Plantaardige voedingspatronen

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Index

1 Introduction

In 2014, a background document[1] on dietary patterns was created for the Dutch Dietary Guidelines 2015.[2] One of the dietary patterns of interest was a plant-based diet (including vegetarian and vegan diets). This literature search was conducted until July 2014. In the Dutch Dietary Guidelines 2015 report, the committee concluded that there was convincing evidence for an association of a vegetarian dietary pattern with a reduced risk of coronary heart disease (-25%) as compared to a non-vegetarian diet.[2] The committee also concluded that a vegetarian diet reduced systolic blood pressure by 5 mmHg and diastolic blood pressure by 2 mmHg.[2]

Since then, the interest in the potential health benefits associated with plant-based diets is increasing. The aim of the current background document was to update the literature since 2014 on plant-based diets (including vegetarian and vegan diets).

2 Main findings and conclusions

2.1 Main findings

Results from systematic reviews (SRs) and meta-analyses (MAs) of observational studies since 2015 show inverse associations of plant-based and vegetarian diets with coronary heart disease (mortality):

- A plant-based diet was associated with a lower risk of coronary heart disease mortality: HR= 0.77 (95%CI 0.70-0.86) – MA of 8 cohort studies
- Plant-based diet was associated with a lower risk of coronary heart disease: RR= 0.88 (95%CI 0.81-0.94) – 6 cohort studies
- Vegetarian diet was associated with a lower risk of coronary heart disease mortality: HR= 0.76 (95%CI 0.68-0.85) – 7 cohort studies.

In addition, an association of plant-based diets with lower risk of all-cause mortality, cardiovascular disease and type 2 diabetes was observed:

- Plant-based diet - all-cause mortality: RR= 0.90 (95%CI 0.82-0.99) Meta-analysis of 12 prospective cohort studies
- Plant-based diet – cardiovascular disease: RR= 0.84 (95%CI 0.79-0.89) – 9 cohort studies
- Plant-based diet – type 2 diabetes: RR= 0.77 (95%CI 0.71-0.84) – 9 cohort studies
- Vegetarian diet – cardiovascular mortality: HR= 0.92 (95%CI 0.85-0.99) – 5 cohort studies

Risk estimates of other exposure and health outcome associations were not statistically significant.

Results from SRs and MAs of controlled trials with intermediate outcomes show that, as compared to omnivorous diet:

- vegetarian diets reduce systolic blood pressure (5 mmHg) and diastolic blood pressure (2 mmHg) (1 MA).
- vegetarian diets reduce LDL-cholesterol and body weight but with heterogeneity in effect sizes. vegan diets reduce LDL-cholesterol (4 RCTs) and body weight (8 RCTs), but not blood pressure.

2.2 Conclusions

- Current findings were not weighed for strength of evidence and hence interpreted as supporting evidence for earlier conclusions on plant-based diets.
- The inverse associations of plant-based and vegetarian diets with coronary heart disease (mortality) support the conclusion of the 2015 advisory report that there

is convincing evidence for an association of a vegetarian dietary pattern with a reduced risk of coronary heart disease.

- Additional findings on associations of plant-based diets with lower risk of all-cause mortality, cardiovascular disease and type 2 diabetes are seen by the committee as additional support for the health benefits of plant-based diets.
- Results from intervention trials with intermediate outcomes (blood pressure, LDL-cholesterol and body weight) indicate that plant-based diets reduce some risk factors outcomes and hence have no adverse effects on any of these risk factors.

3 Methodology

3.1 Exposures

In this background document, the committee evaluated the exposure plant-based dietary patterns, including vegetarian and vegan dietary patterns. The committee considered studies on different types of plant-based diets including adherence to the Plant-based Dietary Index (PDI), vegetarian, vegan, flexi, semi, lacto-, lacto-ovo-, and pesco-vegetarian diet. Although rich in plant-based foods, the Mediterranean diet, Nordic diet and other healthy diets were not included since these diets also include other dietary changes (e.g. limited salt or alcohol). Included evidence is restricted to dietary patterns that were defined in advance (*a priori*), such as a Plant-based Dietary Index (PDI), a Plant-based Diet Quality Index (PDQI), and a vegetarian or vegan diet. Findings on *a posteriori* defined dietary patterns are not considered by the committee. While *a posteriori* studies are suitable for hypothesis generating, *a priori* defined dietary patterns are suitable for hypothesis testing.

Dietary patterns that were based on nutrients or on the nutrient density instead of on food groups were not considered in this document.

Definitions of plant-based dietary patterns varied considerably between studies, as they englobe a range from slightly more plant-based products in the diet (as compared to the reference diet) to fully plant-based diets. In addition they can differ based on the underlying country-specific diet or dietary guidelines. Furthermore, some analyses identified healthy versus unhealthy plant-based diets.

Plant-based diets often (but not only) include vegetarian and/or vegan diets in their definition. Vegetarian and vegan diets were most often considered separately in MA, but sometimes vegetarian diets included a vegan diet in its definition. For this reason, an overview of the different definitions for plant-based diets, vegetarian, and vegan diets used in each SR is provided at the beginning of each chapter. Related to the overlap in definitions, there is some overlap in results between chapters in this background document.

The fact that definitions of plant-based diets were broad could be a source of heterogeneity within the included MAs. This is especially the case for the exposures ‘plant-based diets’ and ‘vegetarian diets’, as compared to the exposure ‘vegan diets’, where definitions between studies are more similar.

3.2 Health outcomes

The committee aimed at describing the available evidence on the associations between plant-based dietary patterns and disease outcomes and mortality. The outcomes that were considered by the committee for this background document are the long-term health outcomes that were included in the Dutch Dietary Guidelines 2015.[3] The committee considered fractures as an additional potentially relevant health outcome:

- All-cause mortality
- Coronary heart disease
- Cerebrovascular disease/stroke
- Cardiovascular disease/myocardial infarction
- Type 2 Diabetes
- Chronic Obstructive Pulmonary Disease (COPD)
- Breast cancer
- Colorectal cancer
- Lung cancer
- Dementia
- Depression
- Fractures

In line with the methodology for the Dutch Dietary Guidelines 2015,[3] the committee considered controlled trials with intermediate outcomes which are causal risk factors for disease outcomes:

- Blood pressure
- LDL-cholesterol
- Body weight

3.3 Study types

Selected studietypes were SRs and MAs (and pooled analyses). With respect to health outcomes, SRs of prospective cohort studies and/or controlled trials were eligible for inclusion. For the intermediate outcomes (blood pressure, LDL-cholesterol and body weight), only controlled trials were included.

3.4 Literature selection

The present background document provides an update of the literature on plant-based diets since the Dutch Dietary Guidelines 2015.[2] The literature search for the Dutch Dietary Guidelines 2015 included scientific papers that were published until July 2014. Therefore, the current literature search started from that date and captured literature until May 2022 (see Appendix A). A MA should contain at least three individual studies (prospective cohort studies or controlled trials) per association to be included.

Furthermore, if there were three prospective cohort studies describing an association, there had to be at least 300 cases in order for the committee to describe the association. When there were less than three prospective cohort studies, the committee did not describe the results found for the association in this background document.

3.5 Data extraction

Study characteristics and outcomes

Information on exposures and health outcomes was extracted from papers as well as a description of the study population, the number of participants, number of cases, risk estimates.

Heterogeneity

Heterogeneity was addressed as follows: the committee indicated in the summary Table that there was no heterogeneity between studies if I^2<25% or if heterogeneity was moderate (I^2 25-50%). In the latter case, heterogeneity was considered in the text. The committee indicated that there was heterogeneity between individual cohort studies if I^2 was 50% or higher and p<0.10. Furthermore, possible explanations for this heterogeneity were discussed in the text. The committee distinguishes between heterogeneity in the direction and size of the risk estimates. When heterogeneity is present in the size of the risk estimate there is uncertainty about the size of the association, and when heterogeneity is present in the direction of the risk estimate, the association is ambiguous.

Conflicts of interest and funding

None of the authors of the included SRs and MAs in this background document declared any conflicts of interests. Most had no funding declared, and the ones that did declared that funders did not have any role in the design, analysis, write-up, or decision to submit the publication.

4 Results from observational studies: health outcomes

In this chapter, the committee describes the evidence on the relation between plant-based dietary patterns and the effect on disease outcomes and mortality.

Based on the available evidence the committee could distinguish three plant-based dietary patterns: 1) plant-based diets, 2) vegetarian diets, and 3) vegan diets.

4.1 Plant-based diets

This paragraph describes the scientific evidence from SRs of prospective cohort studies on the associations between a plant-based diet and the disease outcomes all-cause mortality, risk of cardiovascular disease and mortality, risk of coronary heart disease and mortality, risk of stroke, and risk of type 2 diabetes. First, an overview of the different definitions of plant-based diets used in the different SRs is provided in Table 1. Since definitions of plant-based diets and its subtypes can vary, the definitions used in the individual prospective cohort studies of one of the SRs (Jafari et al. 2022)[4] are shown in Table 2 in order to elucidate the different definitions that exist.

Table 1 Definitions plant-based diets in the included systematic reviews

SR	Definition plant-based diet
Jafari et al. (2022)[4]	Plant-based eating style including Plant-based Dietary Index (PDI) score, and vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diets
Quek et al. (2021)[5]	Plant-based dietary patterns, defined as higher consumption of plant-based foods and lower consumption or exclusion of animal-based foods. Vegetarian or vegan dietary patterns are classified under plant-based dietary patterns. What higher and what lower consumption specifically means is not described.
Gan et al. (2021)[6]	Plant-based diets (PBDs) are generally characterized by a lower consumption or avoidance of animal foods and a higher intake of plant foods. Vegetarian and vegan diets are the most restrictive, but PBDs may include eating patterns that are plant-dominant, while consuming some but fewer animal foods. What fewer specifically means is not described.
Qian et al. (2019)[7]	Defined as higher consumption of plant-based food and lower consumption or exclusion of animal-based foods. By this definition, vegetarian dietary patterns or vegan dietary patterns were also considered PBDs. Included studies with exposure: Plant-based dietary patterns, defined by emphasis of plant-based foods and de-emphasis or avoidance of animal foods, assessed using validated dietary assessment methods (i.e. the primary dietary method was compared to another method, e.g. food diary or blood biomarkers). No specific definition for an emphasis on plant-based foods is provided.

Abbreviations: PBD: Plant-based diet; PDI: Plant-based Dietary index

Table 2 Definitions plant-based diets used in the individual prospective cohort studies within the SR of Jafari et al. (2022)[4]

Diet	Individual study within Jafari et al. (2022)	Definition
Plant-based Dietary Quality Index (PDQI)	Keaver et al. (2021)	The Comprehensive Diet Quality Index (cDQI) assesses the quality of seventeen foods based on the healthfulness and separately scored the quality of eleven plant-based foods (whole grains, vegetables excluding white potatoes, whole fruits, nuts/seeds/legumes, vegetable oils, coffee/tea, refined grains, fruit juices, sugar-sweetened beverages and sweets/desserts) in a plant-based Diet Quality Index (pDQI) and six animal foods (fish/seafood, dairy products, poultry, processed meats, unprocessed red meats, and eggs) in an animal-based Diet Quality Index (aDQI). Healthful plant- and animal foods scored positively, while unhealthful plant-and animal foods scored reversely. A total of 85 points could be scored (55 for plant-based foods and 30 for animal-based foods).
Plant-based Dietary Index (PDI; healthy and unhealthy, ad provegetarian diet index)	Kim et al. (2019); Kim, Caulfield, and Rebholz (2018)	For the *overall* PDI, participants with a higher intake of healthy and less healthy plant foods received higher scores than those with a lower intake. Intake of animal foods was reversly scored. For the *healthy* PDI, higher intake of only the healthy plant foods received higher scores, while intake of less healthy plant foods and intake of animal foods received reverse scores. For the *unhealthy* PDI, higher intake of only the less healthy plant foods received higher scores, while healthy plant foods and animal foods received reverse scores. For the provegetarian diet index, higher intake of selected plant foods (including grains, fruits, vegetables, nuts, legumes, and potatoes) received higher scores while animal foods received reverse scores. Specific definitions of healthy and unhealthy foods are not provided.

Diet	Individual study within Jafari et al. (2022)	Definition
Vegetarian	Mihrshahi et al. (2017)	Mihrshahi 2017: no meat consumption
	Orlich et al. (2013)	Orlich 2013: combination of four categories (vegan, lacto-ovo-, semi- and pesco-vegetarian) as vegetarian diets
	Key et al. (2009)	Key 2009: vegetarians (those that do not eat meat or fish but do eat dairy products or eggs or both)
	Chang-Claude et al. (2005)	Chang- Claude 2005: vegetarians are combination of vegans (those who avoid meat, fish, eggs, and dairy products) and lacto-ovo vegetarians (those who avoid meat and fish but eat eggs and/or dairy products)
	Key et al. (1996)	Key 1996: NR
	Thorogood et al. (1994)	Thorogood 1994: did not eat meat or fish or ate these foods less than once a week, but did eat eggs or dairy products, or both
	Snowdon (1988)	Snowdon 1988: animal product consumption (analyses on meat consumption, egg, milk, cheese, where per food group people with highest intakes are compared with those with lowest intakes)
Vegan	Orlich et al. (2013)	Consumption of eggs/dairy, fish, and all other meats less than 1 time/mo
Semi-vegetarian	Mihrshahi et al. (2017)	Mihrshahi 2017: eat meat 0 or ≤1 times per week
	Orlich et al. (2013)	Orlich 2013: consumption of nonfish meats ≥1 time/mo AND all meats combined (fish included) ≥1 time/mo but ≤1 time/wk
Lacto-ovo-vegetarian	Orlich et al. (2013)	Lacto-ovo–vegetarians consumed eggs/dairy 1 time/mo or more but fish and all other meats less than 1 time/mo
Pesco-vegetarian	Mihrshahi et al. (2017)	Mihrshahi 2017: Consumption of fish ≥1 per week and no consumption of other meats
	Orlich et al. (2013)	Orlich 2013: fish 1 time/mo or more but all other meats less than 1 time/mo
Provegetarian	Martínez-González et al. (2014)	In this context, a food pattern that positively weighs vegetable-derived foods and negatively weighs animal-derived foods can be conceptualized as a progressive and gentle approach to vegetarianism (ie, a “pro- vegetarian” food pattern) that incorporates a range of progressively increasing proportions of plant-derived foods (vegetables, fruit, legumes, cereals, potatoes, nuts, olive oil) and concomitant reductions in animal-derived foods (meats/meat products, animal fats for cooking and spreads, eggs, fish and other seafood, dairy products).

Abbreviations: cDQI: Comprehensive Diet Quality Index; PBD: Plant-based diet; PDI: Plant-based Dietary index; PDQI: Plant-based Dietary Quality Index; NR: not reported

4.1.1 All-cause mortality

Summary plant-based diets and all-cause mortality

Aspect	Explanation
Selected studies	1 MA of 12 prospective cohort studies (Jafari et al. 2022)[4] and 1 additional prospective cohort study (Baden et al. 2019)[8]
Heterogeneity	Yes (high heterogeneity of 91% in the MA, p<0.001)
Strength of the association	HR MA= 0.90 (95%CI 0.82-0.99) HR individual cohort study= 0.95 (95%CI 0.90-1.00)
Study population	General adult population (≥18y), Western countries

Abbreviations: CI: confidence interval; HR: hazard ratio; y: years

There were two SRs of prospective cohort studies on the association between plant-based diets (PBDs) and the risk of all-cause mortality (Boushey et al. 2020, and Jafari et al. 2022).[4,9] The SR by Jafari et al. (2022)[4] investigated the association between PBDs and all-cause mortality, as well as with cause-specific mortality. Besides being more recent, the SR of Jafari et al. (2022)[4] performed a MA (MA) of twelve prospective cohort studies on the association between PBDs and the risk of all-cause mortality. All but one (Baden et al. 2019)[8] of the prospective cohort studies on the association between PBDs and all-cause mortality included in the SR of Boushey et al. (2020)[9] were included in the MA of Jafari et al. (2022)[4]. For this reason, only the MA of Jafari et al. (2022)[4] is described in Table 3a. The prospective cohort study included in Boushey et al. (2020)[9] and excluded by Jafari et al. (2022)[4] (due to lack of information on cause-specific mortality) is described separately (Baden et al. 2019)[8] and presented in Table 3b.

The MA by Jafari et al. (2022)[4] investigated the association between PBDs with the risk of all-cause mortality in the general adult population. A total of twelve prospective cohort studies were included that looked at this association. Included studies had follow-up periods ranging from 4.8 to 25 years and considered different types of PBDs including adherence to (*a priori*) defined Plant-based Dietary Index (PDI; healthy (hPDI) and unhealthy (uPDI)), or to a vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet as exposure of interest. When a cohort study had results on different types of diet indexes (e.g. healthy or unhealthy) or diets (e.g. vegetarian, vegan, semi-, lacto- vegetarian diet, etc.), only the results on PDI or the main vegetarian diet were included in the main analysis of Jafari et al. (2022)[4]. For collecting dietary intakes, five cohort studies used a food-frequency questionnaire (FFQ), one cohort study used a dietary recall, and six cohort studies used a short general questionnaire. Three of the included studies compared the highest vs. lowest category of PBDs, three studies compared vegetarians vs. meat-eaters, five studies compared vegetarians vs. non-

vegetarians, and one study reported risk estimates based on the per 10-unit increase in dietary scores.
In their overall MA, Jafari et al. (2022)[4] found a statistically significant association between adherence to PBDs (referring to highest vs. lowest category PDI, or to vegetarian vs non-vegetarian or meat-eaters) and the risk of all-cause mortality (pooled RR= 0.90; 95%CI 0.82-0.99, n=12 prospective cohort studies). Heterogeneity was high (I^2=91%, p<0.001). Visual inspection of the forest plot indicated that heterogeneity was present in the direction and size of the risk estimates. The authors were not able to identify the potential sources of heterogeneity from the subgroup analyses. Sensitivity analyses showed that the risk estimate remained statistically significant when omitting one cohort at a time. Subgroup analyses showed that when pooling cohort studies that controlled for BMI or for alcohol consumption, the association was no longer statistically significant (adjusting for BMI: RR= 0.93, 95%CI 0.77-1.11, I^2= 93.4%, p<0.001, n= 4 cohort studies; adjusting for alcohol consumption: RR= 0.91, 95%CI 0.81-1.02, I^2= 91.5%, p<0.001, n= 9 cohort studies). These findings do not explain the large heterogeneity found in the main analysis. Other subgroup analyses showed a statistically non-significant inverse association between adherence to a vegetarian diet and risk of all-cause mortality (RR= 0.96, 95%CI 0.87-1.05, I^2= 81%, p= 0.00, n= 8 prospective cohort studies). This finding will be discussed more in detail in the chapter on vegetarian diets. Subgroup analysis showed a statistically non-significant association between the adherence to a PBD assessed with PDI and the risk of all-cause mortality (RR= 0.80, 95%CI 0.61-1.05, I^2= 97.3%, p= 0.00, n= 3 studies and >300 cases. Subgroup analyses on vegan, lacto-ovo-, pesco-, semi-, and provegetarian diet, as well as on hPDI, and uPDI were presented in the paper but had too few studies (maximum of two) and are therefore not described in this background document.

The prospective cohort study by Baden et al. (2019)[8] investigated the associations between 12-year changes in PBD quality and all-cause and cause-specific mortality in 49,407 healthy women from the Nurses Health Study and 25,907 healthy men from the Health Professionals Follow-Up Study. PBD quality was assessed by three PBD indices, namely an overall plant-based diet index (PDI), a healthful PDI (hPDI), and an unhealthful PDI (uPDI). There were a total of 17,176 deaths and results showed that participants with the greatest increases in PDI and hPDI scores had a lower risk of all-cause mortality compared with participants whose indices remained stable (HR= 0.95, 95%CI 0.90-1.00 for PDI and HR= 0.90, 95%CI 0.85-0.95 for hPDI), whereas participants with the greatest increases in uPDI scores had a higher risk of all-cause mortality (HR= 1.12, 95%CI 1.07-1.18 for uPDI). Participants whose indices remained stable (n= 11,735 participants) had similar initial diet scores than participants who

showed increases or decreases in diet scores (decreases in diet scores: n= 10,861 participants; increases in diet scores: n= 9,550 participants).

Table 3a Results from the mZeta-analysis of Jafari et al. (2022)[4] on the association between plant-based diets and the risk of all-cause mortality.

Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
12	Highest versus lowest category of adherence to PBD	508,861	42,697	0.90 (0.82-0.99)	91%	General adult population (≥18y); Europe, USA, Australia

Abbreviations: PBD: plant-based diet; CI: confidence interval; N: number; RR: relative risk; USA: United States of America; y: years

Table 3b Results from the individual cohort study of Baden et al. (2019)[8] on the association between change in plant-based diet score and the risk of all-cause mortality.

Exposure	N participants	N cases	RR estimate (95% CI)	Study population
Change in PBD quality score	75,314	17,176	0.95 (0.90-1.00)	Healthy adults - USA

Abbreviations: PBD: plant-based diet; CI: confidence interval; N: number; RR: relative risk

4.1.2 Cardiovascular disease mortality

Summary plant-based diets and cardiovascular disease mortality

Aspect	Explanation
Selected studies	1 MA of 7 prospective cohort studies each (Jafari et al. 2022)[4]
Heterogeneity	Yes (high heterogeneity of 78%, p<0.001)
Strength of the association	HR= 0.90 (95%CI 0.79- 1.02)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; HR: hazard ratio; y: years

The committee found two MAs of both seven prospective cohort studies on the association between plant-based diets (PBDs) and cardiovascular disease (CVD) mortality (Jafari et al. 2022, and Quek et al. 2021).[4,5] The MAs of Jafari et al. (2022)[4] and Quek et al. (2021)[5] seem to overlap in four of the included prospective cohort studies (Orlich et al. 2013, Martinez-Gonzalez et al. 2015, Kim, Caulfield, and Rebholz 2018, and Kim et al. 2019). However, Quek et al. (2021)[5] lacked a description on which seven cohort studies their MA on CVD mortality was based on. Therefore, the overlap in studies between Jafari et al. (2022)[4] and Quek et al. (2021)[5] could only be judged based on the description of the overall included cohort studies in both MAs (respectively 12 and 13). Moreover, due to the minimal description provided in Quek et al. (2021)[5] the committee was not able to fully comprehend their results. Therefore, the committee based its description of the association between PBDs and CVD mortality on the findings of Jafari et al. (2022) (Table 4).[4] It is worth noting that the results on the association between PBDs and CVD mortality of Quek et al. (2021)[5] were very similar to those of Jafari et al. (2022)[4]: pooled HR= 0.92, 95%CI 0.86-0.99, I^2= 88.5%, n= 7 cohort studies.

The study by Jafari et al. (2022)[4] investigated the association between PBDs with the risk of all-cause mortality and cause-specific mortality in the general adult population. A total of twelve prospective cohort studies were included with follow-up periods ranging from 4.8 to 25 years and that considered different types of PBDs including adherence to (*a priori*) defined Plant-based Dietary Index (PDI; healthy (hPDI) and unhealthy(uPDI)), or to a vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet as exposure of interest. When a cohort study had results on different types of diet indexes (e.g. healthy or unhealthy) or diets (e.g. vegetarian, vegan, semi-, lacto- vegetarian diet, etc.), only the results on PDI or the main vegetarian diet were included in the main analyses of Jafari et al. (2022).[4] Seven of the twelve cohort studies reported on the association between PBDs and the risk of CVD mortality. Of these, four studies used a FFQ and three studies used a short general questionnaire to assess dietary intake. Five studies compared vegetarians vs. non-vegetarians, one

study compared the highest vs. lowest category of PBDs, and one study reported effect estimates based on the per 10-unit increase in dietary scores. All cohort studies adjusted for age and smoking status, six cohort studies adjusted for sex, four cohort studies adjusted for physical activity, and two cohort studies adjusted for energy intake and BMI.

Results showed a non-significant association between adherence to PBDs (referring to highest vs. lowest category PDI, or to vegetarian vs non-vegetarian or meat-eaters) and the risk of CVD mortality (HR= 0.90; 95%CI 0.79-1.02, I2= 78%, p<0.001, n= 7 prospective cohort studies). Heterogeneity was high (hence: I^2= 78%). Visual inspection of the forest plot indicated that heterogeneity was present in the direction and size of the risk estimates. One study (Kim et al. 2018) had a risk estimate in opposite direction of the other six studies. It is not clear why this study showed results in opposite direction. Subgroup analyses showed that when pooling cohort studies that did not control for blood pressure or for energy intake, the association was statistically significant (without adjustment for blood pressure: HR= 0.85, 95%CI 0.72-0.99, I^2= 69%, p= 0.02, n= 4 cohort studies; and without adjustment for energy intake: HR= 0.90, 95%CI 0.82-0.99, I^2= 0%, p= 0.96, n= 4 cohort studies). Subgroup analysis on cohort studies that investigated the adherence to a vegetarian diet and the risk of CVD mortality showed a statistically significant inverse association (HR= 0.92, 95%CI 0.85-0.99, I^2= 0%, n= 5 prospective cohort studies). This finding will be discussed in more detail in the chapter on vegetarian diets. However, the committee notes that type of diet might be a potential explanation for the difference in heterogeneity between the main analysis and this subgroups analysis on vegetarian diets. Subgroup analyses on vegan, lacto-ovo-, pesco-, semi-, and provegetarian diet, as well as on PDI, hPDI, and uPDI were presented by the authors but had too few studies (maximum of two) and are therefore not described in this background document.

Table 4 Results from the meta-analysis of Jafari et al. (2022)[4] on the association between plant-based diets and the risk of cardiovascular disease mortality.

Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
7	Highest versus lowest category of adherence to PBD	168,294	5,349	0.90 (0.79-1.02)	78%	General adult population (≥18y); Europe, USA, Australia

Abbreviations: PBD: plant-based diet; CI: confidence interval; N: number; RR: relative risk; USA: United States of America; y: years

4.1.3 Coronary heart disease mortality

Summary plant-based diets and coronary heart disease mortality

Aspect	Explanation
Selected studies	1 MA of 8 prospective cohort studies (Jafari et al. 2022)[4]
Heterogeneity	No (moderate heterogeneity of 36%, p=0.01)
Strength of the association	HR= 0.77 (95%CI 0.70-0.86)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; HR: hazard ratio; y: years

There was one MA that investigated the association between plant-based diets (PBDs) with the risk of coronary heart disease (CHD) mortality (Jafari et al. 2022) (Table 5).[4]

The study by Jafari et al. (2022)[4] investigated the association between PBDs with the risk of all-cause mortality and cause-specific mortality in the general adult population. A total of twelve prospective cohort studies were included with follow-up periods ranging from 4.8 to 25 years and that considered different types of PBDs including adherence to (*a priori*) defined Plant-based Dietary Index (PDI; healthy (hPDI) and unhealthy (uPDI)), or to a vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet as exposure of interest. When a cohort study had results on different types of diet indexes (e.g. healthy or unhealthy) or diets (e.g. vegetarian, vegan, semi-, lacto-vegetarian diet, etc.), only the results on PDI or the main vegetarian diet were included in the main analyses of Jafari et al. (2022). Eight of the twelve cohort studies reported on the association between PBDs and CHD mortality. Of these, two used a food-frequency questionnaire (FFQ), one study used a dietary recall, and five studies used a short general questionnaire to assess dietary intake. One study compared the highest vs. lowest category of PBDs, two studies compared vegetarians vs. meat-eaters, and five studies compared vegetarians vs. non-vegetarians.
Results showed a statistically significant association between adherence to PBDs (referring to highest vs. lowest category PDI, or to vegetarian vs non-vegetarian or meat-eaters) and the risk of CHD mortality (HR= 0.77; 95%CI 0.70-0.86, n= 8 prospective cohort studies). Heterogeneity was moderate (I^2= 36%, p= 0.01). Visual inspection of the forest plot indicated that heterogeneity was present in the size of the risk estimates. Sensitivity analyses leaving one study out at a time and subgroup analyses on study characteristics did not give the committee indication to interpret the results of the main analysis differently. The subgroup analysis on the association between adherence to a vegetarian diet and the risk of CHD mortality showed an inverse statistically significant association (HR= 0.76, 95%CI 0.68-0.85, I^2= 35.3%, p= 0.159, n= 7 prospective cohort studies). This analysis will be discussed in more detail in the chapter on vegetarian diets. Further subgroup analyses on vegan, lacto-ovo-,

pesco-, and semi-vegetarian diet, as well as on PDQI were presented in the paper but had too few studies (maximum of one) and are therefore not described in this background document.

Table 5 Results from Jafari et al. (2022)[4] on the association between plant-based diets and the risk of coronary heart disease mortality.

Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
8	Highest versus lowest category of adherence to PBD	234,202	3,168	0.77 (0.70-0.86)	36%	General adult population (≥18y); Europe, USA, Australia

Abbreviations: PBD: plant-based diet; CI: confidence interval; N: number; RR: relative risk; USA: United States of America; y: years

4.1.4 Cardiovascular disease

Summary plant-based diets and risk of cardiovascular disease

Aspect	Explanation
Selected studies	1 MA of 9 prospective cohort studies (6 publications) (Gan et al. 2021)[6]
Heterogeneity	Yes (high heterogeneity of 65%, p<0.01)
Strength of the association	RR= 0.84 (95%CI 0.79-0.89)
Study population	General adult population (≥18y) free of CVD diseases at baseline

Abbreviations: CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; y: years

The committee found two MAs of nine (six publications) and seven prospective cohort studies, respectively, that investigated the association between plant-based diets (PBDs) and the risk of cardiovascular disease (CVD) (Gan et al. 2021, and Quek et al. 2021).[5,6] The MAs of Gan et al. (2021)[6] and Quek et al. (2021)[5] seem to overlap in 7 of the included prospective cohort studies. The study by Quek et al. (2021)[5], however, lacked a description on which seven cohort studies their MA on risk of cardiovascular disease was based on. Therefore, the overlap in studies between Gan et al. (2021)[6] and Quek et al. (2021)[5] could only be judged based on the description of the overall included cohort studies in both MAs (respectively nine (ten publications) and thirteen). Moreover, due to the minimal description in Quek et al. (2021)[5] the committee was not able to fully comprehend their results. Therefore, the committee based its description of the association between PBDs and risk of CVD on the findings of Gan et al. (2021) (Table 6).[6] Worth noting is that the results of Quek et al. (2021)[5] were very similar to those of Gan et al. (2021)[6]: pooled HR= 0.90, 95%CI 0.82-0.98, I^2= 87.2%, n= 7 cohort studies.

The MA by Gan et al. (2021)[6] aimed at investigating the associations between PBDs and the risk of total CVD (composite of any fatal or non-fatal CVD, CHD, or stroke event), risk of CHD, and risk of stroke (total, ischemic, and haemorrhagic stroke). A total of nine prospective cohort studies (described in six publications) investigating the association between PBDs and the risk of CVD were included in this MA. These prospective cohort studies had follow-up periods ranging from 5 to 36 years and included adult participants (≥18 y) free of CVD diseases during enrolment. Four of the cohorts (described in three publications) compared vegetarians vs. non-vegetarians, while five cohorts (described in three publications) compared the highest vs. lowest category of PBDs. All six publications used a food-frequency questionnaire (FFQ) to assess dietary intake. The cohorts considered different types of PBDs including: 1) adherence to (*a priori*) defined Plant-based Dietary Index (PDI; healthy (hPDI) and unhealthy (uPDI)) (four cohorts described in two publications); 2) adherence to a pre-defined diet such as vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet as exposure of interest (four cohorts described in three publications), or adherence to PBDs which were derived *a posteriori* with factor analysis approach (one cohort). For studies that used dietary scores or *a posteriori*-defined methods to categorize PBD pattern adherence, the risk estimate that compared the highest to the lowest adherence category was used in the MA. For the other studies, risk estimates comparing the diet category that represents the greatest restriction of animal foods (vegan, vegetarian or pesco-vegetarian) with the least restrictive diet category (omnivorous or non-vegetarian) were included. All included studies adjusted for age, sex, BMI, physical activity and smoking status. Most studies further adjusted for alcohol consumption, energy intake, menopause status (in females), personal history of hypertension, dyslipidaemia, and type 2 diabetes. All studies were deemed of high quality according to the Newcastle-Ottawa scale (all studies ≥7 points/9 points). Results (including the *a posteriori* study by Shikany et al. 2015) showed that a PBD pattern was associated with a lower risk of CVD (RR= 0.84, 95%CI 0.79-0.89) when comparing the highest vs. the lowest adherence categories (n= 9 unique cohorts from 6 publications). No separate analysis was available for *a priori* defined PBDs. However, according to the committee, the results of the *a posteriori* cohort did not have a large influence on the results of the overall analysis as they ecompassed only 4.1% of the total weight of the analysis. Furthermore, sensitivity analysis using the leave-one-out method showed that the exclusion of any single study from the analysis did not appreciably alter the pooled risk estimate. There was high heterogeneity (I^2= 65%, p<0.01). Visual inspection of the forest plot showed that heterogeneity was mainly present in the size of the risk estimates. Despite the existence of heterogeneity, the direction and the statistical significance of the findings were generally consistent. No significant publication bias was detected by the authors.

In addition, the dose-response associations of adherence to PDI patterns and the risk of total CVD were investigated (five cohorts described in three publications). Results showed that each additional 25% increase in the overall PDI and hPDI scores was associated with a 15% (RR= 0.85, 95%CI 0.80-0.90) and 16% (RR= 0.84, 95%CI 0.75-0.94) reduction in CVD risk, respectively. An uPDI was significantly associated with a higher CVD risk (RR= 1.13, 95%CI 1.02, 1.26) per 25% increase in the unhealthful PDI. The differences in the model fit between the linear and nonlinear models were all non-significant, suggesting linear relationships between PDIs and CVD risk.

Table 6 Results from the meta-analysis of Gan et al. (2021)[6] on the association between plant-based diets and the risk of cardiovascular disease.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
9 (6 publications)	Highest vs. lowest category of adherence to PBD	698,707	137,968	0.84 (0.79-0.89)	65%	Adult population (≥18y) free of CVD diseases at baseline; UK, USA, Taiwan

Abbreviations: PBD: plant-based diet; CI: confidence interval; CVD: cardiovascular disease; N: number; RR: relative risk; UK: United Kingdom; USA: United States of America; y: years

4.1.5 Coronary heart disease

Summary plant-based diets and risk of coronary heart disease

Aspect	Explanation
Selected studies	1 MA of 6 prospective cohort studies (described in 4 publications) (Gan et al. 2021)[6]
Heterogeneity	No (moderate heterogeneity of 48%, p=0.09)
Strength of the association	RR= 0.88 (95%CI 0.81-0.94)
Study population	General adult population (≥18y) free of CVD diseases at baseline

Abbreviations: CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; y: years

There was one MA that investigated the association between plant-based diets (PBDs) and the risk of coronary heart disease (CHD) (Gan et al. 2021)[6] (Table 7).

The MA by Gan et al. (2021)[6] aimed at investigating the associations between PBDs and total CVD incidence (composite of any fatal or non-fatal CVD, CHD, or stroke event), CHD incidence, and stroke incidence (total, ischemic, and haemorrhagic stroke). A total of six prospective cohort studies (described in four publications)

investigating the association between PBDs and the risk of CHD were included. These prospective cohort studies had follow-up periods ranging from 5 to 36 years and included adult participants (≥18 y) free of CVD diseases during enrolment. Two of the cohorts (described in two publications) compared vegetarians vs. meat-eaters, while four cohorts (described in two publications) compared the highest vs. lowest category of PBDs. All four publications used a food-frequency questionnaire (FFQ) to assess dietary intake. The cohorts considered different types of PBDs including: 1) adherence to (*a priori*) defined Plant-based Dietary Index (PDI; healthy (hPDI) and unhealthy (uPDI)) (three cohorts described in one publication); 2) adherence to a pre-defined diet such as vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet as exposure of interest (two cohorts), or adherence to PBDs which were derived *a posteriori* with factor analysis approach (one cohort). For studies that used dietary scores or *a posteriori*-defined methods to categorize PBD pattern adherence, the risk estimate that compared the highest to the lowest adherence category was used in the MA. For the other studies, risk estimates comparing the diet category that represents the greatest restriction of animal foods (vegan, vegetarian or pesco-vegetarian) with the least restrictive diet category (omnivorous or non-vegetarian) were included. All included studies adjusted for age, sex, BMI, physical activity and smoking status. Most studies further adjusted for alcohol consumption, energy intake, menopause status (in females), personal history of hypertension, dyslipidaemia, and type 2 diabetes. All studies were deemed of high quality according to the Newcastle-Ottawa scale (all studies ≥7 points/9 points).

Results showed a significant inverse association between the highest and the lowest adherence of PBD patterns and CHD (RR= 0.89, 95%CI 0.81-0.97) (n= 6 cohorts described in 4 publications). No separate analysis was available for *a priori* defined PBDs. However, according to the committee, the results of the *a posteriori* cohort (Shikany et al. 2015) did not have a large influence on the results of the overall analysis as they ecompassed only 8% of the total weight of the analysis. Furthermore, sensitivity analysis using the leave-one-out method showed that the exclusion of any single study from the analysis did not appreciably alter the pooled risk estimate. There was moderate heterogeneity between the studies (I^2= 48%). Visual inspection of the forest plot showed that heterogeneity was mainly present in the size of the risk estimates. Despite the existence of heterogeneity, the direction and the statistical significance of the findings were generally consistent. No significant publication bias was detected by the authors.

Table 7 Results from Gan et al. (2021)[6] on the association between plant-based diets and the risk of coronary heart disease.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
6 (4 publications)	Highest vs. lowest category of adherence to PBD	694,191	At least 36,781	0.88 (0.81-0.94)	48%	Adult population (≥18y) free of CVD diseases at baseline; UK, USA, Taiwan

Abbreviations: PBD: plant-based diet; CI: confidence interval; CVD: cardiovascular disease; N: number; RR: relative risk; UK: United Kingdom; USA: United States of America; y: years

4.1.6 Stroke

Summary plant-based diets and risk of stroke

Aspect	Explanation
Selected studies	1 MA of 8 prospective cohort studies (described in 5 publications) (Gan et al. 2021)[6]
Heterogeneity	Yes (high heterogeneity of 76%, p<0.01)
Strength of the association	RR= 0.87 (95%CI 0.73- 1.03)
Study population	General adult population (≥18y) free of CVD diseases at baseline

Abbreviations: CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; y: years

The committee found two MAs of eight (five publications) and seven prospective cohort studies, respectively, that investigated the association between plant-based diets (PBDs) and risk of stroke (Gan et al. 2021, and Quek et al. 2021).[5,6] The MAs of Gan et al. (2021)[6] and Quek et al. (2021)[5] seem to overlap in seven of the included prospective cohort studies. The study by Quek et al. (2021)[5], however, lacked a description on which seven cohort studies their MA on risk of stroke was based on. Therefore, the overlap in studies between Gan et al. (2021)[6] and Quek et al. (2021)[5] could only be judged based on the description of the overall included cohort studies in both MAs (respectively nine (ten publications) and thirteen). Moreover, due to the minimal description in Quek et al. (2021)[5] the committee was not able to fully comprehend their results. Therefore, the committee based its description of the association between PBDs and risk of stroke on the findings of Gan et al. (2021)[6] (Table 8). Worth noting is that the results of Quek et al. (2021)[5] were similar to those of Gan et al. (2021)[6]: pooled HR= 0.86, 95%CI 0.69-1.08, I^2= 79.1%, n= 7 cohort studies.

The MA by Gan et al. (2021)[6] aimed at investigating the associations between PBDs and the risk of total CVD (composite of any fatal or non-fatal CVD, CHD, or stroke event), CHD incidence, and stroke incidence (total, ischemic, and haemorrhagic

stroke). Included cohort studies had follow-up periods ranging from 5 to 36 years and included adult participants (≥18 y) free of CVD diseases during enrolment. A total of eight prospective cohort studies (described in five publications) investigating the association between PBDs and risk of stroke were included. Four of the cohorts (described in three publications) compared vegetarians vs. non-vegetarians or vs. meat-eaters, while four cohorts (described in two publications) compared the highest vs. lowest category of PBDs. All five publications used a food-frequency questionnaire (FFQ) to assess dietary intake. The cohorts considered different types of PBDs including: 1) adherence to (*a priori*) defined Plant-based Dietary Index (PDI; healthy (hPDI) and unhealthy (uPDI)) (five cohorts described in four publications); 2) adherence to a pre-defined diet such as vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet as exposure of interest (four cohorts described in four publications), or adherence to PBDs which were derived *a posteriori* with factor analysis approach (one cohort described in two publications). For studies that used dietary scores or *a posteriori*-defined methods to categorize PBD pattern adherence, the risk estimate that compared the highest to the lowest adherence category was used in the MA. For the other studies, risk estimates comparing the diet category that represents the greatest restriction of animal foods (vegan, vegetarian or pesco-vegetarian) with the least restrictive diet category (omnivorous or non-vegetarian) were included. All included studies adjusted for age, sex, BMI, physical activity and smoking status. Most studies further adjusted for alcohol consumption, energy intake, menopause status (in females), personal history of hypertension, dyslipidaemia, and type 2 diabetes. All studies were deemed of high quality according to the Newcastle-Ottawa scale (all studies ≥7 points/9 points).
Results showed a statistically non-significant inverse association between the highest and the lowest adherence of PBD patterns and stroke (RR= 0.87, 95%CI 0.73, 1.03, I^2= 76%, n= 5 publications from 8 separate cohorts). There was no separate analysis available on studies that used *a priori* PBDs. However, the only cohort study that used an *a posteriori* method to define PBD and looked at stroke (Judd et al. 2013) showed similar results (RR= 0.85, 95%CI 0.65- 1.12) as the studies that used *a priori* method. Sensitivity analysis using the leave-one-out method showed that the exclusion of the study by Tong et al. (2019) resulted in a significant inverse association between PBDs and stroke (RR= 0.81, 95%CI 0.68- 0.96, I^2= NR). The authors do not give an explanation for this. The committee notes that the study by Tong et al. (2019) was the only study that showed results in opposite direction compared to the other seven cohorts. There was high heterogeneity between studies (I^2= 76%). Visual inspection of the forest plot indicated that it was in the size and direction of the risk estimates. The authors described that the mean age at baseline, outcome definition, study region, and

study quality were sources of heterogeneity based on subgroup analyses. No significant publication bias was detected by the authors.

Table 8 Results from the MA of Gan et al. (2021)[6] on the association between plant-based diets and the risk of stroke.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
8 (5 publications)	Highest vs. lowest category of adherence to PBD	720,926	13,370	0.87 (0.73-1.03)	76%	Adult population (≥18y) free of CVD diseases at baseline; UK, USA, Taiwan

Abbreviations: PBD: plant-based diet; CI: confidence interval; CVD: cardiovascular disease; N: number; RR: relative risk; UK: United Kingdom; USA: United States of America; y: years

4.1.7 Type 2 Diabetes

Summary plant-based diets and risk of Type 2 Diabetes

Aspect	Explanation
Selected studies	1 MA of 9 prospective cohort studies (described in 7 publications) (Qian et al. 2019)[7]
Heterogeneity	No (moderate heterogeneity of 44.5%, p=0.07)
Strength of the association	RR= 0.77 (95%CI 0.71-0.84)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; RR: relative risk; y: years

There was one MA that investigated the association between plant-based diets (PBDs) and the risk of type 2 diabetes (Qian et al. 2019) (Table 9).[7]

The MA by Qian et al. (2019)[7] aimed at investigating the association between PBDs and the risk of type 2 diabetes. It included nine relevant prospective cohort studies (seven publications) with follow-up periods ranging from 2 to 28 years and including a total of 307,099 adult participants (≥18y). PBDs were defined as a higher consumption of plant-based foods and lower consumption or exclusion of animal-based foods. Vegetarian and vegan dietary patterns were also considered PBDs. Five prospective cohort studies (described in three publications) characterized adherence to PBDs using PDIs, three prospective cohort studies compared individuals following a vegetarian or vegan dietary patterns with those who were not following a vegetarian dietary pattern, and one prospective cohort study derived a vegetarian dietary pattern using a factor analysis approach (i.e. *a posteriori*). For studies that used dietary indices, the risk estimate that compared the highest with lowest quantiles were used, which represent

the best (highest quantile) and poorest (lowest quantile) adherence to the PBD. For studies looking at vegan and vegetarian diet, study estimates comparing diets with the most restrictive of animal-based foods (vegan or semi-vegetarian) with the least restrictive, such as omnivorous diets, were considered. All studies used food-frequency questionnaires to assess dietary intake. Most studies adjusted for confounders including age, BMI, smoking status, and family history of diabetes.
Results showed a statistically significant inverse association between a higher adherence to an overall PBD and the risk of type 2 diabetes, compared to poorer adherence (pooled RR= 0.77, 95%CI 0.71-0.84, n= 9 prospective cohort studies (7 publications)). The heterogeneity across studies was moderate (I^2 = 44.5%, p= 0.07). Visual inspection of the forest plot indicated that heterogeneity was present in the size of the risk estimates. A subgroup analysis was performed considering the 'healthful PDI' (including only more healthful plant-based foods) instead of the 'overall PDI'. This analysis included 4 prospective cohort studies and showed a modestly strengthened association between higher adherence to a healthful PBD and the risk of type 2 diabetes (RR= 0.70, 95%CI 0.62-0.79) vs. lower adherence to a healthful PBD. No heterogeneity estimate was presented by the authors for this analysis. Other subgroup analyses, based on type of PBD (PDI and dietary patterns), showed similar results as the main analysis. Studies using predefined dietary patterns showed a stronger inverse relationship with type 2 diabetes than studies that used PDIs. No subgroup analysis excluding only the *a posteriori* study (Koloverou et al. 2016) was performed. However, all risk estimates (including the risk estimate of the *a posteriori* study) were in the same direction and the weight of the *a posteriori* study by Koloverou et al. (2016) was very low (3.26%). Moreover, sensitivity analysis removing one study at a time did not substantially change the results of the main estimate of the analysis. For these reasons, the committee does not expect that the *a posteriori* study did have a substantial influence on the main risk estimate.

Further subgroup analyses did not show other sources of heterogeneity by age, sex, BMI, sex, duration of follow-up, or study quality scores. An additional exploratory analysis was performed in 6 of the prospective cohort studies in order to assess the influence of BMI adjustment on the association between PBDs and risk of type 2 diabetes. The association was substantially altered with adjustment for BMI, but pooled results remained statistically significant in both analyses (without adjustment for BMI: RR= 0.53, 95%CI 0.49-0.58, and after adjusting for BMI: RR= 0.79, 95%CI 0.74-0.85). According to the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, all but one studies were of high quality (≥10 points out of 14 points). Sensitivity analysis excluding the study of lower quality (9/14 points) (Vang et al. 2008) did not alter the risk estimate of the main analysis (RR= 0.77, 95%CI 0.70-0.85, I^2=

50.6%). Furthermore, a dose-response analysis was performed for the five prospective cohort studies using PDI. A statistically significant inverse association between PDIs and risk of type 2 diabetes was found.

Table 9 Results from the meta-analysis by Qian et al. (2019)[7] on the association between plant-based diets and the risk of Type 2 diabetes.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
9 (7 publi-cations)	Highest vs. lowest category of adherence to PBD	307,099	23,544	0.77 (0.71-0.84	44.5%	General adult population (≥18y); Europe, USA, Asia

Abbreviations: PBD: plant-based diet; CI: confidence interval; N: number; RR: relative risk; USA: United States of America; y: years

4.2 Vegetarian diets

This paragraph describes the scientific evidence from SRs of prospective cohort studies on the associations between a vegetarian diet and the disease outcomes all-cause mortality, risk of cardiovascular disease and mortality, risk of cerebrovascular disease and mortality, risk of coronary heart disease mortality, risk of breast cancer and mortality, risk of colorectal cancer and mortality, lung cancer mortality, risk of stroke, risk of diabetes, risk of depression, and risk of fractures. First, an overview of the different definitions of vegetarian diets used in the different SRs is provided (Table 10).

Table 10 Definitions vegetarian diets in the included systematic reviews

SR	Definition vegetarian diet
Oussalah et al. (2020)[10] (Umbrella review)	Typically, a vegetarian diet excludes the consumption of all types of meat, fish, and seafood. There are several subgroups that can be identified in literature: 1) *vegan diets*: include only fruits, vegetables, legumes, whole grains, and nuts, and which may exclude honey, roots, or tubers, 2) *lacto-, ovo-, or lacto-ovo-vegetarian diets:* vegan diets that incorporate dairy products, eggs, or both of them, respectively, 3) *flexitarian diets*: following primarily but not strictly a vegetarian diet, occasionally eating meat, fish or chicken (two main categories of flexitarian diets: semi-vegetarian diets, which are vegetarian diets that incorporate a low consumption of meat between once per month to less than once per week, and pesco- or pollo-vegetarian diets which are characterized by typical lacto-ovo-vegetarian diets that incorporate the consumption of fish or chicken, respectively.
Lu et al. (2021)[11]	A vegetarian diet is defined as a diet that excludes the consumption of meat, poultry, fish, or seafood and may or may not include dairy and eggs.
Godos et al. (2017)[12]	A vegetarian diet is defined as a dietary profile characterised by abstention from consuming meat (including red meat, fish, and poultry). In all included studies but one diet characteristics were based on the response frequencies of key dietary components: pure vegetarian diet characterised by eating meat less than once per month; semi-vegetarian diet characterised by low consumption of meat (more than once per month but less than once per week); pesco-vegetarian diet characterised by consumption of fish more than once per month; and non-vegetarian diet characterised by eating meat more than once per week.
Jafari et al. (2022)[4]	A vegetarian diet is described as a type of plant-based diet which includes vegan (no animal products), lacto-ovo-vegetarian (including dairy and eggs), lacto-vegetarian (including dairy products), pesco-vegetarian (including fish and seafood), and semi-vegetarian (consuming meat infrequently) diets.
Molina-Montes et al. (2020)[13]	A vegetarian diet is defined as a diet excluding meat and meat products, and flesh from any animal.
Kwok et al. (2014)[14]	NR (Definitions of vegetarian diet of each included individual cohort study were provided, but not an overall definition)
Dinu et al. (2017)[15]	A vegetarian diet is defined as a dietary profile characterized by abstention from consuming meat and meat products, poultry, seafood and flesh from any other animal.
Iguacel et al. (2019)[16]	A vegetarian diet is defined as a diet without consumption of meat, poultry, fish, seafood, and flesh from any animal, but includes dairy products and/or eggs in the diet.

Abbreviations: NR: not reported.

The committee found an umbrella review of SRs and MAs investigating the association between vegetarian diets and multiple different health outcomes, including health outcomes related to diabetes, cardiovascular diseases, overall cancer and cause-specific cancer, and all-cause mortality.[10] No pooled estimates were calculated separately for the included health outcomes, but an overall risk estimate for all negative health outcomes was calculated. This analysis included four MAs regarding the following negative health outcomes: risk of ischemic heart disease, risk of cardiovascular disease, risk of cerebrovascular disease, risk of circulatory diseases,

risk of diabetes, risk of cancer and mortality, risk of breast cancer and mortality, risk of colorectal cancer and mortality, risk of prostate cancer and mortality, lung-cancer mortality, and all-cause mortality (Huang et al. 2012, Lee et al. 2017, Dinu et al. 2017, and Godos et al. 2017). The results of this analysis showed that vegetarian diets were associated with a significantly reduced risk of negative health outcomes (RR= 0.89, 95%CI 0.85-0.93). There was moderate heterogeneity (I^2= 43%, p= 0.02). Visual inspection of the forest plot indicated that heterogeneity was present in the size of the risk estimates.

4.2.1 All-cause mortality

Summary vegetarian diets and all-cause mortality

Aspect	Explanation
Selected studies	1 meta-analysis of 8 prospective cohort studies (Jafari et al. 2022)[4]
Heterogeneity	Yes (high heterogeneity of I^2= 81%, p=0.00)
Strength of the association	RR= 0.96 (95%CI 0.87-1.05)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; RR: relative risk; y: years

The committee found one umbrella review of SRs (Oussalah et al. 2020)[10] and two MAs (Dinu et al. 2017, and Jafari et al. 2022)[4,15] investigating the association between vegetarian diets and all-cause mortality. The umbrella review by Oussalah et al. (2020)[10] included a total of three MAs investigating this association, one of them being the MA by Dinu et al. (2017)[15] that was found by the committee as well. The umbrella review by Oussalah et al. (2020)[10] included two other MAs investigating this association (Huang et al. 2012, and Kwok et al. 2014).[14,17] The MA by Huang et al. (2012)[17] has been described in the background document Dietary Patterns of the Dutch Dietary Guidelines 2015.[1] The MA by Kwok et al. (2014),[14] however, was not included in the background document Dietary Patterns of the Dutch Dietary Guidelines 2015. Since the umbrella review by Oussalah and colleagues[10] does not provide a pooled risk estimate and includes a MA that has been previously described in the Dutch Dietary Guidelines, the committee decided not to further describe the umbrella review by Oussalah et al. (2020) and decided to include the MAs by Kwok et al. (2014),[14] Dinu et al. (2017),[15] and Jafari et al. (2022)[4] in this background document.
The most recent MA (Jafari et al. 2022)[4] included all but one of the individual studies included in the MA by Dinu et al. (2017),[15] namely the study by Appleby et al. (2002).[18] The study by Appleby et al. (2002)[18] described the results of two cohorts that are described in two separate prospective cohort studies included in the MA by Jafari et al (2021)[4] (Thorogood et al. 1994, and Key et al. 1996). For this reason, the MA by Dinu et al. (2017)[15] is not further described in this background document. The MA by Jafari

et al. (2022)[4] included all the cohort studies that were included in the MA of Kwok et al. (2014),[14] except for one, namely the Adventists Netherlands Study described in the publication of Berkel & Waard (1983). The committee therefore describes the MA by Jafari et al. (2022) in this background document for the description of the association between vegetarian diets and the risk of all-cause mortality (Table 11).

The MA by Jafari et al. (2022)[4] investigated the association between plant-based diets (PBDs), including adherence to *a priori* defined vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet, with the risk of all-cause mortality in the general adult population. A total of eight prospective cohort studies were included that looked at the association between vegetarian diets and the risk of all-cause mortality. When a cohort study had results on different types of diets (e.g. vegetarian, vegan, semi-, lacto-vegetarian diet, etc.), only the results on the main vegetarian diet were included in the analysis of Jafari et al. (2022).[4] For collecting dietary intakes, two cohort studies used a food-frequency questionnaire (FFQ), and six cohort studies used a short general questionnaire. Five studies compared vegetarians vs. non-vegetarians, and three studies compared vegetarians vs. meat-eaters. Results showed a statistically non-significant inverse association between adherence to a vegetarian diet and risk of all-cause mortality (RR= 0.96, 95%CI 0.87-1.05, n= 8 prospective cohort studies). Heterogeneity was high (I^2= 81%, p= 0.00). Visual inspection of the forest plot indicated that heterogeneity was present in the direction and in the size of the risk estimates. No subgroup analyses were performed on study characteristics. Potential sources of the high heterogeneity found for this analysis are not reported by the authors. Subgroup analyses on vegan, lacto-ovo-, pesco-, semi-, and provegetarian diet, included too few studies (maximum of two) and are therefore not described by the committee in this background document.

Table 11 Results from the meta-analysis by Jafari et al. (2022)[4] on the association between a vegetarian diet and the risk of all-cause mortality.

First author	Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
Jafari et al. (2022)[4]	8	Vegetarian diet vs non-vegetarians or meat-eaters	411,881	27,695	0.96 (0.87-1.05)	81%	General adult population (≥18y); Europe, USA, Australia

Abbreviations: CI: confidence interval, N: number; NR: not reported; RR: relative risk; UK: United Kingdom; USA: United States of America; y: years

4.2.2 Cardiovascular disease mortality

Summary vegetarian diets and cardiovascular disease mortality

Aspect	Explanation
Selected studies	1 MA of 5 prospective cohort studies (Jafari et al. 2022)[4]
Heterogeneity	No
Strength of the association	Jafari et al. (2022)[4]: HR= 0.92 (95%CI 0.85-0.99)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; HR: hazard ratio; y: years

The committee found one umbrella review of SRs (Oussalah et al. 2020)[10] and two MAs (Dinu et al. 2017, and Jafari et al. 2022)[4,15] on the association between a vegetarian diet and mortality of cardiovascular disease. The MA by Dinu et al. (2017)[15] was included in the umbrella review by Oussalah et al. (2020).[10] The umbrella review by Oussalah et al. (2020)[10] a second MA investigating the association between a vegetarian diet and circulatory diseases, namely the MA by Huang et al. (2012). This MA was, however, included and described in the background document Dietary Patterns of the Dutch Dietary Guidelines 2015. Moreover, the umbrella review by Oussalah et al. (2020)[10] did not provide a pooled estimate of the included MAs. For these reasons, only the MAs by Dinu et al. (2017)[15] and by Jafari et al. (2022)[4] were further considered by the committee to describe the association between vegetarian diets and the risk of cardiovascular mortality.

The MA by Jafari et al (2022)[4] overlapped in all but one of the studies included in the MA by Dinu et al. (2017),[15] namely the study by Appleby et al. (2002).[18] The study by Appleby et al. (2002)[18] described the results of two cohort studies that were described in two separate prospective cohort studies included in the MA by Jafari et al. (2022)[4] (Thorogood et al. 1994, and Key et al. 1996). As the MA of Jafari et al. (2022)[4] was the most recent and included all cohort studies described in Dinu et al. (2017),[15] only the MA by Jafari et al. (2022)[4] was described (Table 12).

The MA by Jafari et al. (2022)[4] investigated the association between plant-based diets (PBDs), including adherence to *a priori* defined vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet, with the risk of all-cause mortality in the general adult population. A total of five prospective cohort studies were included in the analysis on the association between vegetarian diets and the risk of cardiovascular disease mortality. When a cohort study had results on different types of diets (e.g. vegetarian, vegan, semi-, lacto- vegetarian diet, etc.), only the results on the main vegetarian diet were included in the analyses of Jafari et al. (2022).[4] All five studies compared

vegetarians vs. non-vegetarians. Two of the five studies used a FFQ and three studies used a short general questionnaire to assess dietary intake. Results showed a statistically significant inverse association between adherence to a vegetarian diet with the risk of cardiovascular disease mortality (HR= 0.92, 95%CI 0.85-0.99, I^2= 0%, n= 5 prospective cohort studies). Subgroup analyses on vegan, lacto-ovo-, pesco-, semi-, and provegetarian diet, were presented by the authors but had too few studies (maximum of two) and are therefore not described in this background document.

Table 12 Results from the meta-analysis by Jafari et al. (2022)[4] on the association between vegetarian diets and the risk of cardiovascular disease mortality.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
5	Vegetarian diet vs. Non-vegetarians	144,247	3,241	0.92 (0.85-0.99)	0%	General adult population (≥18y); Europe, USA, Australia

Abbreviations: CI: confidence interval; N: number: RR: relative risk; USA: United States of America; y: years

4.2.3 Coronary heart disease mortality

Summary vegetarian diets and coronary heart disease mortality

Aspect	Explanation
Selected studies	1 MA of 7 prospective cohort studies (Jafari et al. 2022)[4]
Heterogeneity	No (moderate heterogeneity of 35.3%, p= 0.159)
Strength of the association	HR= 0.76 (95%CI 0.68-0.85)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; HR: hazard ratio; y: years

There was one MA that investigated the association between vegetarian diets with the risk of coronary heart disease (CHD) mortality (Jafari et al. 2022) (Table 13).[4]

The MA by Jafari et al. (2022)[4] investigated the association between plant-based diets (PBDs), including adherence to *a priori* defined vegetarian, vegan, semi-, lacto-, lacto-ovo-, and pesco-vegetarian diet, with the risk of CHD mortality in the general adult population. A total of seven prospective cohort studies were included that looked at the association between vegetarian diets and the risk of CHD mortality. When a cohort study had results on different types of diets (e.g. vegan, semi-, lacto- vegetarian diet, etc.), only the results on the usual vegetarian diet were included in the analyses of Jafari et al. (2022). Two of the seven studies used a food-frequency questionnaire (FFQ), while five studies used a short general questionnaire to assess dietary intake. Two studies compared vegetarians vs. meat-eaters, and five studies compared

vegetarians vs. non-vegetarians.
Results showed an inverse statistically significant association between adherence to a vegetarian diet and the risk of CHD mortality (HR= 0.76, 95%CI 0.68-0.85, n=7 prospective cohort studies). Heterogeneity was moderate (I^2= 35.3%, p= 0.159). Visual inspection of the forest plot indicated that heterogeneity was present in the size of the risk estimates. No subgroup analyses were performed on study characteristics. Further subgroup analyses on vegan, lacto-ovo-, pesco-, and semi-vegetarian diet were presented in the paper but had too few studies (maximum of one) and are therefore not described in this background document.

Table 13 Results from the meta-analysis by Jafari et al. (2022)[4] on the association between vegetarian diets and the risk of coronary heart disease mortality.

Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
7	Vegetarian diet vs. Non-vegetarians or meat-eaters	168,785	2,370	0.76 (0.68-0.85)	35.3%	General adult population (≥18y); Europe, USA, Australia

Abbreviations: CI: confidence interval; N: number: RR: relative risk; USA: United States of America

4.2.4 Cerebrovascular disease mortality

Summary vegetarian diets and cerebrovascular disease mortality

Aspect	Explanation
Selected studies	2 meta-analyses of 6 (described in 5 publications) and 5 prospective cohort studies, respectively (Kwok et al. 2014 and Jafari et al. 2022)[4,14]
Heterogeneity	Kwok et al. (2014): Yes, high heterogeneity of 79%, Jafari et al (2022): No, moderate heterogeneity of 45%, p=0.12
Strength of the association	Kwok et al. (2014): RR=0.93 (95%CI 0.70-1.23) Jafari et al. (2022): RR= 0.93 (95%CI 0.78-1.10)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; RR: relative risk; y: years

The committee found one umbrella review of SRs (Oussalah et al. 2020)[10] and two MAs (Dinu et al. 2017, and Jafari et al. 2022)[4,15] that investigated the association between vegetarian diets with the risk of cerebrovascular disease mortality. The MA by Dinu et al. (2017)[15] was included in the umbrella review by Oussalah et al. (2020).[10] The umbrella review included two other MAs that investigated this association (Huang et al. 2012, and Kwok et al. 2014). Of these, the MA by Huang et al. (2012) was included and described in the background document Dietary Patterns of the Dutch Dietary Guidelines 2015. The umbrella review by Oussalah et al. (2020)[10] did not

provide a pooled estimate of the included MAs for the association between a vegetarian diet and the risk of cerebrovascular disease or mortality due to cerebrovascular disease. For these reasons, the MAs by Kwok et al. (2014),[14] Dinu et al. (2017)[15] and by Jafari et al (2022)[4] were further considered by the committee.
The most recent MA (Jafari et al. 2022)[4] included all but one of the individual studies included in the MA by Dinu et al. (2017), namely the study by Appleby et al. (2002).[18] The study by Appleby et al. (2002)[18] described the results of two cohort studies that were included in two separate prospective cohort studies included in Jafari et al. (2022) (Thorogood et al. 1994, and Key et al. 1996). For this reason, the MA by Dinu et al. (2017) was not further described by the committee. The MA by Jafari et al. (2022)[4] included all the cohort studies that were included in the MA of Kwok et al. (2014),[14] except for two, namely the Adventists Netherlands Study described in the publication of Berkel & Waard (1983), and the German Vegetarian Study described in the publication of Key et al. (1999). The committee therefore describes the MA by Jafari et al. (2022) in this background document for the description of the association between vegetarian diets and the risk of all-cause mortality (Table 14).

The MA by Jafari et al. (2022)[4] aimed at investigating the association between PBDs with the risk of all-cause mortality and cause-specific mortality in the general adult population. A total of five prospective cohort studies that investigate the risk of cerebrovascular disease mortality were included in the MA. These were studies including participants who followed a vegetarian diet vs. a non-vegetarian diet or vs. meat eaters. Four of the five cohorts used a short general questionnaire, and one used a food-frequency questionnaire (FFQ) for collecting dietary intakes. No statistically significant association was found between adherence to a vegetarian diet (vs. non-vegetarian or meat-eaters) and the risk of cerebrovascular disease mortality (pooled RR= 0.93; 95%CI 0.78-1.10, n= 5 prospective cohort studies). Heterogeneity was moderate (I^2= 45%, p= 0.12). Visual inspection of the forest plot indicated that heterogeneity was present in the direction and size of the risk estimates between the studies.

Table 14 Results from the MA of Jafari et al. (2022)[4] on the association between vegetarian diets and the risk of cerebrovascular disease mortality.

First author	Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
Jafari et al. (2022)[4]	5	Vegetarian diet vs. Non-vegetarians or meat-eaters	122,165	1,088	0.93 (0.78-1.10)	45%	General adult population (≥18y); Europe, USA, Australia

Abbreviations: CI: confidence interval; N: number; NR: not reported; RR: relative risk; UK: United Kingdom; USA: United States of America; y: years

4.2.5 Breast cancer mortality

Summary vegetarian diets and breast cancer mortality

Aspect	Explanation
Selected studies	1 MA of 6 prospective cohort studies (described in 3 publications) (Molina-Montes et al. 2020)[13]
Heterogeneity	Yes (high heterogeneity of 58%, p=0.05)
Strength of the association	RR= 0.99 (95%CI 0.67-1.47)
Study population	General adult female population (≥18y)

Abbreviations: CI: confidence interval; RR: relative risk; y: years

The committee found one umbrella review of SRs (Oussalah et al. 2020)[10] and three MAs that investigated the association between vegetarian diets with the risk of breast cancer mortality (Dinu et al. 2017,[15] Molina-Montes et al. 2020,[13] and Jafari et al. 2022).[4] The umbrella review by Oussalah et al. (2020)[10] included only one of both MAs found by the committee, namely the MA by Dinu et al. (2017).[15] The MAs by Dinu et al. (2017)[15] and Jafari et al. (2022)[4] overlapped in all the included prospective cohort studies in their analyses for the association between a vegetarian diet and the risk of breast cancer mortality. The MA by Molina-Montes et al. (2020) included all the cohorts that were present in the MAs by Dinu et al. (2017) and Jafari et al. (2022), as well as another cohort study that was not included in Dinu et al. (2017) and Jafari et al. (2022). For this reason, the MA of Molina-Montes et al. (2020) is described below and in Table 15.

The MA by Molina-Montes et al. (2020) aimed at investigating the association between a vegetarian diet and different health outcomes, including the risk of breast cancer mortality.[13] A total of six prospective cohort studies (described in three publications) were included in this MA that investigated this association. These prospective cohort

studies accounted for a total of 83,985 participants and 228 cases of breast cancer. Follow-up periods ranged from 5.6 to 18.7 years. All prospective cohort studies adjusted for age, sex, and smoking status in their analyses. The committee notes that the risk estimates were calculated in a population of both males and females, while breast cancer occurs most often in women. Results showed a statistically non-significant association between a vegetarian diet and risk of mortality from breast cancer (RR= 0.99, 95%CI 0.67-1.47, n= 6 cohort studies) as compared to an omnivore diet. There was high heterogeneity (I^2= 58%, p= 0.05). Heterogeneity was present in the direction of the risk estimates. The authors mention that heterogeneity was probably due to differences in socio-demographic factors among the populations (some were Seventh Day Adventists) and varying definitions of a vegetarian diet. Seventh Day Adventists are characterized by their religious beliefs that include not eating meat, and not consuming alcohol or drugs. Therefore, it is expected that these populations are generally healthier than the average population. Exclusion of the Heidelberg Study lowered the heterogeneity but did not make the association significant (Chang-Claude et al. 2005). This was a cohort study performed in the general German population.

Table 15 Results from the meta-analysis of Molina-Montes et al. (2020) on the association between vegetarian diets and the risk of breast cancer mortality.[13]

First author	Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
Molina-Montes et al. (2020)[13]	6 (described in three publications)	Vegetarian diet vs. Omnivore diet	83,985	228	0.99 (0.67-1.47)	58%	General adult population (≥18y); Europe, USA,

Abbreviations: CI: confidence interval; N: number; RR: relative risk; USA: United States of America; y: years

4.2.6 Colorectal cancer mortality

Summary vegetarian diets and colorectal cancer mortality

Aspect	Explanation
Selected studies	1 meta-analyss of 6 prospective cohort studies (described in 3 publications) (Molina-Montes et al. 2020)[13]
Heterogeneity	No
Strength of the association	RR= 1.03 (95%CI 0.84-1.26)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; RR: relative risk; y: years

The committee found one umbrella review of SRs (Oussalah et al. 2020)[10] and three MAs that investigated the association between vegetarian diets with the risk of colorectal cancer mortality (Dinu et al. 2017,[15] Molina-Montes et al. 2020,[13] and Jafari et al. 2022).[4] The umbrella review by Oussalah et al. (2020)[10] included only one of both MAs found by the committee, namely the MA by Dinu et al. (2017).[15] The MAs by Dinu et al. (2017)[15] and Jafari et al. (2022)[4] overlapped in all the included prospective cohort studies in their analyses for the association between a vegetarian diet and the risk of colorectal cancer mortality. The MA by Molina-Montes et al. (2020) included all the cohorts that were present in the MAs by Dinu et al. (2017) and Jafari et al. (2022), as well as another cohort study that was not included in Dinu et al. (2017) and Jafari et al. (2022). For this reason, the MA of Molina-Montes et al. (2020) is described below and in Table 16.

The MA by Molina-Montes et al. (2020) aimed at investigating the association between a vegetarian diet and different health outcomes, including the risk of colorectal cancer mortality.[13] A total of six prospective cohort studies (described in three publications) were included in this MA that investigated this association. These prospective cohort studies accounted for a total of 83,985 participants and 279 cases of colorectal cancer. Follow-up periods ranged from 5.6 to 18.7 years. All prospective cohort studies adjusted for age, sex, and smoking status in their analyses. Results showed a statistically non-significant association between a vegetarian diet and risk of mortality from colorectal cancer (RR=1.03, 95%CI 0.84-1.26, n=6 cohort studies) as compared to an omnivore diet. There was no heterogeneity.

Table 16 Results from the meta-analysis of Molina-Montes et al. (2020) on the association between vegetarian diets and the risk of colorectal cancer mortality.[13]

First author	Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
Molina-Montes et al. (2020)	6 (described in three publications)	Vegetarian diet vs. Omnivore diet	83,985	279	1.03 (0.84-1.26)	0%	General adult population (≥18y); Europe, USA

Abbreviations: CI: confidence interval; N: number; RR: relative risk; USA: United States of America; y: years

4.2.7 Lung cancer mortality

Summary vegetarian diets and lung cancer mortality

Aspect	Explanation
Selected studies	1 meta-analysis of 5 prospective cohort studies (described in 3 publications) (Molina-Montes et al. 2020)[13]
Heterogeneity	No
Strength of the association	RR= 0.95 (95%CI 0.75-1.21)
Study population	General adult population (≥18y)

Abbreviations: CI: confidence interval; RR: relative risk; y: years

The committee found one umbrella review of SRs (Oussalah et al. 2020)[10] and three MAs that investigated the association between vegetarian diets with the risk of lung cancer mortality (Dinu et al. 2017,[15] Molina-Montes et al. 2020,[13] and Jafari et al. 2022).[4] The umbrella review by Oussalah et al. (2020)[10] included only one of both MAs found by the committee, namely the MA by Dinu et al. (2017).[15] The MAs by Dinu et al. (2017)[15] and Jafari et al. (2022)[4] overlapped in all the included prospective cohort studies in their analyses for the association between a vegetarian diet and the risk of lung cancer mortality. The MA by Molina-Montes et al. (2020) included all the cohorts that were present in the MAs by Dinu et al. (2017) and Jafari et al. (2022), as well as another cohort study that was not included in Dinu et al. (2017) and Jafari et al. (2022). For this reason, the MA of Molina-Montes et al. (2020) is described below and in Table 17.

The MA by Molina-Montes et al. (2020) aimed at investigating the association between a vegetarian diet and different health outcomes, including the risk of lung cancer mortality.[13] A total of five prospective cohort studies (described in three publications) were included in this MA that investigated this association. These prospective cohort studies accounted for a total of 83,985 participants and 204 cases of colorectal cancer. Follow-up periods ranged from 5.6 to 18.7 years. All prospective cohort studies adjusted for age, sex, and smoking status in their analyses. Results showed a statistically non-significant association between a vegetarian diet and risk of mortality from colorectal cancer (RR= 0.95, 95%CI 0.75-1.21, n= 5 cohort studies) as compared to an omnivore diet. There was no heterogeneity.

Table 17 Results from the meta-analysis of Molina-Montes et al. (2020) on the association between vegetarian diets and the risk of lung cancer mortality.[13]

First author	Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
Molina-Montes et al. (2020)	5 (described in three publications)	Vegetarian diet vs. Omnivore diet	83,985	204	0.95 (0.75-1.21)	0%	General adult population (≥18y); Europe, USA

Abbreviations: CI: confidence interval; N: number; RR: relative risk; USA: United States of America; y: years

4.2.8 Stroke

Summary vegetarian diets and the risk of stroke

Aspect	Explanation
Selected studies	1 meta-analysis of 7 prospective cohort studies (described in 4 publications) (Lu et al. 2021)[11]
Heterogeneity	No (moderate heterogeneity of 68%, p=0.004)
Strength of the association	HR= 0.86 (95%CI 0.67-1.11)
Study population	General adult population

Abbreviations: CI: confidence interval; HR: hazard ratio

There was one MA that investigated the association between vegetarian diets and the risk of stroke (Lu et al. 2021) (Table 18).[11]

The study by Lu et al. (2021)[11] investigated the risk of stroke among vegetarians (diets excluding meat, poultry, fish, and seafood) compared to non-vegetarians (diets containing either meat, poultry, fish, or seafood). A MA was performed on seven prospective cohort studies (described in four publications) with average follow-up periods ranging from 6 to 32 years and with a total of 657,433 participants, of which 29,705 were vegetarians. All cohort studies used a food-frequency questionnaire (FFQ) to assess dietary intake, except one which used a 24-hour recall. Two publications (describing two cohort studies) used the baseline intake to assess vegetarian status, while the other two publications (describing five cohort studies) used longitudinal follow-up dietary data. Results showed that there was no statistically significant association between vegetarian dietary patterns and the risk of incident stroke (HR= 0.86, 95%CI 0.67-1.11, n= 7 prospective cohort studies). Heterogeneity was moderate (I^2= 68%, p= 0.004). Visual inspection of the forest plot indicated that heterogeneity was present in the direction and the size of the risk estimates. Sensitivity analysis removing one study at a time did not substantially change the results of the main

estimate of the analysis. The authors found indications of publication bias. Overall, the authors describe the certainty of the evidence as low as judged with the NutriGrade tool. The results on the subtypes ischaemic and haemorrhagic stroke are present in the paper but are not described by the committee in this background document because there were, respectively, too few cases (3 cohort studies, <300 cases), or too few cohort studies available (maximum of 2). Subgroup analyses by age groups showed a statistically significant inverse association between a vegetarian diet and the risk of stroke in participants with an age between 50 and < 65 years old compared to participants with an age <50y and participants with an age ≥65y (HR= 0.66, 95%CI 0.45-0.95, I^2= 54%, n= 3 cohort studies, n cases= NR). Moreover, studies that used the baseline intake to assess the vegetarian status showed a lower risk of stroke in vegetarians vs. non-vegetarians (HR= 0.66, 95%CI 0.45-0.99, I^2= 54, n= 3 cohort studies, n cases= NR), while studies that used longitudinal follow-up data showed a higher risk of stroke in vegetarians compared to non-vegetarians (HR= 1.15, 95%CI 1.00-1.32, I^2= 0%, n= 4 cohort studies). The authors do not comment on the reasons behind these findings. Based on subgroup analyses on study characteristics the authors indicated that age, region, BMI category, and dietary assessment moment were potential sources of heterogeneity.

Table 18 Results from the meta-analysis by Lu et al. (2021)[11] on the association between vegetarian diets and the risk of stroke.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
7 (described in 4 publications)	Vegetarian diet vs. Non-vegetarian diet	657,433	13,434	0.86 (0.67-1.11)	68%	General adult population; USA, Taiwan, UK

Abbreviations: CI: confidence interval; N: number; RR: relative risk; UK: United Kingdom; USA: United States of America

4.2.9 Type 2 Diabetes

The committee found one umbrella review of SRs (Oussalah et al. 2020)[10] and one MA (MA) (Lee & Park 2017)[19] on the association between a vegetarian diet and the risk of diabetes. The umbrella review by Oussalah et al. (2020)[10] included only one MA investigating this association, namely the MA by Lee and Park (2017)[19]. Therefore, the committee describes the results of the original MA rather than the umbrella review.

The MA by Lee and Park (2017)[19] included twelve cross-sectional studies and two prospective cohort studies. Whether the association of a vegetarian diet was with the risk of diabetes type 1 and/or diabetes type 2 was not specified in the paper. An overall

analysis was performed where all cross-sectional and prospective studies were included, as well as separately by study design. Results for the association between a vegetarian diet and the risk of diabetes in prospective cohort studies showed a statistically significant inverse association (OR= 0.64, 95%CI 0.57-0.74, I^2= 59.5, p= 0.116, n= 49,788 participants, n cases= NR n= 2 cohort studies). However, since there were only two prospective cohort studies available the committee does not further describe this study.

4.2.10 Breast cancer

Summary vegetarian diets and risk of breast cancer

Aspect	Explanation
Selected studies	1 MA of 5 prospective cohort studies (described in 4 publications) (Godos et al. 2017)[12]
Heterogeneity	No
Strength of the association	RR= 0.96 (95%CI 0.88-1.05)
Study population	General adult female population

Abbreviations: CI: confidence interval; RR: relative risk

The committee found one umbrella review (Oussalah et al. 2020)[10] and two MAs (Godos et al. 2017, and Dinu et al. 2017)[12,15] describing the association between vegetarian diets and the risk of breast cancer. The umbrella review by Oussalah et al. (2020)[10] included the same MAs on this association (Godos et al. (2017)[12] and Dinu et al. (2017)[15]). As the umbrella review by Oussalah et al. (2020)[10] did not present a pooled estimate for the included MAs, the committee considers the individual MAs. The MA by Dinu et al. (2017)[15] included two prospective cohort studies that investigated the association between vegetarian diets and risk of breast cancer (Cade et al. 2010, and Orlich et al. 2015). Both prospective cohort studies were included in the MA by Godos et al. (2017). For this reason, only the MA by Godos et al. (2017),[12] which included five cohort studies, is described below and presented in Table 19.

The MA by Godos et al. (2017)[12] aimed at investigating the association between vegetarian diets and the risk of breast cancer, colorectal cancer and prostate cancer. A total of five cohort studies (described in four publications) were included that reported on the association between vegetarian diets and the risk of breast cancer. The included cohort studies had follow-up periods ranging from 5 to 20 years. In this MA, a vegetarian diet (meat consumption <1 time per month), was compared with a non-vegetarian diet (consumption of meat >1 time per week). Moreover, a non-vegetarian diet was compared with a semi-vegetarian diet (consumption of meat >1 time per month but <1 time per week) and with a pesco-vegetarian diet (consumption of fish >1

time per month). All studies used a food-frequency questionnaire (FFQ) to assess dietary intake. All studies adjusted for sex, BMI, smoking status, physical activity, energy intake, and hormonal and partiy status in women. The quality of all included publications was high according to the Newcastle- Ottawa Quality Assessment Scale. Results showed a statistically non-significant inverse association between a vegetarian diet and risk of breast cancer compared to a non-vegetarian diet (RR= 0.96, 95%CI 0.88-1.05, n= 5 cohort studies described in four publications). There was no heterogeneity (I^2= 0%, p= 0.93). Subgroup analysis by menopausal status showed similar findings, with no significant results in premenopausal (RR = 0.99, 95% CI: 0.82, 1.20; I^2 = 0%, p= 0.63) and postmenopausal women (RR = 0.93, 95% CI: 0.81, 1.06; I^2 = 0%, p= 0.55). However, the number of studies included in this subgroup analysis was not reported by the authors. Results also showed a statistically non-significant inverse association between a pesco-vegetarian with the risk of breast cancer compared to a non-vegetarian diet (RR= 0.98, 95%CI 0.83- 1.16, I^2= 45%, p= 0.14, n= 5 cohort studies described in four publications). Results on the association between a semi-vegetarian diet (vs. a non-vegetarian diet) and the risk of breast cancer were also reported in the paper but had too few studies (n= 2 cohort studies). For this reason, the committee did not describe these results in this background document.

Table 19 Results from the meta-analysis by Godos et al. (2017)[12] on the association between vegetarian diets and the risk of breast cancer.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
5 (described in 4 publications)	Vegetarian diet vs. Non-vegetarian diet	>35,000[a]	3,441	0.96 (0.88-1.05)	0%	General adult female population; Europe and North America

Abbreviations: CI: confidence interval; N: number; RR: relative risk

[a] The exact number of participants was not calculated by the committee because one study did not provide the number of included women.

4.2.11 Colorectal cancer

Summary vegetarian diets and risk of colorectal cancer

Aspect	Explanation
Selected studies	1 meta-analysis of 4 cohorts (described in 3 publications) (Godos et al. 2017)[12]
Heterogeneity	No
Strength of the association	RR= 0.88 (95%CI 0.74-1.05) (vegetarian vs. non-vegetarian) RR= 0.67 (95%CI 0.53- 0.83) (pesco-vegetarian vs. non-vegetarian) RR= 0.86 (95%CI 0.79-0.94) (semi-vegetarian vs. non-vegetarian)
Study population	General adult population

Abreviations: CI: confidence interval; RR: relative risk

The committee found one umbrella review (Oussalah et al. 2020)[10] and one MA (MA) (Godos et al. 2017)[12] describing the association between vegetarian diets and the risk of colorectal cancer. The umbrella review by Oussalah et al. (2020)[10] included one MA that investigated this association, namely the MA by Godos et al. (2017)[12]. For this reason, the individual MA of Godos et al. (2017)[12] is described below and presented in Table 20.

The MA by Godos et al. (2017)[12] aimed at investigating the association between vegetarian diets and the risk of breast, colorectal and prostate cancer. A total of four prospective cohort studies (described in three publications) were included that reported on the association between vegetarian diets and colorectal cancer risk. The included cohort studies had follow-up periods ranging from 5 to 20 years. In this MA, a vegetarian diet (meat consumption <1 time per month), was compared with a non-vegetarian diet (consumption of meat >1 time per week). Moreover, a non-vegetarian diet was compared with a semi-vegetarian diet (consumption of meat >1 time per month but <1 time per week) and with a pesco-vegetarian diet (consumption of fish >1 time per month). All studies used a food-frequency questionnaire to assess dietary intake. All studies adjusted for sex, BMI, smoking status, physical activity, energy intake, and hormonal and partiy status in women. The quality of all included publications was high according to the Newcastle- Ottawa Quality Assessment Scale. Results showed a statistically non-significant inverse association between a vegetarian diet and the risk of colorectal cancer compared to a non-vegetarian diet (RR= 0.88, 95%CI 0.74-1.05, n= 4 cohort studies described in three publications). There was no heterogeneity (I^2= 22%, p= 0.28). Results showed a statistically significant inverse association between a pesco-vegetarian diet with the risk of colorectal cancer compared to a non-vegetarian diet (RR=0 .67, 95%CI 0.53- 0.83, I^2= 0%, p= 0.46, n= 4 cohort studies described in three publications). Subgroup analysis by cancer localisation showed a statistically non-significant decreased risk of colon (RR= 0.74,

95%CI= 0.52-1.06; I^2= 6%, p= 0.30) and rectal cancer (RR= 0.70, 95% CI= 0.43-1.13; I^2= 0%, p= 0.97). However, the number of studies included in these subgroup analyses was not reported by the authors. The analysis on semi-vegetarians included four datasets from three cohort studies (described in three publications) with a total of 580,175 participants and 4,062 cases of colorectal cancer. The analysis showed a statistically significant association with reduced colorectal cancer risk (RR= 0.86, 95%CI 0.79-0.94). There was no heterogeneity (I^2= 0%, p= 0.82). However, the risk estimate of this analysis was mainly driven by two datasets from the same cohort with weights of 58.8% and 30.2% (Wirfalt et al. 2009). When these two cohorts were excluded, the association was no longer significant. The authors do not give any further explanation for this finding.

Table 20 Results from Godos et al. (2017)[12] on the association between vegetarian diets and the risk of colorectal cancer.

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Heterogeneity (I^2)	Study population
4 (described in 3 publications)	Vegetarian diet vs. Non-vegetarian diet	61,647	1,056	0.88 (0.74-1.05)	22%	General adult population; Europe and North America
	Pesco-vegetarian diet vs. non-vegetarian diet			0.67 (0.53-0.83)	0%	
3 (described in 3 publications)	Semi-vegetarian diet vs. Non-vegetarian diet	580,175	4,062	0.86 (0.79-0.94)	0%	

Abbreviations: CI: confidence interval; N: number; RR: relative risk.

4.2.12 Depression

The committee found two MAs that investigated the association between a vegetarian diet and the risk of depression (Askari et al. 2022 and Iguacel et al. 2021).[20,21] These MAs included both cross-sectional and prospective cohort studies. However, the MA by Askari and colleagues only included one prospective cohort study that established adherence to a vegetarian diet in participants *a priori*. The MA by Iguacel et al. (2021) included ten cross-sectional studies and only one prospective cohort study that looked at the association between a vegetarian diet and the risk of depression.[21] Since one prospective cohort study is too little, both MAs are not further described by the committee in this background document.

4.2.13 Fracture risk

Summary vegetarian diets and risk of fractures:

Aspect	Explanation
Selected studies	1 meta-analysis of 5 cohorts (described in 4 publications) (Iguacel et al. 2019)[16]
Heterogeneity	Yes (high heterogeneity of 92%, p=0.000)
Strength of the association	RR= 1.25 (95%CI 0.92-1.71) (lacto-ovo vegetarian vs. omnivorous)
Study population	General adult population

Abreviations: CI: confidence interval; RR: relative risk

The committee found one MA that investigated the association between a vegetarian diet and fracture risk.[16] This MA included 5 prospective cohort studies (described in 4 publications) looking at this association.[22-25] Inclusion criteria of this MA were studies including lacto-ovo-vegetarian; ovo-vegetarian, or lacto-vegetarian, and omnivorous diets as factors. Studies that included participants participants who had suffered a fracture before starting the vegetarian diet were excluded from the MA. The included prospective cohort studies included a total of 33,131 participants who followed a lacto-ovo vegetarian diet, and had an age range from 25 to 80 years. The included studies had a follow-up ranging from 2 to 5.2 years. Three of the five cohort studies included only women,[23-25] one of the studies included only men,[24] and the remaining study included both men and women.[22] Results showed that individuals following a vegetarian diet had a non-significant higher risk of fractures compared to those following an omnivorous diet (RR= 1.25, 95%CI 0.92-1.71). There was high heterogeneity (I^2= 92%). The forest plot showed that heterogeneity was mostly present in the direction of the estimate. Heterogeneity in the direction of the estimate was mostly influenced by the female cohort study of Appleby et al. (2007),[24] which showed a positive association between a vegetarian diet and the risk of fractures. A sensitivity analysis was performed within the MA excluding the female cohort of Appleby et al. (2007),[24] resulting in a significant positive association between a vegetarian diet and the risk of fracture, as well as lower heterogeneity (RR= 1.48, 95%CI 1.29-1.69, I^2= 16.52, n= 4 prospective cohort studies described in 4 publications). No subgroup analyses were performed for sex or ethnicity within the studies looking at the association between a vegetarian diet and fracture risk. There was no indication for publication bias found for the included studies, and the included studies were of medium quality.

Table 21 Results from the meta-analysis by Iguacel et al. (2019) on the association between vegetarian diets and the risk of fractures.[16]

Number of cohorts	Exposure	N participants	N cases	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
5 (described in 4 publications)	Lacto-ovo vegetarian diet vs. Omnivorous diet	33,131	2,417	1.25 (0.92-1.71)	92%	General adult population; Caucasian and Asian populations

Abbreviations: CI: confidence interval; N: number; RR: relative risk

4.3 Vegan diets

This paragraph described the scientific evidence from SRs of prospective cohort studies on the associations between a vegan diet and the disease outcomes all-cause mortality, risk of cardiovascular disease and mortality, risk of coronary heart disease, risk of myocardial infarction, risk of stroke, and risk of type two diabetes. First, an overview of the different definitions of vegetarian diets used in the different SRs is provided (Table 21).

Table 22 Definitions vegan diets in the included systematic reviews

	Definition vegan diet
Kaiser et al. (2021)[26]	A vegan diet is defined as the complete exclusion of animal products and byproducts, including meat, fish, poultry, seafood, dairy and eggs from the diet
Pollakova et al. (2021)[27]	A vegan diet is defined as a dietary pattern that omits all the animal-derived products
Iguacel et al. (2019)[16]	A vegan diet is defined as a dietary pattern that excludes any kind of animal product

4.3.1 All-cause mortality

There was one MA that investigated the association between a vegan diet and all-cause mortality (Dinu et al. 2017).[15] However, this MA only included two prospective cohort studies investigating this association (Key et al. 1999, and Orlich et al. 2013). Since these are too few cohort studies, the committee did not describe this MA further in this background document.

4.3.2 Cardiovascular events

The committee found one SR including three prospective cohort studies that investigated the association between a vegan diet and cardiovascular events (Kaiser et al. 2021) (Table 22).[26]

The study by Kaiser et al. (2021)[26] aimed at systematically reviewing studies that assessed the association between a vegan diet (vs. a non-vegan diet) and the risk of primary cardiovascular events (including risk of total cardiovascular disease and mortality, risk of coronary heart disease and mortality, risk of acute myocardial infarction, and risk of stroke and mortality), intermediate, and recurrent cardiovascular events.[26] When a study compared a vegan diet with several predefined diets (e.g. vegetarian diets and omnivorous diets), the least restrictive diet was considered as the comparison group (e.g. omnivorous diets). No MA was performed in this SR due to high heterogeneity between studies. A total of three prospective cohort studies investigating the association between a vegan diet and the risk of primary cardiovascular events were included in this SR (Orlich et al. 2013, Tong et al. 2019, and Key et al. 1999).

The prospective cohort study by Orlich et al. (2013) investigated the association between a vegan diet and the risk of cardiovascular disease mortality, as well as with the risk of coronary heart disease mortality. This prospective cohort study included 40,907 participants, of which 13.6% were vegans, and had a follow-up period of 5.8 years. Dietary assessment was performed with a food-frequency questionnaire (FFQ). Adjustment in the analysis was performed for age, sex, region, race, income, education, marital status, smoking, exercise, alcohol intake, sleep, menopausal status (females), and hormone replacement therapy (if post-menopausal). Results of this prospective cohort study showed that there was no statistically significant association between adherence to a vegan diet (compared to a non-vegan diet) with the risk of cardiovascular disease mortality (HR= 0.91, 95%CI 0.71-1.16), and with the risk of coronary heart disease mortality (HR= 0.90, 95%CI 0.60-1.33). According to the Agency for Healthcare Research and Quality (AHRQ) standards, the cohort study by Orlich et al. (2013) was of fair quality.

The prospective cohort study by Key et al. (1999) investigated the association between a vegan diet and the risk of coronary heart disease mortality, as well as with the risk of cerebrovascular disease mortality. This prospective cohort study included 32,519 participants, of which 753 were vegans, and had a follow-up period of 11.7 years. Dietary assessment was performed with a food-frequency questionnaire (FFQ). Adjustment in the analysis was performed for age, sex, and smoking. Results of this prospective cohort study showed that there was no statistically significant association between adherence to a vegan diet (compared to a non-vegan diet) and the risk of coronary heart disease mortality (HR= 0.74, 95%CI 0.46-1.21), as well as with the risk of cerebrovascular disease (HR= 0.70, 95%CI 0.25-1.98). According to the Agency for Healthcare Research and Quality (AHRQ) standards, the cohort study by Key et al. (1999) was of fair quality.

The prospective cohort study by Tong et al. (2019) investigated the association

between a vegan diet with the risk of acute myocardial infarction, the risk of coronary heart disease, and the risk of stroke. This prospective cohort study included 26,260 participants (7% vegans) and had follow-up period of maximum 18.1 years. Dietary assessment was performed with a food-frequency questionnaire (FFQ). Adjustment in the analyses was performed for age, sex, region, recruitment mehod and year, Townsend deprivation index, education, smoking, exercise, alcohol intake, supplement use, hormone replacement therapy (females), and oral contraceptive use.
Results of this prospective cohort study showed that there was no statistically significant association between adherence to a vegan diet (compared to a non-vegan diet) and the risk of acute myocardial infarction (HR= 0.77, 95%CI 0.46-1.27), coronary heart disease (HR= 0.82, 95%CI 0.64-1.05), and stroke (HR= 1.35, 95%CI 0.95-1.92). Subgroup analyses on stroke subtype showed a statistically non-significant association between adherence to a vegan diet and haemorrhagic stroke (HR= 1.09, 95%CI 0.53-2.26, n cases= 300), as well as with ischaemic stroke (HR= 1.54, 95%CI 0.95-2.48, n cases= 519). According to the Agency for Healthcare Research and Quality (AHRQ) standards, the prospective cohort study by Tong and colleagues was of fair quality.

Table 23 Results from the systematic review by Kaiser et al. (2021)[26] on the association between vegan diets and the risk of cardiovascular events.

Included cohorts	Exposure	N participant	Outcome	N cases	RR estimate (95% CI)	Study population
Orlich et al. (2013)	Vegan diet vs. Non-vegan diet	40,907	CVD mortality	987	0.91 (0.71-1.16)	General adult population; USA
			CHD mortality	372	0.91 (0.60-1.33)	
Key et al. (1999)	Vegan diet vs. Non-vegan diet	32,519	CHD mortality	1,743	0.74 (0.46-1.21)	General adult population; USA, UK, Europe
			Cerebrovascular disease mortality	617	0.70 (0.25-1.98)	
Tong et al. (2019)	Vegan diet vs. Non-vegan diet	26,260	Acute myocardial infarction	788	0.77 (0.46-1.27)	General adult population; UK
			CHD	2,820	0.82 (0.64-1.05)	
			Stroke	1,072	1.35 (0.95-1.92)	

Abbreviations: CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; N: number; RR: relative risk; UK: United Kingdom; USA: United States of America

4.3.3 Type 2 diabetes

There was one SR that investigated the association between a vegan diet and the risk of type 2 diabetes (Pollakova et al. 2021).[27] However, this MA only included two prospective cohort studies investigating this association. Since these are too few cohort studies, the committee did not describe this SR further in this background document.

4.3.4 Fracture risk

Summary vegan diets and risk of fractures

Aspect	Explanation
Selected studies	1 MA of 4 cohorts (described in 3 publications) (Iguacel et al. 2019)[16]
Heterogeneity	Yes (high heterogeneity of 88%, p=0.000)
Strength of the association	RR=1.44 (95%CI 1.05-1.98) (vegan vs. omnivorous)
Study population	General adult population

Abreviations: CI: confidence interval; RR: relative risk

The committee found one MA that investigated the association between a vegan diet and fracture risk.[16] This MA included 4 prospective cohort studies (described in 3 publications) looking at this association. Studies that included participants participants who had suffered a fracture before starting the vegan diet were excluded from the MA. The included prospective cohort studies included a total of 33,131 participants who followed a vegan diet, and had an age range from 25 to 80 years. The included studies had follow-up years ranging from 2 to 25 years. Two of the four cohort studies included only women, one of the studies included only men, and the remaining study included both men and women. Results showed that individuals following a vegan diet had a higher risk of fractures compared to those following an omnivorous diet (RR= 1.44, 95%CI 1.05-1.98). This association was statistically significant. There was high heterogeneity (I^2= 88%). The forest plot showed that heterogeneity was mostly present in the size of the estimate. No subgroup analyses were performed for sex or ethnicity within the studies looking at the association between a vegan diet and fracture risk. There was no indication for publication bias found for the included studies, and the included studies were of medium quality.

Table 24 Results from the meta-analysis by Iguacel et al. (2019) on the association between vegetarian diets and the risk of fractures.[16]

Number of cohorts	Exposure	N participant	N cases	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
4 (described in 3 publications)	Lacto-ovo vegetarian diet vs. Omnivorous diet	33,131	1,519	1.44 (1.05-1.98)	88%	General adult population; Caucasian and Asian populations

Abbreviations: CI: confidence interval; N: number; RR: relative risk

5 Results from controlled trials: intermediate outcomes

In this chapter, the committee describes the evidence about effects of plant-based diets on intermediate outcomes from SRs and MAs of (randomized or non-randomised) controlled trials. In line with the evidence described in the previous chapter on health outcomes, the committee distinguished three types of plant-based diets: 1) plant-based diets, 2) vegetarian diets, and 3) vegan diets.

5.1 Plant-based diets

Summary results plant-based diets and intermediate outcomes: SRs of controlled intervention studies with a broad definition of plant-based diets (including vegetarian, vegan or partially plant-based diets) suggest beneficial effects of these diets on blood pressure, LDL-cholesterol and body weight. However, quantification of effects cannot be given since MAs of controlled studies with this broad definition of plant-based diets are not found. MAs on effects of vegetarian and vegan diets on intermediate outcomes are reported separately in subsequent paragraphs.

5.1.1 Blood pressure

The MAs of Gibbs et al.[28] reviews a number of different dietary patterns which are labelled as plant-based including the Dietary Approaches to Stop Hypertension, Mediterranean diet, vegan, lacto-ovo vegetarian, Nordic, high-fiber, high-fruit and vegetable. The results of the MAs for the vegan en lacto-ovo vegetarian diets are described in the next sections. Other diets from this review were not considered plant-based according to the definition of the current background report and are not described here.

Remde et al.[29] conducted a SR of the literature of controlled interventions with plant-based diets on cardiometabolic risk factors. Plant-based diets were plant-based diets with whole foods, vegetarian and vegan diets. There were 14 controlled trials and most of the studies that reported on blood pressure showed a reduction. It is not clear from the review how many studies showed a reduction and effects were not quantified.

5.1.2 LDL-cholesterol and body weight

Identified studies of Medawar et al.,[30] Remde et al.[29] and Tran et al.[31] were SRs without MAs (Table 25). The studies of Medawar and Remde reported on both body weight

and LDL-cholesterol. The SR of Tran et al. included non-controlled studies as well and results are therefore not reported here.

The review of Medawar et al.[30] systematically reviewed controlled intervention trials with a range of different outcomes including body weight and LDL-cholesterol. Plant-based diets were defined as pesco-vegetarian, lacto-ovo-vegetarian or vegan. Among other outcomes, authors concluded that in 26 out of 32 studies beneficial effects of plant-based diets versus conventional diets (duration ≤ 24 months) on weight status and LDL-cholesterol were found. The study populations were healthy participants, obese and type-2 diabetes patients. Since no MA was performed in the study, there was no quantification of results.

Remde et al.[29] conducted a SR of the literature of controlled intervention trials with plant-based diets on cardiometabolic risk factors. Plant-based diets were plant-based diets with whole foods, vegetarian and vegan diets. The majority of sixteen RCTs in the SR showed a statistically significant association between plant-predominant diets with decreased lipids, compared with various controls, such as usual diet, or other health-oriented diets. Five out of 6 RCTs studying effects on body weight showed a significant reduction in body weight. Authors concluded that plant-based diets demonstrated improved weight control and lipids compared with usual diets.

Table 25 Systematic reviews of plant-based diets and intermediate outcomes

First author	Number of studies	Exposure	Study duration	N participant	Outcomes	Study population
Medawar 2019[30]	32 controlled trials	Plant-based (vegetarian or vegan)	≤ 24 months	-	Body weight, LDL-cholesterol	Healthy, obese, type 2 diabetes
Remde 2022[29]	34 controlled trials	Plant-based whole foods, vegetarian, vegan	At least 4 weeks	-	Body weight, LDL-cholesterol (16 controlled trials)	Adults, most with overweight, hypertensuin or diabetes

Abbreviations: CI: confidence interval; N: number; SBP: systolic blood pressure; DBP: diastolic blood pressure

5.2 Vegetarian diets

Summary results vegetarian diets and intermediate outcomes: One SR and MA of controlled trials published after 2015 confirms the reduction in systolic blood pressure (5 mmHg) and in diastolic blood pressure (2 mmHg) by vegetarian diets as compared to omnivorous diets, as concluded in the 2015. SRs and MAs of controlled trials show heterogeneous effect sizes of vegetarian diets on LDL-cholesterol and body weight.

5.2.1 Blood pressure

The umbrella review of Oussalah et al.[10] included one MA on the effect of a vegetarian diet on blood pressure, namely the MA by Yokoyama et al. (2014).[32] This is the MA that substantiated the conclusion in the Dietary Guidelines 2015 that a vegetarian diet reduces systolic blood pressure by 5 mmHg and diastolic blood pressure by 2 mmHg. In addition to that, the current literature search identified one MA of different plant-based diets including a lacto-ovo vegetarian diet on blood pressure (Table 26).[28] Lacto-ovo vegetarian dietary patterns are defined as those that exclude the consumption of all meat, poultry, and fish but still include the consumption of dairy and eggs. The 5 identified studies were conducted between 1983 and 1993 and similar to the studies in the MA of Yokoyama.

Table 26 Results from the meta-analysis on vegetarian diets and blood pressure

First author	Number of studies	Exposure	Study duration	N participant	Effect estimate (95% CI)	Hetero-geneity (I^2)	Study population
Gibbs 2021 [28]	5 controlled trials	Lacto-ovo vegetarian versus habitual or conventional advice diet	6-52 weeks	116 in intervention and 71 in control diet	SBP: -5.47 mmHg (-7.60 to -3.34) DBP: -2.49 mmHg (-4.17 to -0.80)	0% 84%	49.2 years

Abbreviations: CI: confidence interval; N: number; SBP: systolic blood pressure; DBP: diastolic blood pressure

5.2.2 LDL-cholesterol

The umbrella review of SRs/MAs of Oussalah et al. 2020[10] included two MAs of clinical trials on the effect of a vegetarian diet on LDL-cholesterol (Table 27). The MA were both published after 2015, hence not part of the background documents for the RGV 2015 and therefore described here. No other SRs/MAs were identified by the search.

The MA of Wang et al.[33] included vegetarian as well as vegan diets, results were not reported separately. There was substantial heterogeneity in size of the results but results were in the same direction. Authors mention the subgroup analyses which indicated that effects were greater in trials conducted in participants with lower BMI or analyzed on a per-protocol analysis, which could partly explain the heterogeneity.

The MA of Yokoyama et al.[32] included lacto-ovo vegetarian diets and vegan diets. The subgroup analysis in the present study showed that a vegan diet had larger effects on LDL-c than a lacto-ovo vegetarian diet, but the effects were not separately quantified. Authors explained heterogeneity by type of diet, BMI (effects were larger

with lower BMI) and use of lipid-lowering medication (effects were greater among those not using such mediation). Heterogeneity was present in the effect size, not the direction of the effects.

Table 27 Results from meta-analyses on vegetarian diets and LDL-cholesterol

First author	Number of studies	Exposure	Study duration	N participant	RR estimate (95% CI)	Hetero-geneity (I^2)	Study population
Wang 2015[33]	7 randomised controlled trials	Vegetarian, including vegan, ovovegetarian, lactovegetarian and lacto-ovovegetarian *versus* omnivorous	4-74 weeks	832	-0.34 mmol/L; 95% CI: -0.57 to -0.11	72.4%	Adult healthy participants, diabetes patients, overweight and obese
Yoko-yama 2017[32]	19 clinical trials	Vegetarian including vegan *versus* omnivorous (in some cases also calorie/fat retricted)	4-74 weeks	1484	-12.2 mg/dL; 95% CI: -17.7 to -6.7 (=-0.31 mmol/L)	79%	Adults

5.2.3 Body weight

Two SR and MAs of controlled trials on the effect of a vegetarian diet on body weight were found (Table 28). Huang et al included randomised controlled trials only and reported an non-significant reduction on body weight with heterogeneity in effect size.[34] Heterogeneity was attributed to different study designs, the variety of vegetarian diets, the presence or absence of energy restriction, suboptimal study quality, dietary adherence and the intervention strategy (e.g., provided food or dietician instruction-based).

Barnard et al reported results of 4 controlled trials, of which one vegetarian and 3 vegan diets as primary analysis.[35] A significant reduction in body weight was observed, but with heterogeneity in effect size. Greater weight loss was reported in studies with higher baseline weights, smaller proportions of female participants, older participants, or longer durations, and in studies in which weight loss was a goal.

Table 28 Results from meta-analyses on vegetarian diets and weight loss

First author	Number of studies	Exposure	Study duration	N participant	effect estimate (95% CI)	Hetero-geneity (I^2)	Study population
Barnard 2015[35]	4 controlled trials	Lacto-ovovegetarian (n=1) and vegan (n=3) *versus* habitual or conventional advice diet	12 weeks to 13 months	453	-3.4 kg (-4.4 to -2.4)	52%	Overweight, rheumatoid arthritis
Huang 2016[34]	5 randomised controlled trials	Lacto-ovovegetarian diets versus non-vegetarian diets (habitual or standard advice diet)	9-72 weeks	315	-1.48 kg (95% CI: -3.43 to 0.47).	83.6%	Adults, overweight

5.3 Vegan diets

Summary results vegan diets and intermediate outcomes: Results from SRs and MAs show that as compared to omnivorous diets, vegan diets significantly reduce LDL-cholesterol and body weight, but not blood pressure.

5.3.1 Blood pressure

The current literature search identified four SR and MA on vegan diets in relation to blood pressure (Table 29). The MA of Gibbs et al.[28] described results of studies conducted between 1999 and 2018. The vegan diet did not significantly reduce blood pressure. Comparable results were found in the Cochrane SR and MA of Rees et al.[36] In this MA, randomised controlled trials with vegan dietary interventions were grouped as: vegan dietary intervention compared to no or minimal intervention for primary prevention; vegan dietary intervention as compared to another dietary intervention for primary prevention; and a vegan dietary intervention compared to another dietary intervention for the secondary prevention of cardiovascular diseases. There was no significant change in SBP and DBP after vegan dietary intervention as compared to no or minimal intervention. Other comparisons yielded comparable results. Lopez et al. performed a MA of 11 RCTs on vegan diets and blood pressure outcomes.[37] The authors found no significant reduction in blood pressure as compared to less retrictive diets. The authors mentioned that in patients with a systolic blood pressure above 130 mm Hg, a vegan diet could have additional benefit toward a greater reduction in blood pressure readings.

The effects of vegan diets on blood pressure among patients with type 2 diabetes have been examined in a SR of Pollakova et al.[27] In this SR vegan diets were compared with omnivorous diets and 8 studies reported SBP and DBP. Only one out of the eight

studies reported a between group differences which was due to an increase in SBP and DBP in the control group and no changes in the intervention group.

Table 29 Results from systematic reviews and meta-analyses on vegan diets and blood pressure

First author	Number of studies	Exposure	Study duration	N participant	effect estimate (95% CI)	Hetero-geneity (I^2)	Study population
Gibbs 2021[28]	9 controlled trials	Vegan diet *versus* habitual or standard advice diet		339 in intervention and 339 in control diet	SBP: -1.30 mmHg (-3.90 to 1.29) DBP: -0.81 mmHg (-2.91 to 1.28)	26% 51%	49.2 years
Rees 2021[36]	3 RCTs	Vegan dietary intervention as compared to no or minimal intervention	16 to 26 weeks	374 participants	SBP: 0.94 mmHg (-1.18 to + 3.06) DBP: -0.27 mmHg (-1.67 to + 1.12)	0% 0%	General population and people at high risk of CVD
Pollakova 2021[27]	8 RCTs	Vegan diets versus omnivorous diets	6 to 74 weeks	347	No MA. One out of 8 studies found a between group difference with lower SBP and DBP after vegan diet	-	Type 2 diabetes patients
Lopez 2019[37]	11 RCTs	Vegan diet compared with less restrictive diets		983	SBP: −1.33 mm Hg (95%CI, −3.50 to 0.84) DBP: −1.21 mm Hg (95% CI − 3.06 to 0.65		individuals ≥ 18 years of age and older

5.3.2 LDL-cholesterol

In the Cochrane MA of Rees et al.[27] randomised controlled trials with vegan dietary interventions were grouped as: vegan dietary intervention compared to no or minimal intervention for primary prevention; vegan dietary intervention as compared to another dietary intervention for primary prevention; and a vegan dietary intervention compared

to another dietary intervention for the secondary prevention of cardiovascular diseases. As compared to no or minimal intervention, vegan dietary intervention lowered LDL-cholesterol (Table 30). This effect was not significant when vegan dietary intervention was compared to another dietary intervention (data not shown). Furthermore, there was only one intervention for the secondary prevention found in this SR and therefore these results were not reported here.

The effects of vegan diets on blood pressure among patients with type 2 diabetes have been examined in a SR of Pollakova et al.[27] In this SR vegan diets were compared with omnivorous diets and 6 studies reported LDL-cholesterol as an outcome. One out of the 6 studies reported a significant reduction in LDL-cholesterol in the intervention group as compared to the control group, other studies reported no between group differences.

Table 30 Results from the meta-analyses on vegan diets and LDL-cholesterol

First author	Number of studies	Exposure	Study duration	N participant	Effect estimate (95% CI)	Hetero-geneity (I^2)	Study population
Rees 2021[36]	4 RCTs	Vegan dietary intervention versus no intervention or minimal intervention	16 to 26 weeks	227	-0.22 [-0.32 - 0.11] mmol/L	0%	General population and people at high risk of CVD
Pollakova 2021[27]	6 RCTs	vegan diets were compared with omnivorous diets	12 to 74 weeks	329	No MA. One out of 6 studies found a reduction in LDL-cholesterol after vegan diet	-	Type 2 diabetes patients

5.3.3 Body weight

In the Cochrane MA of Rees et al.[36] pooled results on body weight of four randomised controlled trials with vegan dietary interventions as compared to no or minimal intervention were not reported because of substantial heterogeneity. Vegan dietary interventions as compared to another dietary intervention for primary prevention led to a small decrease in body weight with the intervention compared to other dietary interventions (Table 31). Furthermore, there was only one intervention for the secondary prevention found in this SR and therefore these results were not reported here.

Huang et al.[34] included 8 randomised controlled trials and reported a significant reduction on body weight after vegan diets, as compared to non-vegetarian diets, with low heterogeneity. There were three studies overlapping in the MA of Rees et al. and Huang et al. with respect to vegan diets and body weight.

The effects of vegan diets on blood pressure among patients with type 2 diabetes have been examined in a SR of Pollakova et al.[27] In this SR vegan diets were compared with omnivorous diets and 5 studies reported changes in BMI (kg/m2) as an outcome. Two out of the 5 studies reported a significant reduction in BMI in the intervention group as compared to the control group, other studies reported no between group differences.

Table 31 Results from systematic reviews and meta-analyses on vegan diets and body weight

First author	Number of studies	Exposure	Study duration	N participants	effect estimate (95% CI)	Hetero-geneity (I^2)	Study population
Rees 2021[36]	Three trials Seven trials	Vegan dietary interventions versus no intervention or minimal intervention		374	Not pooled	93%	General population and people at high risk of CVD
		…versus another dietary intervention		275	-1.89 [-2.85 , -0.93] kg	0%	
Huang 2016[34]	8 RCTs	vegan diets *versus* non-vegetarian diets	12-96 weeks	836	-2.52 kg (95% CI: -3.02 to -1.98);	3.0%	Adults, overweight
Pollakova 2021[27]	5 RCTs	vegan diets versus omnivorous diets	12 to 74 weeks	307	No MA. Two out of 5 studies found a reduction in BMI after vegan diet	-	Type 2 diabetes patients

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