascular outcomes

In the background document on nuts and seeds belonging to the DDG2015,<sup>34</sup> the effects of the PREDIMED trial<sup>82</sup> on cardiovascular outcomes were described. No conclusions were drawn based on the evidence from this RCT because one RCT is not enough to base a conclusion on.

Due to irregularities in the randomisation procedure, the data of this RCT were re-analysed in 2018. The updated results were not substantially different, and are described below.

In this RCT, people at high risk of cardiovascular disease were randomised into three groups. Two groups were advised to adopt a Mediterranean diet, of which one group was provided 30 g/d of nuts (15 g walnuts, 7.5 g hazelnuts and 7.5 g almonds; n=2454) and one group was provided extra-virgin olive oil (n=2543). The third group (control group) was advised to eat less fat (n=2450). The realised contrast in nut consumption between the group that was provided nuts and the control group was 22 g/d at the end of the intervention period. In the group that was provided the nuts, the incidence of major cardiovascular events (primary outcome) was 28% lower compared to the control group (Hazard ratio [HR] 0.72; 95% CI: 0.54, 0.95). Regarding secondary endpoints, the incidence of stroke was 46% lower (HR=0.54; 95% CI: 0.35, 0.82) and the incidence of myocardial infarction 24% lower (HR 0.76; 95% CI: 0.47, 1.25) in the group provided with nuts compared to the control group. The effect on myocardial infarction was not statistically significant.

The committee noted that concerns have been raised on methodological aspects of the RCT, such as the possibility of inflated risk estimates because the RCT was stopped early, imbalances in medical care between groups, and the unmasked design (including for personnel and outcome assessors).<sup>83-85</sup>

As was addressed in the DDG2015 background document, the group that was provided nuts, was also advised to adopt a Mediterranean style diet. Thus, the observed effects may be attributable to multiple dietary components, including nuts, but also components such as olive oil, fruits, and vegetables.

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# Annexes

## A Working group

The following working group prepared this background document:

### **Working group on nuts and eggs and chronic diseases**

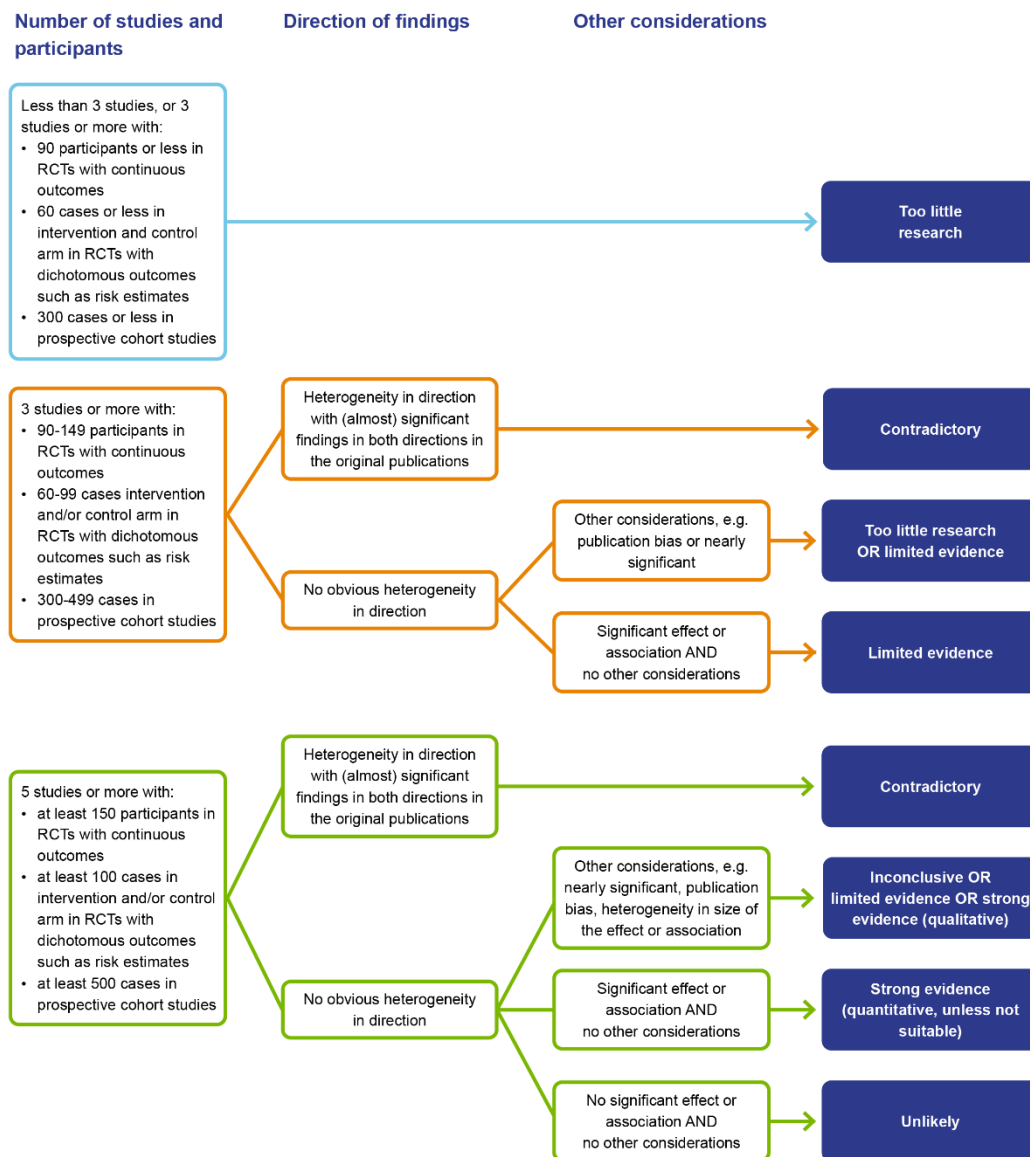
- Prof. J. Plat, Professor of Physiology of Nutrition, Maastricht University, *chair of the working group*
- Prof. L. Afman, Professor Nutrition Metabolism and Genomics, Wageningen University & Research
- Prof. E.E. Blaak, Professor of Humane Biology with special emphasis on Nutrition and Obesity, Maastricht University
- Dr J.A.E. Langius, dietician, principal researcher-lecturer Nutrition and Dietetics, The Hague University of Applied Sciences, The Hague
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## B Decision tree

The decision tree below was used as a guidance tool by the committee on Nutrition for drawing conclusions based on scientific evidence from meta-analyses and pooled analyses of randomised controlled trails or prospective cohort studies.



The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Fisheries, Food Security and Nature. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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

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