

Vlees en vleesproducten en chronische ziekten

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1 Introduction

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

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

1.1 Definition of meat

Meat is a group of products with a very diverse nutrient composition, even if it comes from the same animal. This has to do, for example, with the ratio of muscle tissue and fat tissue in meat. As in the related scientific literature, this background document distinguishes between red meat and white meat, and between unprocessed meat and processed meat. Red meat is meat from mammals, and includes beef, veal, pork, lamb, mutton, goat and horse. White meat is meat from poultry such as chicken, turkey, duck and goose, and from domestic rabbit.²⁻⁴ The distinction between unprocessed and processed meat relates to the preservation method used. Meat is regarded as unprocessed if it is merely sliced or minced for domestic food preparation, possibly after being chilled or frozen. Meat is considered to be processed if it is smoked, salted, cured or fermented to enhance flavour or improve preservation, or if preservatives such as nitrate or nitrite have been added. The term processed meat covers all meat products including cold cuts, such as ham, bacon, salami and sausage, and the small proportion of minced meat that is sold as a ready-to-eat cooked product.²⁻⁴

The distinction between unprocessed and processed meat refers to the product as bought by consumers; food preparation in the consumers home is not taken into account in this specification. A third aspect on which meat types are regularly distinguished is the fat content. Generally, meat or meat products are considered lean if the fat content is no more than 20% or, for minced meat, 15%.⁵

In this background document, the committee focused on cohort studies comparing a higher with a lower consumption of meat in relation to health outcomes. It also included randomised controlled trials (RCTs) comparing different types of meat, such as red

meat with white meat, RCTs comparing meat with a non-meat food product, such as fish or legumes, or RCTs comparing a diet with more (or less) meat with a usual diet. The committee considered all these comparisons relevant because together they provide the fullest insight into the effects of meat within the context of a whole dietary pattern. In a separate background document, *Substitution between dietary protein sources and chronic diseases*,⁶ the committee evaluated associations between substitution of meat with other dietary protein sources and chronic disease outcomes based on cohort studies.

The evaluation of health effects of plant-based meat substitutes is not part of the current background document, but is described in the background document *Meat substitutes and dairy substitutes and chronic diseases*.⁷

1.2 Intake of meat in the Netherlands

According to the most recent Dutch National Food Consumption Survey (DNFCS) from 2019-2021, Dutch adults consume meat on 5 to 6 days a week on average.

The average daily amount of meat consumed is approximately 92 grams, of which about three-quarters is red meat and about one-quarter is white meat (Table 1).

About half of the meat consumed is processed, and most processed meat is red meat (>90%). Women eat on average less meat in total and also less red and/or processed meat than men (71 and 55 g/d for women and 113 and 88 g/d for men, respectively).⁸

In recent years, the average amount of meat eaten by 7-69-year-olds has decreased by 18%: from 110 g/d in 2007-2010 to 101 g/d in 2012-2016 to 91 g/d in 2019-2021. A similar trend is seen for red and/or processed meat: the intake has decreased by 21%: from 92 to 83 to 72 g/d in 2007-2010, 2012-2016 and 2019-2021, respectively.^{9,10}

Table 1 Observed intake of total meat and its subtypes in Dutch adults aged 18-79 years according to the Dutch National Food Consumption Survey 2019-2021

	Mean ^a
Total meat excl. meat substitutes	92 g/d
Processed (red or white) meat	46 g/d
Unprocessed (red or white) meat	44 g/d
Total red meat (processed and unprocessed)	68 g/d
Processed red meat	42 g/d
Unprocessed red meat	26 g/d
Total white meat	22 g/d
Processed white meat	4 g/d
Unprocessed white meat	18 g/d
Unclassified meat, offal and game	2 g/d

^a Mean intakes per subgroup were estimated by the committee based on the report The diet of the Dutch. Results of the Dutch National Food Consumption Survey 2019-2021 on food consumption and evaluation with dietary guidelines (2022)⁹ and the StatLine database,⁸ both presenting data from the Dutch National Food Consumption Survey 2019-2021, and via personal communication with the National Institute for Public Health and the Environment (RIVM). Numbers reported reflect the means calculated considering all measurement days (not consumption days only).

2 Methodology

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

2.1 Health outcomes

The committee focused on the health outcomes described below.

Chronic diseases:

Similar to the approach used for the Dutch dietary guidelines 2015 (DDG2015),¹¹ the committee focused on the most common chronic diseases (that are potentially nutrition related) in the Netherlands.^{12,13} These include: coronary heart disease (CHD), stroke, heart failure, type 2 diabetes, cancer subtypes (colorectal cancer and breast cancer), obesity (in some evaluations combined with overweight), depression, chronic obstructive pulmonary disease (COPD) and dementia. Furthermore, evidence for total cardiovascular disease (CVD) and total cancer was included, but only in case the committee expected (based on the quick scans, described below) that such evidence would provide additional insights (on top of the evidence focused on the afore and below listed outcomes) that could be of added value for drawing up or changing a dietary guideline. The committee preferred to use evidence for CVD subtypes and cancer subtypes because these may have different aetiologic pathways related to different dietary exposures. Total CVD and total cancer comprise different subtypes and therefore provide less specific insights in the aetiology underlying the relationships between dietary factors and chronic diseases.

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

Causal risk factors and other short-term outcomes:

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

Causal risk factors are thought to capture the causal pathway that leads to the disease outcome and can be seen as replacement endpoints for the disease of interest.¹⁴ Because of this, the committee considers that an effect on a causal risk factor will also lead to an effect on chronic disease risk. An example is LDL cholesterol as causal risk factor for CHD and stroke. The advantage of using causal risk factors (and other short-term outcomes) in experimental studies is that they usually need considerably fewer participants and shorter study durations (usually several weeks to months) than studies investigating morbidity or mortality outcomes. For instance, dietary effects on LDL cholesterol can be identified in just a few weeks, compared to several years for CHD. Similar to the approach used in 2015, blood pressure, LDL cholesterol and body weight were selected as causal risk factors. As explained in the DDG2015 background document on methodology,¹¹ these factors have been shown to have a causal relationship with at least one of the following chronic diseases: CHD, stroke, heart failure and type 2 diabetes. More recent evidence confirms the causality, presented below.

Blood pressure: A meta-analysis of 48 randomised controlled trials (RCTs) confirmed that multiple blood pressure lowering treatments, including more versus less intensive treatments, reduce the risk of cardiovascular events, including CHD and stroke. This was found in people with and without CVD.¹⁵ Moreover, Mendelian randomisation studies support that blood pressure is causally associated with the risk of CHD and stroke.^{16,17}

LDL cholesterol: Recent reports confirmed that numerous and different types of studies, including prospective cohort studies, RCTs and Mendelian randomisation studies, have convincingly shown that higher LDL cholesterol causes cardiovascular events, such as CHD.¹⁸ The evidence from RCTs is based on various interventions performed among both primary and secondary prevention trials: A meta-analysis of 49 RCTs showed that the use of statin and various non-statin therapies, including diet, that reduce LDL cholesterol, reduce the risk of cardiovascular events.¹⁹ In line with the committee, the European Food Safety Authority (EFSA) also acknowledges that reducing blood LDL cholesterol (by dietary modification and drugs) would generally reduce the risk of development of CHD.²⁰

Body weight: Recent reports confirmed the importance of weight loss via various interventions for the prevention of type 2 diabetes, based on RCTs.^{21,22} Moreover, the causal role of both general and central adiposity, indicated by body mass index and waist-to-hip ratio respectively, in the development of type 2 diabetes and other chronic diseases has been confirmed in Mendelian randomisation studies.²³ Besides body weight, the committee also searched for literature with waist circumference as

outcome, because this may also reflect the causal pathway from adiposity to type 2 diabetes. However, very few relevant studies with this endpoint were found, and that evidence did not contribute to the guidelines.

HbA1c and eGFR: These factors were not yet included in 2015, and were added for the 2025 advisory report because these are important diagnostic indicators of chronic diseases (elevated HbA1c for type 2 diabetes and long-term decline in eGFR for chronic kidney disease).²⁴⁻²⁶ However, in practice, insufficient research focussed on these factors was found to include in the committee's evaluations.

Other outcomes:

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

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

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

2.2 Type of studies

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

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

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

Substitution analyses

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

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

Mendelian randomisation studies

The committee additionally considered evidence from Mendelian randomisation studies, to serve as potential supportive evidence for certain guidelines. In Mendelian randomisation studies, genetic variants are used to investigate causal associations between dietary intake and risk of chronic diseases.²⁷ Only for the topic of dairy products, relevant Mendelian randomisation studies were found, as further explained in the background document on dairy products and chronic diseases.²⁸

2.3 Quick scans

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

To identify differences and similarities compared to the DDG2015, the guidelines for each specific dietary factor (e.g. fruits and vegetables, fats and oils or dairy products) were compared to the recent advices on these dietary factors of the *Nordic Nutrition Recommendations 2023 (NNR2023)*,²⁹ and the *Dietary Guidelines for Americans 2020-2025 (DGA2020)*.³⁰ Moreover, the conclusions and findings regarding the relationships of dietary factors with health outcomes reported in the DDG2015 were compared to conclusions and findings reported in the background documents of the NNR2023 and of the DGA2020. In addition, and based on the above referred documents, the committee identified topics for which there may now be sufficient evidence to draw conclusions on, where this was not yet possible in 2015. Specifically for the topic of meat and meat products, the committee also consulted the report of EAT-Lancet.³¹

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

- Most international dietary guidelines (including the DDG2015) and scientific studies distinguish between red and white meat, and between processed and unprocessed meat, because there are indications that health effects differ between these meat subtypes. For red and processed meat, the DDG2015 guideline is to limit its consumption, particularly processed meat.³² The guideline was not quantified because there was no strong evidence from RCTs for effects of red or processed meat consumption on causal risk factors, which is a requirement for guideline quantification (in Chapter 2 of the advisory report is further explained

which types of evidence are required for drawing up a quantified dietary guideline¹). Based on the quick scan, the committee noted that more cohort studies on red meat and processed meat were published since the publication of the DDG2015, also on health outcomes for which the evidence in 2015 was considered limited (e.g. CHD). Moreover, there appeared to be a few more (MAs of) RCTs examining effects of red meat on causal risk factors (e.g. LDL cholesterol). As this may potentially contribute to quantifying the guideline, the committee decided to evaluate effects and associations of red meat and processed meat consumption. For white meat, no dietary guideline was set in 2015. This was because relatively few studies were found on white meat consumption in relation to health outcomes, and, based on the studies that were available, it was concluded either that an association or effect was unlikely or that the evidence was inconclusive. Based on the quick scan, the committee noted that more (MAs or pooled analyses of) cohort studies on white meat were published since the publication of the DDG2015. Since this could potentially contribute to drawing up a guideline for white meat, the committee decided to evaluate effects and associations of white meat consumption.

- The extent of processing of meat was shown to affect (the magnitude of) the association or effect on health outcomes. Therefore, in its evaluation, the committee aimed to distinguish between unprocessed meat and processed meat within the subgroups of red meat and white meat, to the extent possible.
- Due to the interest in the field with regard to the health effects relating to the fat content of meat, the committee aimed to evaluate health effects of lean meat and high-fat meat separately. However, based on the quick scans, there seemed to be very little studies on this topic. Nevertheless, in its evaluation, the committee aimed to distinguish between lean meat and high-fat meat to the extent possible.
- The committee noted that for the following health outcomes, there is new and relevant literature that may be leading or supportive for the dietary guideline on meat and meat products: CHD, stroke, type 2 diabetes, colorectal cancer, LDL cholesterol, blood pressure and body weight. For white meat, also new and potentially relevant literature was found for fatal CVD and fatal cancer, the two health outcomes that the committee only evaluated by exception (see section 2.1). Because the committee noted that there is relatively little research on white meat consumption and health outcomes in general and that the findings from the available studies were mostly insufficient to draw conclusions with a strong level of evidence, the committee decided to evaluate associations of white meat consumption with fatal CVD and fatal cancer as well.

2.4 Consulted literature

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

- The committee used MAs or scientific reports addressed in the NNR2023 advisory report²⁹ or the NNR2023 background paper on meat and meat products (scoping review).³³ For the NNR2023 background paper, studies published until 13 September 2021 (PubMed) and 29 October 2021 (Web of Science) were included.
- For cancer outcomes, the committee additionally used scientific reports from the World Cancer Research Fund (WCRF), which reported on systematic literature reviews and MAs performed as part of the Cancer Update Programme (CUP). Relevant for meat consumption is the (most recent) WCRF report on meat, fish and dairy products from 2018.²
- The committee additionally used pooled analyses of cohorts that contributed to the European Prospective Investigation into Cancer and Nutrition (EPIC). The committee used such pooled analyses on associations of meat consumption with health outcomes in case these were not included in the above referred MAs, or in case these could give additional insights into the exposure-health outcome relationship being evaluated. EPIC publications were searched by the committee via a systematic literature search (search last updated on 8 July 2024). This resulted in four publications relevant for this background document on meat.^{3,4,34,35}
- In addition to the above, the committee consulted the EAT-Lancet report.³¹
- For a selection of dietary factors, the committee additionally performed systematic literature searches in PubMed and Scopus to search for more recent literature (than the NNR). This was only done if the committee expected such a search would yield additional information that could potentially impact the conclusions drawn by the committee. This was applicable to the following situations:
 - for dietary factors on which, after publication of the recent reports (referred to above), there are scientific advances that could impact the dietary guidelines;
 - for dietary factors on which there is relatively much scientific discussion and/or no consensus on the health effects/associations in the field.
- For the topic of meat and meat products, the committee decided that there was no need to systematically search for more recent literature.

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

2.5 Evaluation of evidence

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

2.5.1 Drawing conclusions based on a decision tree

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

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

The conclusions on (the certainty of) the evidence regarding the effect or association between meat consumption and health outcomes were based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, the committee took the quality of the studies, in particular the risk of bias, and the heterogeneity in findings between studies, into account. The committee used the decision tree (presented in Annex C) as a guidance tool to support consistency in drawing conclusions. This decision tree was also applied by previous committees of the Health Council,³⁶⁻³⁸ and includes elements that are also present in other evaluation methods for determining the quality and certainty of scientific evidence, such as GRADE (for example: heterogeneity and risk of bias).³⁹ The formulation of conclusions was different for RCTs than for cohort studies: RCTs allowed statements about effects (causality) to be made, whereas cohort studies only allowed statements about associations to be made.

The conclusion was followed by a text in which the conclusion was explained and in which the committee presented the publications assessed in connection with the conclusion. This text was accompanied by a table that showed relevant details related to the included studies.

2.5.2 Extensiveness of evaluation

Per dietary factor-health outcome combination, the committee decided on the level of detail of its evaluation. Extensive evaluations were performed for dietary factor – health outcome combinations of which conclusions could be potentially leading for drawing up a new guideline or changing an existing guideline. Remaining dietary factor – health

outcome combinations, of which conclusions unlikely changed compared to 2015 or could only be supportive to a guideline, were evaluated less extensively.

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

In extensive evaluations, the committee drew formal conclusions based on the decision tree, and presented the evaluation according to the format described in Section 2.5.1.

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

The committee performed, in principle, only (extensive and less extensive) evaluations of dietary factor – health outcome relationships when at least 5 individual studies of a specific study type were included in the selected MAs and/or pooled analyses.

This was done because at least 5 studies are needed to qualify the evidence as strong, and because only conclusions with a strong level of evidence are considered for drawing up the dietary guideline (see Chapter 2 of the advisory report¹). The committee could decide to make exceptions in this approach, based on expert judgement of the evidential value, public interest and extent of scientific discussion.

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

- Based on observational cohort studies:
 - Consumption of total red meat and risk of CHD
 - Consumption of unprocessed red meat and risks of CHD and colorectal cancer
 - Consumption of processed meat and risks of CHD and type 2 diabetes
 - Consumption of red and processed meat combined and risk of CHD
 - Consumption of white meat and risks of CHD, stroke and type 2 diabetes
- Based on RCTs:
 - Consumption of red meat and the effects on LDL cholesterol and blood pressure
 - Consumption of white meat and the effect on LDL cholesterol

Remaining topics were less extensively evaluated.

2.6 Deriving dietary guidelines and recommendations on meat

Effects and associations of meat with chronic disease risk are described in Chapter 3 of this background document. The committee used the totality of conclusions with strong evidence described in this document, together with conclusions based on substitution between dietary protein sources,⁶ environmental and chemical food safety aspects,^{40,41} for drawing up the guideline on meat. The (methodology used for the) translation of the totality of evidence into dietary guidelines is described in the advisory report.¹

3 Evaluation of the evidence

This chapter describes the scientific evidence on the associations or effects of red meat, white meat and processed meat consumption with risks of chronic diseases and causal risk factors. Evaluations are grouped according to health outcome.

3.1 Coronary heart disease

3.1.1 Total red meat

In the DDG2015, it was concluded that there was too little research available to draw any conclusion on the association between total red meat consumption and CHD risk.

The committee now selected one MA for its evaluation of the association between total red meat consumption and CHD risk: Bechthold et al. (2019).⁴² The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the association between total red meat consumption and risk of coronary heart disease

Aspect	Explanation
Available studies	1 meta-analysis of 3 cohorts ⁴²
Heterogeneity	No
Strength of the association	RR (95%CI) for highest vs. lowest intake category: 1.16 (1.08, 1.24)
Consumption level examined	Range: 10 to 205 g/d
Study population	USA, Europe

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

Conclusion: A higher consumption level of total red meat is associated with a higher risk of coronary heart disease

Evidence level: Limited

Additional remark: Based on the non-linear dose-response curve, the risk appears to increase from a consumption level of approximately 65 grams per day

Explanation

The MA by Bechthold et al.⁴² comprises of three cohort studies, two of which were performed among American populations and one among a European population. In total, 151,373 participants were involved and 6,659 cases of fatal and non-fatal CHD were reported (Table 2). The range of red meat consumption across the studies in the MA, as reported by Bechthold et al., was approximately 10 to 205 g/d. The committee calculated that the difference in red meat consumption between the lowest and highest intake category in the included studies ranged between approximately 20 and 85 g/d.

The MA shows a 16% higher CHD risk when comparing the highest with the lowest intake category of red meat consumption. No between-study heterogeneity was observed. The linear dose-response analysis shows that each 100 g/d higher consumption of red meat was associated with a 15% higher CHD risk. Again, there was no evidence of between-study heterogeneity. In one study red meat refers to unprocessed red meat and, in the others, to total red meat, but this did not seem to substantially affect the result given the lack of heterogeneity. The non-linear dose-response analysis, performed based on both American cohorts, provides evidence of a non-linear dose-response association between red meat consumption and CHD risk (P-nonlinearity <0.01). From the non-linear dose-response curve, the committee understood that the risk of CHD is fairly stable from 0 g/d up to an intake of approximately 65 g/d, after which the risk starts to increase to approximately 15% at a consumption level of 100 g/d.

All three studies were judged by Bechthold et al. as having a low risk of bias. Using the NutriGrade scoring system, Bechthold et al. rated the quality of the meta-evidence (i.e. the confidence in the estimate) as moderate. Publication bias was not explored by Bechthold et al., since less than 10 studies were available. Bechthold et al. declared no conflicts of interest. They did not report on the funding sources of the individual studies or their own MA.

Taking all findings together and considering the decision tree, the committee concluded that a higher consumption level of total red meat is associated with a higher risk of CHD. The committee noted that the number of cases (≥ 500), the absence of heterogeneity in direction of the association and the statistically significant association would be sufficient for a conclusion with strong evidence. However, the association was based on only three cohort studies, and therefore, the committee considered the evidence for this association to be limited; for strong evidence at least five studies are required. There were no other considerations that would (further) downgrade the strength of the evidence.

Based on the non-linear dose-response analysis by Bechthold et al., the committee assumed that the risk of CHD starts to increase from an intake of about 65 g/d. The committee did note, however, that this analysis was done on a limited number of studies ($n=2$) and involved only American people. The committee furthermore noted that this dose-response analysis was based on intakes up to 100 g/d. Because of missing data for higher consumption levels, the committee could not draw any conclusions regarding the (increased) disease risk at intakes above 100 g/d.

Table 2 Main characteristics and results of the meta-analysis of cohort studies on the association between total red meat consumption and risk of coronary heart disease

Author, year, study design	Exposure (n): consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: RR (95%CI)	I ²	Study population (n)	Risk of bias (n)
Bechthold 2019 ⁴² MA	Red meat ^a (2), unprocessed red meat (1): 9 to 205 g/d (range) ^b	High vs. low ^c	3	151,373; 6,659	1.16 (1.08, 1.24)	0%	Europe (1), USA (2)	Low (3)
Bechthold 2019 ⁴² MA	Red meat ^a (2), unprocessed red meat (1): 9 to 205 g/d (range) ^b	Per +100 g/d	3	151,373; 6,659	1.15 (1.08, 1.23) P-nonlinearity <0.01 ^d	0%	Europe (1), USA (2)	Low (3)

Abbreviations: CI: confidence interval; MA: meta-analysis; n: number; PCS: prospective cohort study; RR: relative risk.

^a Not further specified.

^b As reported by Bechthold et al. It reflects the range of red meat consumption across all studies in the MA.

^c Differences between the highest and lowest intake category in individual studies ranged from 20 to 85 g/d (calculated by the committee).

^d Based on n=2.

3.1.2 Unprocessed red meat

In the DDG2015, it was concluded that the evidence for an association between unprocessed red meat consumption and CHD risk was ambiguous (inconclusive). This conclusion was based on two MAs and one individual cohort, together covering 8 cohorts. The unexplained heterogeneity in one of the MAs, and the different results between the MAs and the large individual cohort were the main reasons for the conclusion ambiguous evidence.

The committee is now aware of one publication on the association between unprocessed red meat consumption and CHD risk: the pooled analysis of EPIC cohorts by Key et al. (2019).³ The committee furthermore noted that the MA by Bechthold et al. (2019)⁴² included one large study on unprocessed red meat: Bernstein et al. (2010).⁴³ Both the pooled analysis and individual cohort study were included in the committee's evaluation. The evidence is summarised below, followed by the committee's conclusion and explanation.

N.B.: The committee noted that the number of studies on unprocessed red meat consumption in the MA by Bechthold et al. is smaller compared to the number of studies selected for the evaluation in the DDG2015. This is due to the fact that Bechthold et al. excluded studies that specifically assessed fatal CHD. As explained in section 2.1, the DDG2025 committee considered it appropriate to focus particularly on the studies on non-fatal CHD or the combined endpoint (fatal and non-fatal CHD).

Summary of evidence for the association between unprocessed red meat consumption and risk of coronary heart disease

Aspect	Explanation
Available studies	<ul style="list-style-type: none"> • 1 pooled analysis of 9 cohorts³ • 1 individual cohort⁴³
Heterogeneity	<ul style="list-style-type: none"> • NA^{3,43}
Strength of the association	<ul style="list-style-type: none"> • HR (95%CI) per 50 g/d higher intake: 1.10 (1.02, 1.19)³ • RR (95%CI) for ~100 vs. ~25 g/d: 1.13 (0.99, 1.30)⁴³
Consumption level examined	<ul style="list-style-type: none"> • P25 to P75: ♂ 30 to 85 g/d, ♀ 15 to 60 g/d³ • Median in lowest and highest quartile: ~25 and ~100 g/d⁴³
Study population	<ul style="list-style-type: none"> • Europe,³ USA⁴³

Abbreviations: CI: confidence interval; HR: hazard ratio; NA: not applicable; P: percentile; RR: relative risk.

Conclusion: A 50 grams per day higher intake of unprocessed red meat is associated with a 10% higher risk of coronary heart disease

Evidence level: Strong

Explanation

The pooled analysis of EPIC cohorts by Key et al.³ comprises of cohorts from 9 European countries, including a total of 409,885 participants and 7,198 cases of a first fatal ischemic heart disease (IHD) or non-fatal myocardial infarction (MI). The exposure concerned unprocessed red meat, which was defined by the authors as unprocessed beef, veal, pork, lamb, mutton, goat, horse, hamburger, meatballs and minced meat. Analyses were performed using observed intakes (based on food frequency questionnaires) and calibrated intakes (observed intakes calibrated with center- and sex-specific 24-hour recall data from an 8% random sample of the cohort). The committee attached more value to the calibrated intake-based analyses because it assumed that the calibrated intake gives a more accurate estimate of actual intake than the observed intake. The median (P25, P75) observed intake of unprocessed red meat at baseline was 58 (30, 87) g/d in men and 34 (16, 59) g/d in women. Dose-response analyses suggest that each 50 g/d higher (calibrated) consumption of unprocessed red meat is associated with a 10% higher risk of CHD (Table 3). The relative risk was a little smaller (1.06) when based on observed intakes. Analyses by quintiles (Q) of observed intake – those analyses were not performed based on calibrated intake – show a significant increasing linear trend across quintiles. The HR was below 1 and not statistically significant for Q2 compared Q1, but the HR became above 1 from Q3 (versus Q1) onwards and the association became nearly statistically significant for Q5 compared to Q1 (HR: 1.10, 95%CI: 0.99, 1.21). The mean calibrated intakes of unprocessed red meat in Q1 and Q5 were 24 and 69 g/d, respectively. All aforementioned associations were based on the fully adjusted models, including socio-demographic, lifestyle and (bio)medical factors and observed/calibrated

intakes of energy and a selection of food groups or nutrients (see footnote Table 3 for more details). Subgroup analyses by age, smoking status, body mass index (BMI), European region, or history of diabetes, previous hypertension or hyperlipidaemia were only performed for the exposure of unprocessed red and processed meat combined, not for unprocessed red meat separately. For the combined exposure, the following applies: no appreciable heterogeneity was observed in the associations between unprocessed red meat and processed meat consumption combined and CHD risk by subgroups according to the aforementioned characteristics, except for age at recruitment. For the combined exposure was also found that the pooled estimates hardly changed after additionally adjusting the HRs for intakes of poultry, fish, milk, yogurt, cheese and eggs, or excluding the first 4 years of follow-up. No risk of bias assessment was performed by Key et al. The analyses for this publication were supported by the UK Medical Research Council, Cancer Research UK and the Wellcome Trust. The role of the sponsors is not stated. Key et al. reported to have no conflicts of interest to disclose.

Bernstein et al.⁴³ performed a study in the large Nurses' Health Study (NHS) cohort. In total, 84,136 middle-aged women from the USA were included and 3,162 cases of non-fatal and fatal CHD were reported after 26 years of follow-up. The median consumption level of unprocessed red meat ranged from approximately 25 g/d in the lowest quintile to 100 g/d in the highest quintile.

Consumption of 1.17 servings of unprocessed red meat per day as compared to 0.28 servings/d (equivalent to approximately 100 and 25 g/d, respectively) was associated with a borderline statistically significant 13% higher risk of CHD (RR (95%CI): 1.13 (0.99, 1.30); Table 3). A significant linear trend over the quintiles was observed (P-trend=0.02). Each serving (~85 g) per day higher intake of unprocessed red meat was statistically significantly associated with a 19% higher risk of CHD.

These associations were based on the fully adjusted models.

No risk of bias assessment was performed in this study. The study was supported by grants from government agencies. One author of the MA was supported by a fellowship provided by a commercial organisation (Unilever) and one author reported to have received an unrestricted grant from an organisation representing the walnut industry (California Walnut Commission).

Taking all findings together and considering the decision tree, the committee concluded that a higher consumption of unprocessed red meat is associated with a higher risk of morbidity and/or mortality due to CHD. The committee considered the evidence for this association to be strong, because there are more than 5 studies and more than 500 cases, there is no evidence of heterogeneity in direction of the association, the association is statistically significant and there were no major considerations that may downgrade the certainty of the evidence.

Based on the statistically significant linear trend analyses from the pooled analysis of EPIC cohorts (Table 3), the committee assumed that the association between unprocessed meat consumption and CHD risk is linear. So, on the basis of the dose-response analysis based on calibrated intakes, the committee concluded that a 50 g/d higher consumption of unprocessed red meat is associated with a 10% higher risk of CHD. The quintile analyses in EPIC, based on observed intakes, are very much in line, and so are the results from the NHS. The committee considered that the linear association applies (at least) to the consumption range examined in the pooled analysis, which is approximately 15 to 85 g/d, based on the 25th and 75th percentile of unprocessed meat consumption for men (30 and 87 g/d) and women (16 and 59 g/d). The committee assumed, given the results of the NHS, that this association might also be applicable to higher consumption levels, up to 100 g/d. Due to the lack of data on even higher intakes, the committee cannot draw any conclusions regarding the (increased) disease risk at intakes above 100 g/d.

Table 3 Main characteristics and results of the pooled EPIC analysis and the individual cohort study on the association between unprocessed red meat consumption and risk of coronary heart disease

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: RR (95%CI)	I ²	Study population (n)	Risk of bias
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed red meat: ♂ 58 (30, 87) g/d ^a , ♀ 34 (16, 59) g/d ^a	Per +50 g/d of calibrated intake	9 ^b	409,885; 7,198	1.10 (1.02, 1.19) ^c P-linear trend=0.018	NA	Europe (all)	NR
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed red meat: ♂ 58 (30, 87) g/d ^a , ♀ 34 (16, 59) g/d ^a	Per +50 g/d of observed intake	9 ^b	409,885; 7,198	1.06 (1.02, 1.10) ^c P-linear trend=0.002	NA	Europe (all)	NR
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed red meat: ♂ 58 (30, 87) g/d ^a , ♀ 34 (16, 59) g/d ^a	Per quintile of observed intake ^{d,e}	9 ^b	409,885; 7,198	Q2 vs. Q1 ^{c,d} : 0.98 (0.89, 1.08) Q3 vs. Q1 ^{c,d} : 1.05 (0.96, 1.15) Q4 vs. Q1 ^{c,d} : 1.06 (0.97, 1.17) Q5 vs. Q1 ^{c,d} : 1.10 (0.99, 1.21) P-linear trend=0.016	NA	Europe (all)	NR
Bernstein 2010 ⁴³ <i>individual cohort</i>	Unprocessed red meat: ~25 to ~100 g/d ^f	High vs. low	1	84,136; 3,162	1.13 (0.99, 1.30) ^g	NA	USA; only women	NA
Bernstein 2010 ⁴³ <i>individual cohort</i>	Unprocessed red meat: ~25 to ~100 g/d ^f	Per +1 serving/d ^h	1	84,136; 3,162	1.19 (1.07, 1.32) ^g	NA	USA; only women	NA

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; n: number; NA: not applicable; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

^a Median (P25, P75).

^b The 9 European countries covered 19 centres.

^c HRs are stratified by EPIC centre and sex, and adjusted for age, smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, physical activity, employment status, level of education completed, body mass index, current alcohol consumption, and observed/calibrated intakes of energy, fruit and vegetables combined, sugars (% energy) and fibre from cereals.

^d Mean 24-hour recall intakes (g/d) within each fifth of intake of unprocessed red meat were 24, 33, 44, 54 and 69, respectively. Median observed intakes (g/d) within each fifth of intake of unprocessed red meat were 3, 22, 39, 60 and 94, respectively.

^e The analyses per quintile were only performed based on observed intakes, not based on calibrated intakes.

^f Median Q1 to median Q5.

^g RRs are adjusted for age, time period, total energy, cereal fibre, alcohol, trans-fat, body mass index, cigarette smoking, menopausal status, parental history of early myocardial infarction, multivitamin use, vitamin E supplement use, aspirin use and physical exercise.

^h One serving of unprocessed red meat corresponds to approximately 85 g.

After evaluation of this exposure-health outcome relationship, the committee became aware of two relevant and more recent MAs of prospective cohort studies on the

association between unprocessed red meat consumption and CHD risk: Papier et al. (2023)⁴⁴ and Shi et al. (2023).⁴⁵ The committee noted that these MAs included 11 and 12 more cohorts (no full overlap), respectively, than the publications by Key et al. and Bernstein et al. (on which the evaluation is based). It therefore considered it important to evaluate if the findings of these MAs are in line with the committee's conclusion.

The MA by Papier et al.⁴⁴ includes a total of 21 cohorts, of which 12 cohorts originated from Europe, 4 from the USA, 4 from Asia and 1 was a multi-country cohort. In total, 1,437,475 participants and 34,949 cases were involved. The median intake of unprocessed red meat across the cohorts ranged from 0 to 25 g/d in the lowest intake categories and from 10 to 141 g/d in the highest intake categories. The MA showed that higher consumption of unprocessed red meat was associated with a higher risk of CHD (RR (95%CI) for high versus low intake: 1.12 (1.07, 1.17), and per +50 g/d: 1.09 (1.06, 1.12)). Moderate heterogeneity between studies was observed ($I^2=39%$ and 41%, respectively). Results did not substantially differ by subgroups of geographic region (Europe versus USA versus Asia; P-heterogeneity=0.93) or sex (P=0.26).

The MA by Shi et al. (2023)⁴⁵ includes a total of 22 cohorts, of which 12 originated from Europe, 4 from the USA, 5 from Asia and 1 was a multi-country cohort. In total, 1,534,602 participants and 35,312 cases were involved. The consumption level of unprocessed red meat across the cohorts was not reported. The MA showed that higher consumption of unprocessed red meat was associated with a higher risk of CHD (RR (95%CI) per +100 g/d: 1.17 (1.09, 1.27)). There was moderate heterogeneity between studies ($I^2=35%$). Results did not substantially differ by subgroups of geographic region (Europe+USA versus Asia; P-heterogeneity=0.99).

Overall, the committee considered that the findings from these more recent MAs are very much in line with the committee's conclusion that there is strong evidence for an unfavourable association between unprocessed red meat consumption and risk of CHD. The committee saw no indications to change the conclusion or its quantification.

3.1.3 Processed meat

In the DDG2015, it was concluded that there was limited evidence for an unfavourable association between processed meat consumption and CHD risk. This conclusion was based on two MAs, together covering 7 cohorts, and an update (longer follow-up) of one of the included cohorts. The relatively small number of cohorts, the quite broad confidence intervals of the associations observed and the indication that the association weakened with increasing follow-up time were the main reasons to judge the evidence as limited (and not strong).

The committee now selected one MA (Bechthold et al. (2019)⁴²) and one pooled analysis of EPIC cohorts (Key et al. (2019)³) for the evaluation of the association between processed meat consumption and CHD risk. The pooled EPIC analysis was

not included in the MA by Bechthold et al. The evidence is summarised below, followed by the committee’s conclusion and explanation.

Summary of evidence for the association between processed meat consumption and risk of coronary heart disease

Aspect	Explanation
Available studies	<ul style="list-style-type: none"> • 1 meta-analysis of 5 cohorts⁴² • 1 pooled analysis of 9 cohorts³
Heterogeneity	<ul style="list-style-type: none"> • Yes, in magnitude⁴² • NA³
Strength of the association	<ul style="list-style-type: none"> • RR (95%CI) per 50 g/d higher intake: 1.27 (1.09, 1.49)⁴² • HR (95%CI) per 50 g/d higher intake: 1.14 (1.04, 1.24)³
Consumption level examined	<ul style="list-style-type: none"> • Range: 0 to 150 g/d⁴² • P25 to P75: ♂ 10 to 50 g/d, ♀ 10 to 35 g/d³
Study population	<ul style="list-style-type: none"> • Europe,^{3,42} USA,⁴² Australia⁴²

Abbreviations: CI: confidence interval; HR: hazard ratio; NA: not applicable; P: percentile; RR: relative risk.

Conclusion: A 50 grams per day higher intake of processed (red and white) meat is associated with a 15% higher risk of coronary heart disease
Evidence level: Strong

Explanation

The two publications selected for the evaluation of the association between processed meat consumption and CHD risk involve both fatal and non-fatal cases of CHD.

The MA by Bechthold et al.⁴² comprises of five cohort studies and involves 7,038 CHD cases (Table 4). The range of processed meat consumption across the included cohorts was approximately 0 to 150 g/d, according to Bechthold et al. The committee calculated that the difference in processed meat consumption between the lowest and highest intake category in the included studies ranged between approximately 15 and 130 g/d. The highest intake reported was in an cohort of American men (Health Professionals Follow-Up Study).⁴⁶

The MA shows a 15% higher CHD risk when comparing the highest with the lowest category of processed meat consumption. Moderate heterogeneity between the studies was observed, which was not explained. There was no obvious heterogeneity in the direction of the association, but rather in the magnitude of the association. A clear explanation for this was not found. In the European cohort, the meat concerned processed red meat, whereas for the other studies it is unknown whether the processed meat concerns red meat, white meat or a combination. The linear dose-response analysis based on 3 studies (2 American cohorts and 1 European cohort) shows that a 50 g/d higher intake of processed meat is associated with a 27% higher CHD risk. Based on 2 studies (both from America) with consumption levels of 0 to 35

g/d, there was no evidence of a non-linear dose-response association between processed meat and CHD risk (P-nonlinearity=0.41).

Bechthold et al. judged all studies as having a low risk of bias. Using the NutriGrade scoring system, Bechthold et al. rated the quality of the meta-evidence (i.e. the confidence in the estimate) as moderate. Publication bias was not explored by Bechthold et al., since less than 10 studies were available. Bechthold et al. declared no conflicts of interest. They did not report on the funding sources of the individual studies or their own MA.

The pooled analysis of EPIC cohorts by Key et al.³ comprises of cohorts from 9 European countries, including a total of 409,885 participants and 7,198 cases of a first fatal IHD or non-fatal MI (Table 4). The exposure concerned processed meat, which was defined by the authors as meat products, including poultry, preserved by methods other than freezing, such as salting with or without nitrites, smoking, marinating, air drying, or heating, and including ham, bacon, sausages, blood sausages, chicken sausage, meat cuts, liver pâté, salami, bologna, tinned meat, luncheon meat, corned beef and black pudding. Analyses were performed using observed intakes (based on food frequency questionnaires) and calibrated intakes (observed intakes calibrated with centre- and sex-specific 24-hour recall data from an 8% random sample of the cohort). The committee attached more value to the calibrated intake, because it assumed that the calibrated intake gives a more accurate estimate of actual intake than the observed intake. The median (P25, P75) observed intake of processed meat at baseline was 27 (11, 49) g/d in men and 20 (8, 36) g/d in women.

Linear dose-response analyses suggest that each 50 g/d higher (calibrated) consumption of processed meat is associated with a 14% higher risk of CHD. The magnitude of the association was smaller (5%), but statistically significant, when based on observed intakes. Analyses by quintiles of observed intakes – those analyses were not performed based on calibrated intakes – show a significant increasing linear trend across quintiles (P-linear trend<0.01). The HR was below 1 and not statistically significant for Q2 compared Q1, but the HR became above 1 from Q3 (versus Q1) onwards, and the association became nearly statistically significant for Q5 compared to Q1 (HR: 1.10, 95%CI: 0.99, 1.22). The mean intakes based on 24-hour recall data in Q1 and Q5 were 10 and 60 g/d, respectively. All aforementioned associations were based on the fully adjusted models, including socio-demographic, lifestyle and (bio)medical factors and observed/calibrated intakes of energy and a selection of food groups or nutrients (see footnote Table 4 for more details). Subgroup analyses by age, smoking status, BMI, European region, or history of diabetes, previous hypertension or hyperlipidaemia were only performed for the exposure of unprocessed red and processed meat combined, not for processed meat separately. For this combined exposure, the following applies: no appreciable heterogeneity was observed by subgroups according to the aforementioned characteristics, except for age at

recruitment. For the combined exposure was also found that the pooled estimates hardly changed after additionally adjusting the HRs for intakes of poultry, fish, milk, yogurt, cheese and eggs, or excluding the first 4 years of follow-up.

No risk of bias assessment was performed by Key et al. The analyses for this publication were supported by the UK Medical Research Council, Cancer Research UK and the Wellcome Trust. The role of the sponsors is not stated. Key et al. reported to have no conflicts of interest to disclose.

Taking all findings together, the committee concluded that a higher consumption of processed (red and white) meat is associated with a higher risk of morbidity and/or mortality due to CHD. Based on the decision tree, the committee considered the evidence for this association to be strong, because there are more than 5 studies in total, more than 500 cases, there is no obvious evidence of heterogeneity in direction of the associations, the associations are statistically significant and there are no other major considerations that would downgrade the evidence level.

For the quantification of the conclusion, the committee decided to rely mainly on the risk estimates from the pooled EPIC analysis. This is because EPIC concerns only European studies and the intake range of processed meat seems to be smaller in the European cohorts than in the American cohorts. Moreover, the type of meat consumed in the USA might differ (be fattier) from that in Europe. Based on the statistically significant linear trend analysis in the EPIC study, the committee assumed that the association between processed meat consumption and CHD risk is linear. The linear dose-response analysis indicates that each 50 g/d higher (calibrated) consumption of processed meat is associated with a 14% higher risk of CHD (Table 4). The quintile analyses, based on observed intakes, are very much in line. The association observed in the MA by Bechthold et al. was stronger. Therefore, the committee rounded the number off (up) to 15% and concluded that a 50 g/d higher consumption of processed meat is associated with a 15% higher risk of CHD. This linear association applies (at least) to the consumption range examined in the pooled analysis, which is 10 to 60 g/d (mean of Q1 and Q5 of processed meat consumption). The committee assumed, given the results of the MA by Bechthold et al., that this association might also be applicable to higher consumption levels, up to 150 g/d.

Table 4 Main characteristics and results of the meta-analysis and pooled EPIC analysis on the association between processed meat consumption and risk of coronary heart disease

Author, year, study design	Exposure: consumption level examined	Type of analysis	n	n participants; n cases	Strength of the association: RR (95%CI)	I ²	Study population (n)	Risk of bias
Bechthold 2019 ⁴² MA	Processed meat ^a : 0 to 150 g/d ^b	High vs. low ^c	5	196,820; 7,038	1.15 (0.99, 1.33)	44%	USA (3), Europe (1), Australia (1)	Low (all)
Bechthold 2019 ⁴² MA	Processed meat ^a : 0 to 150 g/d ^b	Per +50 g/d	3	151,373; 6,659	1.27 (1.09, 1.49) P-nonlinearity=0.41 ^d	0%	USA (2), Europe (1)	Low (all)
Key 2019 ³ pooled EPIC analysis	Processed meat ^e : ♂ 27 (11, 49) g/d ^f ♀ 20 (8, 36) g/d ^f	Per +50 g/d of calibrated intake	9 ^g	409,885; 7,198	1.14 (1.04, 1.24) ^h P-linear trend=0.003	NA	Europe (all)	NR
Key 2019 ³ pooled EPIC analysis	Processed meat ^e : ♂ 27 (11, 49) g/d ^f ♀ 20 (8, 36) g/d ^f	Per +50 g/d of observed intake	9 ^g	409,885; 7,198	1.05 (1.00, 1.10) ^h P-linear trend=0.035	NA	Europe (all)	NR
Key 2019 ³ pooled EPIC analysis	Processed meat ^e : ♂ 27 (11, 49) g/d ^f ♀ 20 (8, 36) g/d ^f	Per quintile of observed intake ^{ij}	9 ^g	409,885; 7,198	Q2 vs. Q1 ^{h,i} : 0.98 (0.89, 1.09) Q3 vs. Q1 ^{h,i} : 1.03 (0.93, 1.14) Q4 vs. Q1 ^{h,i} : 1.07 (0.97, 1.18) Q5 vs. Q1 ^{h,i} : 1.10 (0.99, 1.22) P-linear trend=0.007	NA	Europe (all)	NR

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; MA: meta-analysis; n: number; NA: not applicable; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

^a It was not reported if the exposure concerned processed red meat, processed white meat or a both.

^b Range of processed meat consumption across the cohorts in the MA, as reported by Bechthold et al.

^c Differences between the highest and lowest intake category in individual studies ranged from 15 to 130 g/d (calculated by the committee).

^d Based on n=2.

^e Processed meat included both processed red meat and processed white meat.

^f Median (P25, P75).

^g The 9 European countries covered 19 centres.

^h HRs are stratified by EPIC centre and sex, and adjusted for age, smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, physical activity, employment status, level of education completed, body mass index, current alcohol consumption, and observed/calibrated intakes of energy, fruit and vegetables combined, sugars (% energy) and fibre from cereals.

ⁱ Mean 24-h recall intakes (g/d) within each fifth of intake of processed meat were 10, 25, 34, 43 and 60, respectively. Median observed intakes (g/d) within each fifth of intake of processed meat were 1, 11, 22, 35 and 61, respectively.

^j The analyses per quintile were only performed based on observed intakes, not based on calibrated intakes.

After evaluation of this exposure-health outcome relationship, the committee became aware of two relevant and more recent MAs of prospective cohort studies on the association between processed meat consumption and CHD risk: Papier et al. (2023)⁴⁴ and Shi et al. (2023).⁴⁵ The committee noted that these MAs included 6 and 9 more cohorts (no full overlap), respectively, then Bechthold et al. and Key et al. (on which the

evaluation is based). It therefore considered it important to evaluate if the findings of these MAs are in line with the committee's conclusion.

The MA by Papier et al.⁴⁴ includes a total of 18 cohorts, of which 12 cohorts originated from Europe, 3 from the USA, 2 from Asia and 1 was a multi-country cohort. In total, 1,276,712 participants and 31,426 cases were involved. The median intake of processed meat across the cohorts ranged from 0 to 10 g/d in the lowest intake categories and from 9 to 78 g/d in the highest intake categories. The committee noted that, in general, reported consumption of processed meat was much lower in the Asian cohorts (9 to 14 g/d in the highest intake category) than in the European and American cohorts. The MA showed that higher consumption of processed meat was associated with a higher risk of CHD (RR (95%CI) for high versus low intake: 1.11 (1.06, 1.16), and per +50 g/d: 1.18 (1.12, 1.25)). Moderate heterogeneity between studies was observed ($I^2=44%$ and $38%$, respectively). Differences in association were observed between subgroups of geographic region (P-heterogeneity=0.01): an unfavourable association was observed in the European and American cohorts, whereas a beneficial association was observed among cohorts from Asia. Corresponding RRs (95%CI) per 50 g/d higher intake were 1.16 (1.09, 1.24), 1.25 (1.12, 1.40) and 0.33 (0.14, 0.80), respectively. Results did not substantially differ by subgroups of sex (P=0.89).

The MA by Shi et al. (2023)⁴⁵ includes a total of 21 cohorts, of which 12 originated from Europe, 4 from the USA, 3 from Asia, 1 from Australia and 1 was a multi-country cohort. In total, 1,318,872 participants and 32,158 cases were involved. The exposure investigated was processed red meat. The consumption level of processed red meat across cohorts was not reported. The MA showed that higher consumption of processed red meat was associated with a higher risk of CHD (RR (95%CI) per +100 g/d: 1.14 (1.06, 1.23)). There was moderate heterogeneity between studies ($I^2=32%$). Associations tended to be different between subgroups of geographic region (Europe+USA versus Asia; P-heterogeneity=0.066): a statistically significantly unfavourable association was observed in the Western cohorts (HR (95%CI): 1.15 (1.10, 1.21); $I^2=0%$), whereas no association was observed among the Asian cohorts (HR (95%CI): 0.45 (0.17, 1.22); $I^2=46%$).

Overall, the committee considered that the findings from these more recent MAs are very much in line with the committee's conclusion that there is strong evidence for an unfavourable association between processed meat consumption and risk of CHD. The committee saw no indications to change the conclusion or its quantification.

3.1.4 Unprocessed red and processed meat combined

In the DDG2015, total red meat, unprocessed red meat and processed meat were evaluated in relation to the risk of CHD, but not unprocessed red and processed meat combined. The committee now selected one pooled analysis of EPIC cohorts for its evaluation of the association of unprocessed red and processed meat consumption

combined with CHD risk: Key et al. (2019).³ The evidence is summarised below, followed by the committee’s conclusion and explanation.

Summary of evidence for the association between consumption of unprocessed red meat and processed meat combined and risk of coronary heart disease

Aspect	Explanation
Available studies	1 pooled analysis of 9 cohorts ³
Heterogeneity	NA
Strength of the association	HR (95%CI) per 100 g/d higher intake: 1.22 (1.09, 1.37)
Consumption level examined	P25 to P75: ♂ 55 to 130 g/d, ♀ 35 to 90 g/d
Study population	Europe

Abbreviations: CI: confidence interval; HR: hazard ratio; NA: not applicable; P: percentile.

Conclusion: A 100 grams per day higher intake of unprocessed red meat and processed meat combined is associated with a 20% higher risk of coronary heart disease

Evidence level: Strong

Explanation

The pooled analysis of EPIC cohorts by Key et al.³ comprises of cohorts from 9 European countries, including a total of 409,885 participants and 7,198 cases of a first fatal IHD or non-fatal MI (Table 5). The exposure concerned unprocessed red and processed meat combined, which was defined by the authors as all unprocessed red meat and processed red and white meat. See sections 3.1.2 and 3.1.3 for the full definitions. Analyses were performed using observed intakes (based on food frequency questionnaires) and calibrated intakes (observed intakes calibrated with centre- and sex-specific 24-hour recall data from an 8% random sample of the cohort). The committee attached more value to the calibrated intake because it assumed that the calibrated intake gives a more accurate estimate of actual intake than the observed intake. The median (P25, P75) observed intake of unprocessed red meat and processed meat combined at baseline was 92 (54, 132) g/d in men and 61 (35, 91) g/d in women.

Dose-response analyses suggest that each 100 g/d higher (calibrated) consumption of unprocessed red meat and processed meat combined is associated with a 22% higher risk of CHD. The size of the association was smaller (12%) when based on observed intakes. Analyses by quintiles of observed intake – those analyses were not performed based on calibrated intake – show a significant increasing linear trend across quintiles. The mean calibrated intake of unprocessed red meat and processed meat combined in Q1 and Q5 of men and women combined was 37 and 126 g/d, respectively.

All aforementioned associations were based on the fully adjusted models, including socio-demographic, lifestyle and (bio)medical factors and observed/calibrated intakes

of energy and a selection of food groups or nutrients (see footnote Table 5 for more details). Additional adjustment of the HRs for intakes of poultry, fish, milk, yogurt, cheese and eggs hardly changed the pooled estimate, nor did excluding the first 4 years of follow-up. No substantial heterogeneity was observed by subgroups of age, smoking status, BMI, European region, or history of diabetes, previous hypertension or hyperlipidaemia, except for age at recruitment.

Key et al. did not perform a risk of bias assessment. The analyses for this publication were supported by the UK Medical Research Council, Cancer Research UK and the Wellcome Trust. The role of the sponsors is not stated. Key et al. reported to have no conflicts of interest to disclose.

Based on the above and considering the decision tree, the committee concluded that a higher consumption of unprocessed red and processed meat combined is associated with a higher risk of morbidity and/or mortality due to CHD. The committee considered the evidence for this association to be strong, because there are more than 5 studies, more than 500 cases, there is no evidence of heterogeneity in direction of the association, the association is statistically significant, the findings remained largely robust in sensitivity analyses, and there are no major consideration that may downgrade the certainty of the evidence.

Based on the statistically significant linear trend analyses (Table 5), the committee assumed that the association is linear. Therefore, the committee relied mainly on the dose-response analysis (based on calibrated intakes) for the quantification of the conclusion and concluded that a 100 g/d higher consumption of unprocessed red and processed meat combined is associated with a 20% higher risk of CHD. The quintile analyses, based on observed intakes, are in line. This linear association applies (at least) to the consumption range examined in this study, which is approximately 35 to 130 g/d, based on the 25th and 75th percentile of unprocessed red and processed meat consumption for men (54 and 132 g/d) and women (35 and 91 g/d). In the absence of data on higher consumption levels, the committee cannot draw any conclusions regarding the (increased) disease risk at intakes above 130 g/d.

Table 5 Main characteristics and results of the pooled EPIC analysis on the association between consumption of unprocessed red meat and processed (red and white) meat combined and risk of coronary heart disease

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: RR (95%CI)	P ²	Study population (n)	Risk of bias
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed red meat and processed (red and white) meat combined: ♂ 92 (54, 132) g/d ^a ♀ 61 (35, 91) g/d ^a	Per +100 g/d of calibrated intake	9 ^b	409,885; 7,198	1.22 (1.09, 1.37) ^{c,d} P-linear trend=0.004	NA	Europe (all)	NR
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed red meat and processed (red and white) meat combined: ♂ 92 (54, 132) g/d ^a ♀ 61 (35, 91) g/d ^a	Per +100 g/d of observed intake	9 ^b	409,885; 7,198	1.12 (1.05, 1.18) ^c P-linear trend=0.0002	NA	Europe (all)	NR
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed red meat and processed (red and white) meat combined: ♂ 92 (54, 132) g/d ^a ♀ 61 (35, 91) g/d ^a	Per quintile of observed intake ^{e,f}	9 ^b	409,885; 7,198	Q2 vs. Q1 ^{c,e} : 1.03 (0.93, 1.13) Q3 vs. Q1 ^{c,e} : 1.05 (0.95, 1.15) Q4 vs. Q1 ^{c,e} : 1.06 (0.96, 1.17) Q5 vs. Q1 ^{c,e} : 1.13 (1.02, 1.26) P-linear trend=0.014	NA	Europe (all)	NR

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; n: number; NA: not applicable; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

^a Median (P25, P75).

^b The 9 European countries covered 19 centres.

^c HRs are stratified by EPIC centre and sex, and adjusted for age, smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, physical activity, employment status, level of education completed, body mass index, current alcohol consumption, and observed/calibrated intakes of energy, fruit and vegetables combined, sugars (% energy) and fibre from cereals.

^d Additional adjustment of the HR for calibrated intakes of poultry, white fish, fatty fish, milk, yogurt, cheese and eggs resulted in a marginal smaller association: HR (95%CI): 1.19 (1.06, 1.33).

^e Mean 24-h recall intakes (g/d) within each fifth of intake of unprocessed red meat and processed meat combined were 37, 61, 75, 93 and 126, respectively. Median observed intakes (g/d) within each fifth of intake of unprocessed red meat and processed meat combined were 12, 45, 67, 93 and 138, respectively.

^f The analyses per quintile were only performed based on observed intakes, not based on calibrated intakes.

3.1.5 White meat

In the DDG2015 it was concluded that there was too little research to draw any conclusions on the association between white meat consumption and CHD risk. This was based on one MA of 3 cohort studies and one individual cohort study, and both did not show an (statistically significant) association.

The committee is now aware of one recent MA of 11 cohorts (Ramel et al. (2023)⁴⁷) and one recent pooled analysis of cohort studies (Key et al. (2019)³) on the association between white meat consumption and risk of CHD. Ramel et al. included the pooled analysis of 9 cohorts by Key et al. together with two large American cohorts (the NHS cohort by Bernstein et al. (2010)⁴³ and the Atherosclerosis Risk in Communities study (ARIC) by Haring et al. (2014)⁴⁸), but did not pool the data. Therefore, the committee described the results from the pooled EPIC analysis and from the other two cohorts in the MA by Ramel et al. separately. The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the association between white meat consumption and risk of coronary heart disease

Aspect	Explanation
Available studies	<ul style="list-style-type: none"> 1 pooled analysis of 9 cohorts³ 2 individual cohorts^{43,48}
Heterogeneity	<ul style="list-style-type: none"> NA^{3,43,48}
Strength of the association	<ul style="list-style-type: none"> HR (95%CI) for highest versus lowest intake category: 1.01 (0.94, 1.10) and per 20 g/d higher intake: 0.99 (0.94, 1.04)³ RR (95%CI) for highest versus lowest intake category in individual cohorts: 0.79 (0.64, 0.98)⁴⁸ to 0.92 (0.80, 1.06)⁴³
Consumption level examined	<ul style="list-style-type: none"> P25 to P75: ♂ 10 to 35 g/d, ♀ 5 to 25 g/d³ 5 to 80 g/d^{43,48}
Study population	<ul style="list-style-type: none"> Europe,³ USA^{43,48}

Abbreviations: HR: hazard ratio; NA: not applicable; P: percentile; RR: relative risk.

Conclusion: The evidence for an association between white meat consumption and risk of coronary heart disease is inconclusive

Evidence level: Not applicable

Explanation

The pooled analysis of EPIC cohorts by Key et al.³ comprises of cohorts from 9 European countries, including a total of 409,885 participants and 7,198 cases of a first fatal IHD or non-fatal MI. The exposure concerned unprocessed poultry, which was defined by the authors as all fresh, frozen or minced chicken, turkey, duck, goose, rabbit, excluding processed poultry. Analyses were performed using observed intakes (based on food frequency questionnaires) and calibrated intakes (observed intakes calibrated with centre- and sex-specific 24-hour recall data from an 8% random sample of the cohort). The committee attaches more value to the calibrated intake because it assumes that it gives a more accurate estimate of actual intake than the observed intake. The median (P25, P75) observed intake of unprocessed poultry at baseline was 16 (8-33) g/d in men and 14 (5-23) g/d in women. The mean calibrated intake of

unprocessed poultry in the lowest and highest intake category of men and women combined were 11 and 27 g/d, respectively.

Both the high-low analysis and the dose-response analyses (based on observed intakes as well on calibrated intakes) did not show an association between consumption of unprocessed poultry and risk of CHD (Table 6). These findings were based on the fully adjusted models, including socio-demographic, lifestyle and (bio)medical factors and observed/calibrated intakes of energy and a selection of food groups or nutrients (see footnote Table 6 for more details). Additional adjustment of the HRs for intakes of red and processed meat, fish, milk, yogurt, cheese and eggs did not change the pooled estimate, neither did exclusion of the first 4 years of follow-up. Subgroup analyses according to history of diabetes, smoking status, sex and BMI did not show substantial differential results.

No risk of bias assessment was performed by Key et al. The analyses for this publication were supported by the UK Medical Research Council, Cancer Research UK and the Wellcome Trust. The role of the sponsors is not stated. Key et al. reported to have no conflicts of interest to disclose.

Bernstein et al.⁴³ included 84,136 middle-aged women from the USA, and 3,162 cases of non-fatal and fatal CHD were reported after 26 years of follow-up. In this study, poultry was defined as chicken with and without skin, chicken sandwich, and chicken/turkey hot dog. The median consumption level of poultry ranged from 0.07 servings/d in the lowest quintile to 0.56 servings/d in the highest quintile, which corresponds to approximately 6 and 48 g/d, respectively.⁴⁴ Both the categorical analyses and the dose-response analysis did not show an association between poultry consumption and CHD risk, although the risk estimates tended towards a beneficial association. The study was judged by Ramel et al. as having a moderate risk of bias. Funding for the study was provided by a government agency.

Haring et al.⁴⁸ included 12,066 middle-aged men and women from the USA, and 1,146 CHD events were reported after 22 years of follow-up. The median consumption level of poultry ranged from 0.1 serving/d in the lowest quintile to 0.8 servings/d in the highest quintile, which corresponds to approximately 8.5 and 68 g/d, respectively. The study tends to show that a higher poultry consumption was associated with a lower risk of CHD. A statistically significant lower risk was only observed for the highest quintile of poultry consumption compared to the lowest quintile (RR (95%CI) for 0.8 versus 0.1 serving/d: 0.79 (0.64, 0.98)). No statistically significant linear trend over the intake categories was observed. The study was judged by Ramel et al. as having a moderate risk of bias. Funding for the study was provided by a government agency. The MA authors reported that there are no relationships with industry.

Based on the above and considering the decision tree, the committee concluded that the evidence for an association between white meat consumption and risk of CHD is inconclusive. This is because the results from the pooled analysis and the individual cohorts were not in line: no indication of an association is observed in the pooled analysis of European cohorts, whereas a tendency towards an inverse association is observed in the 2 individual studies from the USA. The committee initially hypothesised that the association could be dependent on the consumption level, whereby relatively low consumption levels of white meat (as in Europe) might not be associated with CHD risk and relatively high consumption levels (higher than usual in Europe) might be beneficially associated with CHD risk. However, this does not appear to be the case considering the two American studies that tend to show beneficial associations at consumption levels equal to that in Europe and also at higher consumption levels (up to approximately 70 g/d). Because of the (unexplained) inconsistent results between Europe and the USA, the committee concluded that the evidence for an association is inconclusive.

Table 6 Main characteristics and results of the pooled EPIC analysis and the individual cohort studies on the association between white meat consumption and risk of coronary heart disease

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: HR/RR (95%CI)	I ²	Study population (n)	Risk of bias
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 16 (8-33) g/d ^a , ♀ 14 (5-23) g/d ^a	Per +50 g/d of calibrated intake	9 ^b	409,885; 7,198	0.99 (0.94, 1.04) ^c P-linear trend=0.74	NA	Europe (all); men and women	NR
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 16 (8-33) g/d ^a , ♀ 14 (5-23) g/d ^a	Per +50 g/d of observed intake	9 ^b	409,885; 7,198	1.00 (0.98, 1.03) ^c P-linear trend=0.86	NA	Europe (all); men and women	NR
Key 2019 ³ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 16 (8-33) g/d ^a , ♀ 14 (5-23) g/d ^a	Per quintile of observed intake ^{d,e}	9 ^b	409,885; 7,198	Q2 vs. Q1 ^{c,d} : 1.00 (0.92, 1.09) Q3 vs. Q1 ^{c,d} : 0.99 (0.92, 1.08) Q4 vs. Q1 ^{c,d} : 1.00 (0.92, 1.09) Q5 vs. Q1 ^{c,d} : 1.01 (0.94, 1.10) P-linear trend=0.77	NA	Europe (all); men and women	NR

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: HR/RR (95%CI)	P	Study population (n)	Risk of bias
Bernstein 2010 ⁴³ <i>individual cohort</i>	Poultry: ~6 to ~48 g/d ^f	Per number of servings/d ^g	1	84,136; 3,162	0.14 vs. 0.07 serving/d ^{g,h} : 1.07 (0.96, 1.20) 0.24 vs. 0.07 serving/d ^{g,h} : 0.91 (0.80, 1.04) 0.40 vs. 0.07 serving/d ^{g,h} : 0.94 (0.83, 1.06) 0.56 vs. 0.07 serving/d ^{g,h} : 0.92 (0.80, 1.06)	NA	USA; only women	NA
Bernstein 2010 ⁴³ <i>individual cohort</i>	Poultry: ~6 to ~48 g/d ^f	Per +1 serving/d ^g	1	84,136; 3,162	0.90 (0.75, 1.08) ^h	NA	USA; only women	NA
Haring 2014 ⁴⁸ <i>individual cohort</i>	Poultry: ~9 to ~68 g/d ^f	Per number of servings/d ^g	1	12,066; 1,146	0.1 vs. 0.1 serving/d ^{i,j,k} : 0.83 (0.70, 0.99) 0.3 vs. 0.1 serving/d ^{i,j} : 0.93 (0.75, 1.15) 0.4 vs. 0.1 serving/d ^{i,j} : 0.88 (0.73, 1.06) 0.8 vs. 0.1 serving/d ^{i,j} : 0.79 (0.64, 0.98) P-linear trend=0.16	NA	USA; men and women	NA

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; n: number; NA: not applicable; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

^a Median (P25, P75).

^b The 9 European countries covered 19 centres.

^c HRs are stratified by EPIC centre and sex, and adjusted for age, smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, physical activity, employment status, level of education completed, body mass index, current alcohol consumption, and observed/calibrated intakes of energy, fruit and vegetables combined, sugars (% energy) and fibre from cereals.

^d The mean 24-h recall intakes (g/d) within each fifth of intake of unprocessed poultry were 11, 13, 17, 22 and 27, respectively. The median observed intakes (g/d) within each fifth of intake of unprocessed poultry were 0, 7, 15, 22 and 46, respectively.

^e The analyses per quintile were only performed based on observed intakes, not based on calibrated intakes.

^f Median lowest intake category to median highest intake category.

^g One serving of poultry corresponds to ~85 g/d.

^h RRs are adjusted for age, time period, total energy, cereal fibre, alcohol, trans-fat, body mass index, cigarette smoking, menopausal status, parental history of early myocardial infarction, multivitamin use, vitamin E supplement use, aspirin use and physical exercise.

ⁱ Numbers reflect the median number of servings/d in the quintiles. One serving of poultry corresponds to ~85 g/d.

^j HRs are adjusted for age, sex, race, study centre, total energy intake, smoking, education, systolic blood pressure, use of antihypertensive medication, HDL cholesterol, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, physical activity, carbohydrate intake, fibre intake, and magnesium intake.

^k The median intake in both Q1 and Q2 was 0.1 servings/d.

After evaluation of this exposure-health outcome relationship, the committee became aware of another relevant and more recent MA of prospective cohort studies on the association between white meat consumption and CHD risk: the MA by Papier et al. (2023).⁴⁴ The committee noted that this MA included 8 more cohorts as compared to Ramel et al. It therefore considered it important to evaluate if the findings of this MA are in line with the committee's conclusion.

The MA by Papier et al.⁴⁴ comprises of 19 cohorts, of which 12 originated from Europe, 2 from the USA, 4 from Asia and 1 was a multi-country cohort. Among these, is the pooled analysis of 9 EPIC cohorts by Key et al. The outcomes addressed in these cohorts were either CHD incidence (fatal and non-fatal CHD combined; n=13), fatal CHD (n=5) or non-fatal MI (n=1). Among the European cohorts, only 1 study addressed fatal CHD. The median intake of poultry across the cohorts ranged from 0 to 12 g/d in the lowest intake categories and from 15 to 107 g/d in the highest intake categories. Based on a fixed-effect model, the MA did not show an association between poultry consumption and risk of CHD (RR (95%CI) for high versus low intake: 1.03 (0.99, 1.07), and per +50 g/d: 1.02 (0.97, 1.07)). Limited heterogeneity between studies was observed ($I^2=15%$ and $20%$, respectively). However, significant heterogeneity ($P=0.03$) according to geographic region was observed: European studies showed a tendency towards a higher risk of CHD with higher poultry consumption (RR (95%CI) per +50 g/d: 1.07 (1.00, 1.14)), whereas there was a tendency towards a lower risk among the American cohorts (0.92 (0.85, 1.01)). Consumption levels of poultry in the European cohorts and American cohorts overlapped. Results did not substantially differ by subgroups of sex, study quality or level of confounder adjustment, and were unchanged when a random-effects model was used. Also, in sensitivity analyses excluding one study at a time, pooled risk estimates were essentially unchanged. Overall, the committee considered that the findings from this more recent MA are in line with the committee's conclusion that the evidence for an association between white meat consumption and risk of morbidity or mortality due to CHD is inconclusive.

3.2 Stroke

3.2.1 Total red meat

In the DDG2015 it was concluded that consumption of 100 to 120 grams of total red meat per day is associated with a 10% higher risk of stroke. The level of evidence was judged as strong. This conclusion was based on one MA of 5 cohorts.

The committee now identified one more recent MA for its evaluation of the association between total red meat consumption and risk of stroke: Bechthold et al. (2019).⁴²

The MA by Bechthold et al.⁴² comprises of 7 cohort studies and involves a total of 341,767 participants and 10,541 stroke events (Table 7). Reported red meat intake across the cohorts ranged from approximately 6 to 195 g/d. The MA shows that a

higher consumption level of (unprocessed and processed) red meat is associated with a higher risk of morbidity and/or mortality due to stroke, with a 12% higher risk per 100 g/d higher intake. Limited between-study heterogeneity was observed. There was no statistically significant interaction between subgroups according to geographic location (Europe versus America) and no evidence of a non-linear dose-response relationship.

Altogether, the committee considered that those findings based on the current state of science are in line with the conclusion (and its quantification) drawn in the DDG2015.

Table 7 Main characteristics and results of the meta-analysis of cohort studies on the association between total red meat consumption and risk of stroke

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR (95%CI)	I ²
Bechthold 2019 ⁴² MA	Total red meat: 6 to 195 g/d (range)	High vs. low	7; 10,541	1.16 (1.08, 1.25) ^a	0%
Bechthold 2019 ⁴² MA	Total red meat: 6 to 195 g/d (range)	Per +100 g/d	7; 10,541	1.12 (1.06, 1.17) ^a P-nonlinearity=0.91 ^b	0%

Abbreviations: CI: confidence interval; MA: meta-analysis; n: number; PCS: prospective cohort study; RR: relative risk.

^a No statistically significant interaction between subgroups according to geographic location (Europe versus America).

^b Based on n=6.

3.2.2 Unprocessed red meat

In the DDG2015 it was concluded that consumption of 100 to 120 grams of unprocessed red meat per day is associated with a 10% higher risk of stroke. The level of evidence was judged as strong. This conclusion was based on one MA of 6 cohorts.

The committee now identified one more recent MA for its evaluation of the association between unprocessed red meat consumption and risk of stroke: Zeraatkar et al. (2019).⁴⁹ In addition, it selected the recent pooled analysis of EPIC cohorts by Tong et al. (2020)⁴ for its evaluation, which was not included in the MA by Zeraatkar et al.

The MA by Zeraatkar et al.⁴⁹ comprises of 6 cohort studies and involves a total of 254,742 participants (Table 8). The number of stroke events and reported consumption level of unprocessed red meat across the cohorts was not reported. It was found that a 3 servings/week higher intake of unprocessed red meat (corresponding to approximately 51 g/d) was associated with a 6% higher risk of stroke. The magnitude of the association was similar for stroke mortality, but based on fewer studies. There was no heterogeneity between studies observed. Results from the subgroup analyses according to risk of bias showed that the results were essentially unchanged in the subgroup of studies with a low risk of bias (n=4).

The pooled analysis of EPIC cohorts by Tong et al.⁴ comprises of cohorts from 9 European countries, including a total of 418,329 adult participants (Table 8). A total of 7,378 events of stroke (ischaemic, haemorrhagic and unspecified) were reported over a mean follow-up of 12.7 years. Unprocessed red meat was defined by Tong et al. as all fresh, frozen or minced unprocessed red meats, including beef, veal, pork, lamb, mutton, goat, horse, hamburger, meatballs, minced meat. The median (P25, P75) observed consumption level of unprocessed red meat at baseline was 48 (23, 80) g/d in men and 28 (13, 50) g/d in women. Based on the calibrated intake data, it was shown that a 50 g/d higher intake of unprocessed red meat was associated with a 12% higher risk of stroke. There were indications of a linear dose-response relationship (P-linear trend=0.009).

Based on the above, the committee considered that these findings based on the current state of science are generally in line with the DDG2015 conclusion: they also suggest an unfavourable association between consumption of unprocessed red meat and risk of stroke. The observed risk reductions were between approximately 10 and 25% per 100 g/d higher intake of unprocessed red meat.

Table 8 Main characteristics and results of the meta-analysis and pooled analysis of cohort studies on the association between unprocessed red meat consumption and risk of stroke

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR/HR (95%CI)	I ²
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red meat: NR	High vs. low	6; NR ^a	1.11 (1.03, 1.20)	0%
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red meat: NR	Per +3 servings/wk (=51 g/d) ^b	6; NR ^c	1.06 (1.02, 1.11)	0%
Tong 2020 ⁴ Pooled EPIC analysis	Unprocessed red meat; ♂ 48 (23, 80) g/d ^d ♀ 28 (13, 50) g/d ^d	Per +50 g/d of calibrated intake	9; 7,378	1.12 (1.03, 1.22) P-linear trend=0.009	NA
Tong 2020 ⁴ Pooled EPIC analysis	Unprocessed red meat: ♂ 48 (23, 80) g/d ^d ♀ 28 (13, 50) g/d ^d	Per +50 g/d of observed intake	9; 7,378	1.06 (1.02, 1.10) P-linear trend=0.004	NA
Tong 2020 ⁴ Pooled EPIC analysis	Unprocessed red meat: ♂ 48 (23, 80) g/d ^d ♀ 28 (13, 50) g/d ^d	Per quintile ^e of observed intake	9; 7,378	Q2 vs. Q1 ^e : 0.97 (0.89, 1.05) Q3 vs. Q1 ^e : 0.99 (0.91, 1.08) Q4 vs. Q1 ^e : 1.02 (0.94, 1.12) Q5 vs. Q1 ^e : 1.09 (0.99, 1.19)	NA

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; IQR: interquartile range; MA: meta-analysis; n: number; NA: not applicable NR: not reported; Q: quintile; RR: relative risk.

^a n cases = NR; n participants = 102,024.

^b According to Zeraatkar et al., 1 serving of unprocessed red meat is 120 g, so 3 servings/week is approximately 51 g/d.

^c n cases = NR; n participants = 254,742.

^d Median (IQR) of observed intakes.

^e Median observed intakes within each fifth of intake of unprocessed red meat were 4, 19, 33, 53, 88 g/d, respectively. If no P for linear trend was shown, no test for linear trend was performed in the MA.

After the initial selection of MAs and the evaluation, the committee became aware of another relevant and more recent MA of prospective cohort studies on the association between unprocessed red meat consumption and stroke risk: Shi et al. (2023).⁴⁵ The committee noted that this MA included 10 cohorts that were not included in the analyses by Zeraatkar et al. or Tong et al. It therefore considered it important to add these findings to its evaluation, to see if these are in line with the committee's conclusion from 2015.

The MA by Shi et al. (2023)⁴⁵ includes a total of 24 cohorts, of which 14 originated from Europe, 6 from the USA and 4 from Asia. This includes the pooled EPIC analysis by Tong et al.⁴ In total, 1,630,647 participants and 28,308 cases were involved. The consumption level of unprocessed red meat across cohorts was not reported. The MA shows that higher consumption of unprocessed red meat was associated with

a borderline statistically significantly higher risk of stroke (HR (95%CI) per +100 g/d: 1.08 (0.99, 1.18)). There was moderate heterogeneity between studies ($I^2=47\%$). This reflects heterogeneity in magnitude and direction of the association. Associations tended to be different between subgroups of geographic region (Europe+USA versus Asia; P-heterogeneity=0.01): a statistically significantly harmful association was observed in the Western cohorts (HR (95%CI) per +100 g/d: 1.13 (1.06, 1.21); $I^2=16\%$), whereas a tendency towards a protective association was observed among the Asian cohorts (HR (95%CI): 0.71 (0.51, 1.01); $I^2=51\%$). The heterogeneity in the subgroup of Western cohorts was substantially reduced. Overall, the committee considered that those findings based on the current state of science are in line with the conclusion drawn in the DDG2015.

3.2.3 Processed meat

In the DDG2015 it was concluded that consumption of 50 grams of processed (red) meat per day is associated with a 10% higher risk of stroke. The level of evidence was judged as strong. The conclusion was based on two MAs of 5 cohorts in total.

The committee now identified two more recent MAs for its evaluation of the association between processed meat consumption and risk of stroke: Bechthold et al. (2019)⁴² and Zeraatkar et al. (2019).⁴⁹ In addition, it selected the recent pooled analysis of EPIC cohorts by Tong et al. (2020),⁴ which was not included in either MA. The results of these publications are summarised in Table 9 and briefly described below.

The MA by Bechthold et al.⁴² comprises of 6 cohort studies and involves a total of 254,742 participants and 9,492 stroke events. Reported processed meat intake across the cohorts ranged from approximately 0 to 85 g/d. The MA showed a 17% higher risk of stroke per 50 g/d higher intake of processed meat. Substantial heterogeneity between studies was observed, which was at least partly explained by geographic location: the relative risks (95%CI) per 50 g/d higher intake were 1.08 (0.96, 1.22) in Europe and 1.47 (1.16, 1.85) in the USA (P-interaction=0.02). There was no evidence of a non-linear dose-response relationship (P-nonlinearity=0.65).

The MA by Zeraatkar et al.⁴⁹ comprises of 6 cohort studies and involves a total of 254,742 participants. The number of stroke events and reported consumption level of processed meat across the cohorts was not reported. It was found that a 3 servings/week higher intake of processed meat (corresponding to approximately 21 g/d) was associated with a 6% higher risk of stroke. The magnitude of the association was similar for stroke mortality, but based on only 2 studies. There was little to moderate heterogeneity between studies observed. Subgroup analyses showed that the association was slightly stronger among the cohorts with a low risk of bias (n=4).

The pooled analysis of EPIC cohorts by Tong et al.⁴ comprises of cohorts from 9 European countries, including a total of 418,329 adult participants. A total of 7,378 events of stroke (ischaemic, haemorrhagic and unspecified) were reported over a mean follow-up of 12.7 years. Processed meat included both red and white meat and was defined by Tong et al. as processed meat products, including poultry, preserved by methods other than freezing, such as salting with or without nitrites, smoking, marinating, air drying, or heating, and including ham, bacon, sausages, blood sausages, chicken sausage, meat cuts, liver pâté, salami, bologna, tinned meat, luncheon meat, corned beef and black pudding. The median (P25, P75) observed consumption level of processed meat at baseline was 33 (15, 58) g/d in men and 20 (8, 38) g/d in women. Based on the calibrated intake data, it was observed that a 50 g/d higher intake of processed meat was associated with a 9% higher risk of stroke. There were indications of a linear dose-response relationship (P-linear trend=0.056).

Based on the above, the committee considered that these findings based on the current state of science are generally in line with the DDG2015 conclusion: they also suggest an unfavourable association between consumption of processed meat and risk of stroke. The observed risk reductions were between approximately 10 and 15% per 50 g/d higher intake of processed meat.

Table 9 Main characteristics and results of the meta-analysis and pooled analysis of cohort studies on the association between processed meat consumption and risk of stroke

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR/HR (95%CI)	I ²
Bechthold 2019 ⁴² MA	Processed meat: 0 to 85 g/d (range)	High vs. low	6; 9,492	1.16 (1.07, 1.26) ^a	12%
Bechthold 2019 ⁴² MA	Processed meat: 0 to 85 g/d (range)	Per +50 g/d	6; 9,492	1.17 (1.02, 1.34) ^b P-nonlinearity=0.65	56%
Zeraatkar 2019 ⁴⁹ MA	Processed meat: NR	High vs. low	6; NR ^c	1.18 (1.08, 1.25)	0%
Zeraatkar 2019 ⁴⁹ MA	Processed meat: NR	Per +3 servings/wk (= 21 g/d) ^d	6; NR ^e	1.06 (1.02, 1.11)	40%
Tong 2020 ⁴ Pooled EPIC analysis	Processed (red and white) meat: ♂ 33 (15, 58) g/d ^f ♀ 20 (8, 38) g/d ^f	Per +50 g/d of calibrated intake	9; 7,378	1.09 (1.00, 1.19) P-linear trend=0.056	NA
Tong 2020 ⁴ Pooled EPIC analysis	Processed (red and white) meat: ♂ 33 (15, 58) g/d ^f ♀ 20 (8, 38) g/d ^f	Per +50 g/d of observed intake	9; 7,378	1.03 (0.98, 1.07) P-linear trend=0.27	NA
Tong 2020 ⁴ Pooled EPIC analysis	Processed (red and white) meat: ♂ 33 (15, 58) g/d ^f ♀ 20 (8, 38) g/d ^f	Per quintile ^g of observed intake	9; 7,378	Q2 vs. Q1 ^g : 0.99 (0.90, 1.09) Q3 vs. Q1 ^g : 1.03 (0.94, 1.13) Q4 vs. Q1 ^g : 1.03 (0.94, 1.13) Q5 vs. Q1 ^g : 1.07 (0.97, 1.18)	NA

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; IQR: interquartile range; MA: meta-analysis; n: number; NA: not applicable; NR: not reported; Q: quintile; RR: relative risk.

^a No statistically significant interaction between subgroups according to geographic location (Europe versus America).

^b RR (95%CI) among the studies conducted in Europe (n=3): 1.08 (0.96, 1.22), I²=47%; America (n=3): 1.47 (1.16, 1.85), I²=6%; P-interaction=0.02.

^c n cases = NR; n participants = 101,861.

^d According to Zeraatkar et al., 1 serving of processed meat is 50 g, so 3 servings/week is approximately 21 g/d.

^e n cases = NR; n participants = 254,742.

^f Median (IQR) of observed intakes.

^g Median observed intakes within each fifth of intake of processed meat were 2, 13, 24, 39 and 64 g/d, respectively.

If no P for linear trend was shown, no test for linear trend was performed in the MA.

After the initial selection of MAs and the evaluation, the committee became aware of another relevant and more recent MA of prospective cohort studies on the association between processed red meat consumption and stroke risk: Shi et al. (2023).⁴⁵

The committee noted that this MA included 4 cohorts that were not included in the analyses by Bechthold et al., Zeraatkar et al. or Tong et al. It therefore considered it important to add these findings to its evaluation, to see if these are in line with the committee's conclusion from 2015.

The MA by Shi et al. (2023)⁴⁵ includes a total of 18 cohorts, of which 13 originated from Europe, 4 from the USA and 1 from Asia. This includes the pooled EPIC analysis by Tong et al.⁴ In total, 1,163,401 participants and 22,116 cases were involved.

The consumption level of processed red meat across cohorts was not reported.

The MA shows that higher consumption of processed red meat was associated with a statistically significantly higher risk of stroke (HR (95%CI) per +50 g/d: 1.16 (1.04, 1.29)). There was substantial heterogeneity between studies ($I^2=51\%$). This reflects mainly heterogeneity in magnitude of the association, not in direction. There was no indication of heterogeneity due to geographic region (Europe+USA versus Asia; P-heterogeneity=0.639), but this may be the result of only 1 Asian study being included in this MA. The association remained essentially unchanged in the subgroup of studies with a low risk of bias (n=7).

Overall, the committee considered that those findings based on the current state of science are in line with the conclusion drawn in the DDG2015.

3.2.4 Unprocessed red and processed meat combined

In the DDG2015, total red meat, unprocessed red meat and processed meat were evaluated in relation to the risk of stroke, but not unprocessed red and processed meat combined. The committee now selected one MA for its evaluation of the association between consumption of unprocessed red and processed meat combined and risk of stroke: Zeraatkar et al. (2019).⁴⁹ In addition, it selected the recent pooled analysis of EPIC cohorts by Tong et al. (2020),⁴ which was not included in the MA by Zeraatkar et al. The results are summarised in Table 10 and briefly described below.

The general picture of the MA by Zeraatkar et al.⁴⁹ and the pooled analysis of EPIC cohorts by Tong et al.⁴ is that a higher intake of unprocessed red and processed meat combined is associated with a higher risk of stroke. In the MA by Zeraatkar et al., a 3 servings/week higher intake of unprocessed red or processed meat combined (which equals approximately 43 g/d) was statistically significantly associated with a 5% higher stroke risk. No heterogeneity between studies was observed. In the pooled analysis of EPIC cohorts, based on the calibrated intake data, it was observed that a 100 g/d higher intake of unprocessed red and processed meat combined was associated with an 18% higher risk of stroke. There were indications of a linear dose-response relationship (P-linear trend=0.005).

Altogether, the overall picture based on the current state of science for red and processed meat combined is generally in line with the DDG2015 conclusions for total red meat, unprocessed red meat and processed meat with risk of stroke.

Table 10 Main characteristics and results of the meta-analysis and pooled analysis of cohort studies on the association between consumption of unprocessed red and processed meat combined and risk of stroke

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR/HR (95%CI)	I ²
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red and processed meat combined: NR	High vs. low	6; NR ^a	1.18 (1.09, 1.17)	0%
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red and processed meat combined: NR	Per +3 servings/wk (= 43 g/d) ^b	6; NR ^c	1.05 (1.03, 1.09) P-nonlinearity=0.37	0%
Tong 2020 ⁴ Pooled EPIC analysis	Unprocessed red and processed meat ^d : ♂ 90 (51, 131) g/d ^e ♀ 57 (33, 85) g/d ^e	Per +100 g/d of calibrated intake	9; 7,378	1.18 (1.05, 1.33) P-linear trend=0.005	NA
Tong 2020 ⁴ Pooled EPIC analysis	Unprocessed red and processed meat ^d : ♂ 90 (51, 131) g/d ^e ♀ 57 (33, 85) g/d ^e	Per +100 g/d of observed intake	9; 7,378	1.08 (1.02, 1.15) P-linear trend=0.005	NA
Tong 2020 ⁴ Pooled EPIC analysis	Unprocessed red and processed meat ^d : ♂ 90 (51, 131) g/d ^e ♀ 57 (33, 85) g/d ^e	Per quintile ^f of observed intake	9; 7,378	Q2 vs. Q1 ^f : 1.06 (0.98, 1.16) Q3 vs. Q1 ^f : 1.06 (0.97, 1.16) Q4 vs. Q1 ^f : 1.07 (0.98, 1.17) Q5 vs. Q1 ^f : 1.18 (1.07, 1.30)	NA

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; IQR: interquartile range; MA: meta-analysis; n: number; NA: not applicable; NR: not reported; Q: quintile; RR: relative risk.

^a n cases = NR; n participants = 172,581.

^b According to Zeraatkar et al., 1 serving of unprocessed red and processed meat combined is 100 g, so 3 servings/week is approximately 43 g/d.

^c n cases = NR; n participants = 300,747.

^d Processed meat includes both processed red meat and processed poultry.

^e Median (IQR) of observed intakes.

^f Median observed intakes within each fifth of intake of unprocessed red and processed meat combined were 14, 44, 66, 91 and 139 g/d, respectively.

If no P for linear trend was shown, no test for linear trend was performed in the MA.

3.2.5 White meat

The DDG2015 committee was not aware of MAs of cohort studies on white meat consumption in relation to the risk of stroke, so no conclusion on this topic was drawn in the DDG2015.

The committee now selected one recent MA of 3 cohorts (Ramel et al. (2023)⁴⁷) and one recent pooled analysis of cohort studies (Tong et al. (2020)⁴) for its evaluation of the association between white meat consumption and morbidity and/or mortality due to

stroke. The pooled analysis by Tong et al. was not included in the MA by Ramel et al. Ramel et al. also did not pool the data, because of the limited number of studies. Therefore, the committee describes the results from the pooled analysis by Tong et al. and from the other 3 cohorts in the MA by Ramel et al. separately. The 3 cohorts are: the NHS and Health Professionals Follow-up Study (HPFS) by Bernstein et al. (2012)⁵⁰ and the ARIC study by Haring et al. (2015).⁵¹ The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the association between white meat consumption and risk of stroke

Aspect	Explanation
Available studies	<ul style="list-style-type: none"> 1 pooled analysis of 9 cohorts⁴ 3 individual cohorts^{50, 51}
Heterogeneity	<ul style="list-style-type: none"> NA
Strength of the association	<ul style="list-style-type: none"> HR (95%CI) for highest versus lowest intake category: 0.94 (0.87, 1.02), and per +20 g/d: 0.94 (0.89, 1.00)⁴ RR/HR (95%CI) for highest versus lowest intake category: 0.82 (0.71, 0.94)⁵⁰, 0.97 (0.81, 1.17)⁵⁰ and 0.86 (0.65, 1.14)⁵¹
Consumption level examined	<ul style="list-style-type: none"> Median Q1 to median Q5: 0 to 45 g/d⁴ 15 to 90 g/d^{50, 51}
Study population	<ul style="list-style-type: none"> Europe⁴, USA^{50, 51}

Abbreviations: CI: confidence interval; HR: hazard ratio; NA: not applicable; Q: quintile; RR: relative risk.

Conclusion: The evidence for an association between white meat consumption and risk of stroke is inconclusive

Evidence level: Not applicable

Explanation

The pooled analysis of EPIC cohorts by Tong et al.⁴ comprises of cohorts from 9 European countries, including a total of 418,329 adult participants. Over a mean follow-up of 12.7 years, 7,378 cases of first fatal or non-fatal stroke were reported, of which 4,281 strokes were ischaemic and 1,430 haemorrhagic. The exposure concerned unprocessed poultry, which was defined by the authors as all fresh, frozen or minced chicken, turkey, duck, goose, rabbit, excluding processed poultry. Analyses were performed using observed intakes (based on food frequency questionnaires) and calibrated intakes (observed intakes calibrated with centre- and sex-specific 24-hour recall data from an 8% random sample of the cohort). The committee attaches more value to the calibrated intake because it assumes that it gives a more accurate estimate of actual intake than the observed intake. The median (P25, P75) intake of poultry at baseline was 15 (7, 28) g/d in men and 13 (5, 22) g/d in women. The median (observed) intake of poultry in the lowest and highest intake category of men and women combined was 0 and 45 g/d, respectively.

No association between consumption of unprocessed poultry and total stroke risk was

observed in the high-low analysis (Table 11). However, the dose-response analyses (based on both observed intakes and calibrated intakes) showed a small borderline statistically significant lower risk of stroke. Based on the calibrated intakes, a 6% lower stroke risk was observed for each 20 g/d higher poultry intake (HR (95%CI): 0.94 (0.89, 1.00)). Neither the dose-response analyses nor the quintile analysis provides a clear indication of a linear relationship.

With regard to subtypes of stroke (Table 12 and 13), Tong et al. did not find statistically significant associations for either ischaemic stroke or haemorrhagic stroke risk in dose-response or quintile analyses, with the exception of a beneficial association for Q4 compared to Q1 of white meat consumption and ischaemic stroke risk. The committee furthermore noted that, for both subtypes, there was no indication of a linear trend. For ischaemic stroke, HRs did not gradually increase or decrease across the quintiles, but were variable. For haemorrhagic stroke, the HRs in each quintile were close to 1.0, but the confidence intervals were quite broad.

Subgroup analyses according to sex, age, BMI, smoking status and prior disease status were not performed for the outcome of total stroke, but were for ischaemic stroke and haemorrhagic stroke. The associations of poultry consumption with risks of ischaemic stroke and haemorrhagic stroke were not substantially different between subgroups of the aforementioned characteristics. Also, excluding the first 4 years of follow-up did not affect the results.

The analyses for this publication were supported by the UK Medical Research Council, Cancer Research UK and the Wellcome Trust. The role of the sponsors is not stated.

The study by Bernstein et al.⁵⁰ included data from the NHS and HPFS. The NHS included 84,010 middle-aged women from the USA, and 2,633 cases of stroke were reported during 26 years of follow-up. In this study, poultry was defined as chicken with and without skin, chicken sandwich, and chicken/turkey hot dog. The median consumption level of poultry ranged from 0.14 servings/d in the lowest quintile to 0.54 servings/d in the highest quintile, which probably corresponds to approximately 12 and 46 g/d, respectively.⁴⁴ Bernstein et al. found a statistically significantly 18% lower risk of stroke for the highest compared to the lowest quintile of white meat consumption (0.54 versus 0.14 servings/d), and a 39% lower risk per 1 serving per day higher intake of white meat. There were indications of a linear trend (Table 11).

With regard to subtypes of stroke, poultry consumption was shown to be statistically significantly associated with a lower risk of ischaemic stroke, and there was a significant linear trend observed over the quintiles of intake ($P=0.02$). No association was observed with haemorrhagic stroke, and there was no evidence of a linear trend (Table 12 and 13; data shown for linear dose-response analyses, not for categorical analyses). The point estimates for both subtypes were, however, in the same direction ($RR<1.0$). The small(er) number of cases of haemorrhagic stroke may have contributed to the lack of statistical significance for haemorrhagic stroke.

The HPFS included 43,150 middle-aged and older men from the USA, and 1,397 cases of stroke were reported during 22 years of follow-up. Poultry was defined as in the NHS. The median consumption level of poultry ranged from 0.14 servings/d in the lowest quintile to 0.72 servings/d in the highest quintile, which likely corresponds to approximately 12 and 61 g/d, respectively.⁴⁴ Unlike the findings in the NHS, no association between poultry consumption and total stroke risk was observed in the HPFS (Table 11).

With regard to stroke subtypes, no association was observed with either subtype. In general, the RRs for ischaemic stroke tended to be just above 1.0, whereas the RRs for haemorrhagic stroke tended to be just below 1.0 (Table 12 and 13; data shown for linear dose-response analyses, not for categorical analyses). Due to the small number of cases of ischaemic and haemorrhagic stroke, these findings should be interpreted with caution.

Ramel et al. judged the risk of bias in the study by Bernstein et al. as moderate.

Funding for the study by Bernstein et al. was provided by a government agency.

The study by Haring et al.⁵¹ included 11,601 middle-aged men and women from the USA participating in the ARIC study. During a median follow-up of 23 years, 699 stroke events were reported. The median consumption level of poultry ranged from 0.07 serving/d in the lowest quintile to 0.8 servings/d in the highest quintile, which probably corresponds to approximately 8.5 and 68 g/d, respectively.⁴⁴ No association between poultry consumption and total stroke risk was observed, and there was no evidence of a linear trend over the intake categories (Table 11).

Subgroup analyses showed comparable results for subtypes of stroke (ischaemic or haemorrhagic; Table 12 and 13, respectively). Also, in subgroup analyses, results were not substantially different for men and women, and there was no evidence of heterogeneity by sex (P -heterogeneity=0.56). The committee noted, however, that for women the RRs for the 4 intake categories were well below 1 (but not statistically significant), while for men the RRs were mainly around 1.0.

Ramel et al. judged the risk of bias in the study by Haring et al. as moderate. Funding for the study by Haring et al. was provided by a government agency. The MA authors reported that there are no relationships with industry.

Based on the above and considering the decision tree, the committee concluded that the evidence for an association between white meat consumption and risk of morbidity and/or mortality due to stroke is inconclusive. The same applies to the associations with ischaemic stroke risk and haemorrhagic stroke risk. The conclusion is based on the findings of both neutral and some favourable associations, but not unfavourable associations, between white meat consumption and stroke risk. Because the majority of results are not statistically significant, the committee considered the evidence too

weak to conclude that a (small) protective association between white meat consumption and stroke risk might exist.

Table 11 Main characteristics and results of the pooled EPIC analysis and the individual cohort studies on the association between white meat consumption and risk of total stroke

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: HR/RR (95%CI)	P ²	Study population (n)	Risk of bias
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per +20 g/d of calibrated intake	9 ^b	418,329; 7,378	0.94 (0.89, 1.00) ^c P-linear trend=0.071	NA	Europe (all); men and women	NR
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per +20 g/d of observed intake	9 ^b	418,329; 7,378	0.98 (0.95, 1.00) ^c P-linear trend=0.077	NA	Europe (all); men and women	NR
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per quintile of observed intake ^{d,e}	9 ^b	418,329; 7,378	Q2 vs. Q1 ^{c,d} : 0.97 (0.89, 1.05) Q3 vs. Q1 ^{c,d} : 1.00 (0.92, 1.08) Q4 vs. Q1 ^{c,d} : 0.93 (0.86, 1.01) Q5 vs. Q1 ^{c,d} : 0.94 (0.87, 1.02)	NA	Europe (all); men and women	NR
Bernstein 2012 ⁵⁰ – NHS <i>individual cohort</i>	Poultry: ~12 to 46 g/d ^f	Per number of servings/d ^g	1	84,010; 2,633	0.19 vs. 0.14 serving/d ^{h,i} : 1.01 (0.88, 1.15) 0.28 vs. 0.14 serving/d ^{h,i} : 0.91 (0.80, 1.03) 0.40 vs. 0.14 serving/d ^{h,i} : 0.91 (0.80, 1.04) 0.54 vs. 0.14 serving/d ^{h,i} : 0.82 (0.71, 0.94) P-linear trend<0.01	NA	USA; only women	Moderate
Bernstein 2012 ⁵⁰ – NHS <i>individual cohort</i>	Poultry: ~12 to 46 g/d ^f	Per +1 serving/d ^g	1	84,010; 2,633	0.61 (0.45, 0.83) ^j	NA	USA; only women	Moderate
Bernstein 2012 ⁵⁰ – HPFS <i>individual cohort</i>	Poultry: ~12 to 61 g/d ^f	Per number of servings/d ^g	1	43,150; 1,397	0.25 vs. 0.14 serving/d ^{h,i} : 1.01 (0.85, 1.20)	NA	USA; only men	Moderate

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: HR/RR (95%CI)	<i>P</i>	Study population (n)	Risk of bias
					0.40 vs. 0.14 serving/d ^{h,i} : 1.00 (0.84, 1.18) 0.50 vs. 0.14 serving/d ^{h,i} : 1.06 (0.87, 1.28) 0.72 vs. 0.14 serving/d ^{h,i} : 0.97 (0.81, 1.17) P-linear trend=0.74			
Bernstein 2012 ⁵⁰ – HPFS <i>individual cohort</i>	Poultry: ~12 to 61 g/d ^f	Per +1 serving/d ^g	1	43,150; 1,397	0.95 (0.70, 1.28) ^j	NA	USA; only men	Moderate
Haring 2015 ⁵¹ – ARIC <i>individual cohort</i>	Poultry: ~9 to ~68 g/d ^f	Per number of servings/d ^g	1	11,601; 699	0.14 vs. 0.07 serving/d ^{h,j} : 0.90 (0.71, 1.15) 0.28 vs. 0.07 serving/d ^{h,j} : 0.87 (0.65, 1.15) 0.43 vs. 0.07 serving/d ^{h,j} : 0.90 (0.70, 1.16) 0.80 vs. 0.07 serving/d ^{h,j} : 0.86 (0.65, 1.14) P-linear trend=0.55	NA	USA; men and women	Moderate

Abbreviations: ARIC: Atherosclerosis Risk in Communities; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HPFS: Health Professionals Follow-up Study; HR: hazard ratio; n: number; NA: not applicable; NHS: Nurses' Health Study; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

^a Median (P25, P75).

^b The 9 European countries covered 22 centres.

^c HRs are stratified by EPIC centre and sex, and adjusted for age, smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, physical activity, employment status, level of education completed, body mass index, current alcohol consumption, and observed/calibrated intakes of energy.

^d Quintile cut-offs (and median) observed intakes per quintile of unprocessed poultry were <3.4 (0), ≥3.4 to <9.5 (6.6), ≥9.5 to <16.1 (13.5), ≥16.1 to <28.5 (20.4) and ≥28.5 (44.6) g/d.

^e The analyses per quintile were only performed based on observed intakes, not based on calibrated intakes.

^f Median of lowest intake category to median of highest intake category.

^g One serving of poultry corresponds to ~85 g/d.

^h Numbers reflect the median number of servings/d in the quintiles. One serving of poultry corresponds to ~85 g/d.

ⁱ RRs are stratified by age and time period, and adjusted for body mass index, cigarette smoking, physical exercise, parental history of early myocardial infarction, menopausal status (in NHS only), multivitamin use, vitamin E supplement use, aspirin use, and intakes of total energy, cereal fibre, alcohol, trans fat and other protein sources.

^j HRs are adjusted for age, sex, race, study centre, total energy intake, smoking, education, systolic blood pressure, use of antihypertensive medication, HDL cholesterol, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, physical activity, and intakes of carbohydrates, fibre and magnesium.

Table 12 Main characteristics and results of the pooled EPIC analysis and the individual cohort studies on the association between white meat consumption and risk of ischaemic stroke

Author, year, study design	Exposure: consumption level examined	Type of analysis	n	n PCS	n participants; n cases	Strength of the association: HR/RR (95%CI)	P	Study population (n)	Risk of bias
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per +20 g/d of calibrated intake	9 ^b		418,329; 4,281	0.99 (0.91, 1.07) ^c P-linear trend=0.73	NA	Europe (all); men and women	NR
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per +20 g/d of observed intake	9 ^b		418,329; 4,281	0.99 (0.96, 1.03) ^c P-linear trend=0.66	NA	Europe (all); men and women	NR
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per quintile of observed intake ^{d,e}	9 ^b		418,329; 4,281	Q2 vs. Q1 ^{c,d} : 0.95 (0.86, 1.05) Q3 vs. Q1 ^{c,d} : 1.02 (0.92, 1.12) Q4 vs. Q1 ^{c,d} : 0.90 (0.81, 0.99) Q5 vs. Q1 ^{c,d} : 0.97 (0.88, 1.07)	NA	Europe (all); men and women	NR
Bernstein 2012 ⁵⁰ – NHS <i>individual cohort</i>	Poultry: ~12 to 46 g/d ^f	Per +1 serving/d ^g	1		84,010; 1,383	0.61 (0.39, 0.94) ^h	NA	USA; only women	Moderate
Bernstein 2012 ⁵⁰ – HFPS <i>individual cohort</i>	Poultry: ~12 to 61 g/d ^f	Per +1 serving/d ^g	1		43,150; 829	1.07 (0.72, 1.58) ^h	NA	USA; only men	Moderate
Haring 2015 ⁵¹ – ARIC <i>individual cohort</i>	Poultry: ~9 to ~68 g/d ^f	Per number of servings/d ^g	1		11,601; 598	0.14 vs. 0.07 serving/d ^{i,j} : 0.94 (0.72, 1.23) 0.28 vs. 0.07 serving/d ^{i,j} : 0.85 (0.62, 1.16) 0.43 vs. 0.07 serving/d ^{i,j} : 0.92 (0.70, 1.21) 0.80 vs. 0.07 serving/d ^{i,j} : 0.94 (0.70, 1.27) P-linear trend=0.92	NA	USA; men and women	Moderate

Abbreviations: ARIC: Atherosclerosis Risk in Communities; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HFPS: Health Professionals Follow-up Study; HR: hazard ratio; n: number; NA: not applicable; NHS: Nurses' Health Study; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

^a Median (P25, P75).

^b The 9 European countries covered 22 centres.

^c HRs are stratified by EPIC centre and sex, and adjusted for age, smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, physical activity, employment status, level of education completed, body mass index, current alcohol consumption, and observed/calibrated intakes of energy.

^d Quintile cut-offs (and median) observed intakes per quintile of unprocessed poultry were <3.4 (0), ≥3.4 to <9.5 (6.6), ≥9.5 to <16.1 (13.5), ≥16.1 to <28.5 (20.4) and ≥28.5 (44.6) g/d.

^e The analyses per quintile were only performed based on observed intakes, not based on calibrated intakes.

^f Median of lowest intake category to median of highest intake category.

^g One serving of poultry corresponds to ~85 g/d.

^h RRs are stratified by age and time period, and adjusted for body mass index, cigarette smoking, physical exercise, parental history of early myocardial infarction, menopausal status (in NHS only), multivitamin use, vitamin E supplement use, aspirin use, and intakes of total energy, cereal fibre, alcohol, trans fat and other protein sources.

ⁱ Numbers reflect the median number of servings/d in the quintiles. One serving of poultry corresponds to ~85 g/d.

^j HRs are adjusted for age, sex, race, study centre, total energy intake, smoking, education, systolic blood pressure, use of antihypertensive medication, HDL cholesterol, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, physical activity, and intakes of carbohydrates, fibre and magnesium.

Table 13 Main characteristics and results of the pooled EPIC analysis and the individual cohort studies on the association between white meat consumption and risk of haemorrhagic stroke

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: HR/RR (95%CI)	P ²	Study population (n)	Risk of bias
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per +20 g/d of calibrated intake	9 ^b	418,329; 1,430	0.94 (0.82, 1.07) ^c P-linear trend=0.35	NA	Europe (all); men and women	NR
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per +20 g/d of observed intake	9 ^b	418,329; 1,430	0.95 (0.89, 1.01) ^c P-linear trend=0.082	NA	Europe (all); men and women	NR
Tong 2020 ⁴ <i>pooled EPIC analysis</i>	Unprocessed poultry: ♂ 15 (7, 28) g/d ^a , ♀ 13 (5, 22) g/d ^a	Per quintile of observed intake ^{d,e}	9 ^b	418,329; 1,430	Q2 vs. Q1 ^{c,d} : 1.02 (0.86, 1.22) Q3 vs. Q1 ^{c,d} : 1.03 (0.86, 1.23) Q4 vs. Q1 ^{c,d} : 1.00 (0.84, 1.19) Q5 vs. Q1 ^{c,d} : 0.97 (0.82, 1.16)	NA	Europe (all); men and women	NR
Bernstein 2012 ⁵⁰ – NHS <i>individual cohort</i>	Poultry: ~12 to 46 g/d ^f	Per +1 serving/d ^g	1	84,010; 475	0.67 (0.24, 1.89) ^h	NA	USA; only women	Moderate
Bernstein 2012 ⁵⁰ – HPFS <i>individual cohort</i>	Poultry: ~12 to 61 g/d ^f	Per +1 serving/d ^g		43,150; 218	0.55 (0.22, 1.36) ^h	NA	USA; only men	Moderate

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: HR/RR (95%CI)	I ²	Study population (n)	Risk of bias
Haring 2015 ⁵¹ – ARIC <i>individual cohort</i>	Poultry: ~9 to ~68 g/d ^f	Per number of servings/d ^g	1	11,601; 114	0.14 vs. 0.07 serving/d ^h : 0.85 (0.47, 1.52) 0.28 vs. 0.07 serving/d ^h : 1.16 (0.60, 2.23) 0.43 vs. 0.07 serving/d ^h : 0.95 (0.52, 1.74) 0.80 vs. 0.07 serving/d ^h : 0.56 (0.26, 1.20) P-linear trend=0.30	NA	USA; men and women	Moderate

Abbreviations: ARIC: Atherosclerosis Risk in Communities; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HPFS: Health Professionals Follow-up Study; HR: hazard ratio; n: number; NA: not applicable; NHS: Nurses' Health Study; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

a Median (P25, P75).

b The 9 European countries covered 22 centres.

c HRs are stratified by EPIC centre and sex, and adjusted for age, smoking status and number of cigarettes per day, history of diabetes, previous hypertension, prior hyperlipidaemia, physical activity, employment status, level of education completed, body mass index, current alcohol consumption, and observed/calibrated intakes of energy.

d Quintile cut-offs (and median) observed intakes per quintile of unprocessed poultry were <3.4 (0), ≥3.4 to <9.5 (6.6), ≥9.5 to <16.1 (13.5), ≥16.1 to <28.5 (20.4) and ≥28.5 (44.6) g/d.

e The analyses per quintile were only performed based on observed intakes, not based on calibrated intakes.

f Median of lowest intake category to median of highest intake category.

g One serving of poultry corresponds to ~85 g/d.

h RRs are stratified by age and time period, and adjusted for body mass index, cigarette smoking, physical exercise, parental history of early myocardial infarction, menopausal status (in NHS only), multivitamin use, vitamin E supplement use, aspirin use, and intakes of total energy, cereal fibre, alcohol, trans fat and other protein sources.

i Numbers reflect the median number of servings/d in the quintiles. One serving of poultry corresponds to ~85 g/d.

j HRs are adjusted for age, sex, race, study centre, total energy intake, smoking, education, systolic blood pressure, use of antihypertensive medication, HDL cholesterol, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, physical activity, and intakes of carbohydrates, fibre and magnesium.

3.3 Type 2 diabetes

Below, the committee describes the evaluation of the associations of red and/or processed meat consumption with risk of type 2 diabetes based on prospective cohort studies. The committee also identified a MA of RCTs on the effect of red meat consumption on the risk of type 2 diabetes (Zeraatkar et al. (2019)⁵²). However, this MA reported on only one RCT investigating this effect. This is too few to base conclusions on, and the committee therefore disregarded this MA for its evaluation. This means that no evaluation of the effect of red and/or processed meat on type 2 diabetes risk based on RCTs was performed.

3.3.1 Total red meat

The DDG2015 committee concluded that consumption of 100 grams of total red meat per day is associated with a 15% higher risk of type 2 diabetes. The level of evidence was considered strong. This conclusion was based on two MAs of 10 and 14 cohorts.

The committee now selected one MA of 15 cohorts for its evaluation of the association between total red meat consumption and risk of type 2 diabetes: Schwingshackl et al. (2017).⁵³ This MA includes only one study that was not part of the evidence base that informed the DDG2015 conclusion on this topic. This is a European study.

The MA by Schwingshackl et al.⁵³ shows that a higher intake of total red meat (mostly including studies on total red meat, some on unprocessed red meat only) is associated with a higher risk of type 2 diabetes, with a 17% higher risk per 100 g/d higher intake (Table 14). Substantial between-study heterogeneity was observed in magnitude of the association, not in direction. The heterogeneity might be (partially) explained by geographic location: the size of the association was greater in American studies (n=6; RR (95%CI): 1.23 (1.11, 1.36)) compared to European studies (n=6; 1.15 (1.05, 1.27)). Also, the quality of the studies might have affected the results: the magnitude of the association was greater among the studies with a low risk of bias (n=10). Since the majority of studies had a low risk of bias and the association was in the same direction, the quality of the studies does not essentially change the overall conclusion. It is also possible that the degree of meat processing explains part of the heterogeneity.

Altogether, those findings based on the current state of science are in line with the DDG2015 conclusion (and its quantification). This was to be expected, since this more recent MA includes only one additional cohort as compared to the MA used in 2015.

Table 14 Main characteristics and results of the meta-analysis of cohort studies on the association between total red meat consumption and risk of type 2 diabetes

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR (95%CI)	I ²
Schwingshackl 2017 ⁵³ MA	Red meat: 0 to 207 g/d (range)	High vs. low	15; 45,702	1.21 (1.13, 1.30)	65%
Schwingshackl 2017 ⁵³ MA	Red meat: 0 to 207 g/d (range)	Per +100 g/d	14; NR	1.17 (1.08, 1.26) ^{a,b} P-nonlinearity=0.30	83%

Abbreviations: CI: confidence interval; MA: meta-analysis; n: number; NR: not reported; PCS: prospective cohort study; RR: relative risk.

^a RR (95%CI) among the studies with a low risk of bias (n=10): 1.22 (1.13, 1.32), I²=83%.

^b RR (95%CI) among the studies conducted in Europe (n=6): 1.15 (1.05, 1.27), I²=38%; America (n=6): 1.23 (1.11, 1.36), I²=88; Asia/Australia (n=2): 1.03 (0.63, 1.68), I²=89%.

3.3.2 Unprocessed red meat

The DDG2015 committee concluded that consumption of 100 grams of unprocessed red meat per day is associated with a 15% higher risk of type 2 diabetes. The level of evidence was considered strong. This conclusion was based on two MAs of 9 and 14 cohorts.

The committee now selected one MA (Zeraatkar et al. (2019)⁴⁹) and one pooled analysis of EPIC cohorts (Bendinelli et al. (2013)³⁴) for its evaluation of the association between unprocessed red meat consumption and risk of type 2 diabetes. The pooled EPIC analysis was not included in the MA by Zeraatkar et al. (which included, however, a few but not all individual EPIC cohorts).

The pooled analysis by Bendinelli et al.³⁴ was performed in the in the EPIC-InterAct study, a large prospective case-cohort study nested within the EPIC study. It includes cohorts from 8 European countries, and a total of 26,088 participants and 11,559 cases of type 2 diabetes were involved (Table 15). Median consumption in the lowest and highest quintile of unprocessed meat was 7 and 81 g/d in women and 11 and 117 g/d in men, respectively. A substantial harmful association between unprocessed red meat consumption and risk of type 2 diabetes was observed: the HR (95%CI) was 1.50 (1.36, 1.56) for the highest versus lowest intake quintile, and 1.18 (1.13, 1.23) per +50 g/d. There was an indication of a linear dose-response relationship (P-linear trend<0.001). The aforementioned risk estimates are based on the fully adjusted models not including BMI. The committee noted, however, a substantial difference in risk estimates between models with and without adjustment for BMI: risk ratios for unprocessed red meat and type 2 diabetes were substantially smaller (more towards 1) in the multivariable model with BMI compared to the multivariable model without BMI (see Table 15), which may suggest that at least part of the association is explained by BMI. The committee believes that no adjustment should be made for a moderator (which BMI may be in the relationship between unprocessed red meat consumption and type 2 diabetes), and therefore attaches the most value to the models not adjusted for BMI.

The MA by Zeraatkar et al.⁴⁹ includes a total of 12 cohorts, of which 4 originated from Europe, 5 from the USA and 3 from Asia. In total, over 200,000 participants were involved. The consumption level of unprocessed red meat across cohorts was not reported. The MA showed that higher consumption of unprocessed red meat was associated with a higher risk of type 2 diabetes (RR (95%CI) for highest versus lowest intake: 1.10 (1.02, 1.19), and per +3 servings/week (= ~51 g/d): 1.06 (1.02, 1.12)). There was substantial heterogeneity between studies ($I^2=62%$ and $65%$, respectively). It was not reported and could not be assessed (due to the absence of a forest plot) whether this is heterogeneity in direction and/or magnitude of the association. The

heterogeneity may be explained by the quality of the studies: studies with a low risk of bias (n=6) showed a statistically significant higher risk of type 2 diabetes with higher unprocessed red meat consumption, whereas no association was observed among the studies with a high risk of bias (n=5); see Table 15. This difference was statistically significant. The extent of heterogeneity reduced to 0% and 19% in the studies with a low and high risk of bias, respectively. It is unknown if the individual studies in this MA did or did not adjust for BMI.

Considering the above, the committee considered that those findings based on the current state of science are generally in line with the conclusion drawn in the DDG2015: they also suggest an unfavourable association between consumption of unprocessed red meat and risk of type 2 diabetes. The observed risk reductions were approximately between 10 and 20% per 100 g/d higher intake of unprocessed red meat.

Table 15 Main characteristics and results of the meta-analysis and pooled analysis of cohort studies on the association between unprocessed red meat consumption and risk of type 2 diabetes

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR/HR (95%CI)	I ²
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red meat: NR	High vs. low	12; >211,467	1.10 (1.02, 1.19)	62%
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red meat: NR	Per +3 servings/wk (= 51 g/d) ^a	11; 531,843	1.06 (1.02, 1.12) ^b	65%
Bendinelli 2013 ³⁴ Pooled EPIC analysis	Unprocessed red meat: Median Q1 to median Q5: ♀ 7 to 81 g/d ♂ 11 to 117 g/d	Per + 50 g/d	8; 11,559	Model excl. BMI: ^{c,d} 1.18 (1.13, 1.23)	NA
Bendinelli 2013 ³⁴ Pooled EPIC analysis	Unprocessed red meat: Median Q1 to median Q5: ♀ 7 to 81 g/d ♂ 11 to 117 g/d	Per quintile of intake ^e	8; 11,559	Model excl. BMI: ^{c,f} Q2 vs. Q1 ^e : 1.16 (1.06, 1.26) Q3 vs. Q1 ^e : 1.24 (1.13, 1.36) Q4 vs. Q1 ^e : 1.33 (1.21, 1.46) Q5 vs. Q1 ^e : 1.50 (1.36, 1.56) P-linear trend<0.0001	NA

Abbreviations: BMI: body mass index; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; MA: meta-analysis; n: number; NA: not applicable; NR: not reported; PCS: Prospective cohort study; Q: quintile; RR: relative risk.

^a According to Zeraatkar et al., 1 serving of unprocessed red meat is 120 g, so 3 servings/week is approximately 51 g/d.

^b A statistically significant difference between studies with high and low risk of bias was reported (P-interaction=<0.001). The RR (95%CI) for the studies with a low risk of bias (n=6) is 1.11 (1.09, 1.14), I²=0%, P-nonlinearity=0.59.

^c Based on the fully adjusted model: HRs were stratified by centre and adjusted for sex, energy intake, smoking status, alcohol consumption, physical activity and educational level.

^d HR (95%CI) based on the fully adjusted model plus BMI: 1.08 (1.03, 1.13).

^e Quintile cut-offs (and median) observed intakes per quintile of unprocessed red meat consumption were ≤21 (11), >21 to ≤41 (31), >41 to ≤64 (51), >64 to ≤92 (76), >92 (117) g/d in men and ≤14 (7), >14 to ≤28 (20), >28 to 43 (35), >43 to ≤64 (52), >64 (81) g/d in women, respectively.

^f HRs (95%CI) based on the fully adjusted model plus BMI: Q2 vs. Q1: 0.99 (0.89, 1.11), Q3 vs. Q1: 1.10 (1.00, 1.22), Q4 vs. Q1: 1.16 (1.05, 1.29), Q5 vs. Q1: 1.20 (1.07, 1.35); P-linear trend<0.0001.

After the initial selection of MAs and the evaluation, the committee became aware of two other relevant and more recent MAs of prospective cohort studies on the association between unprocessed red meat consumption and risk of type 2 diabetes: Shi et al. (2023)⁴⁵ and Li et al. (2024).⁵⁴ The committee noted that these MAs included 2 and 24 cohorts, respectively, that were not included in the analyses by Zeraatkar et al. or Bendinelli et al. It therefore considered it important to add these findings to its evaluation, to see if these are in line with the committee's conclusion from 2015. The MA by Shi et al. (2023)⁴⁵ includes a total of 23 cohorts, of which 15 originated from Europe, 4 from the USA and 4 from Asia. This includes the pooled analysis of EPIC

cohorts by Bendinelli et al. In total, the MA involved 1,564,454 participants and 70,762 cases. The consumption level of unprocessed red meat across cohorts was not reported. The MA shows that higher consumption of unprocessed red meat was associated with a higher risk of type 2 diabetes (HR (95%CI) per +100 g/d: 1.27 (1.16, 1.39)). There was substantial heterogeneity between studies ($I^2=89\%$). This reflects mainly heterogeneity in magnitude of the association, but also some heterogeneity in direction, mainly due to one Asian study.⁵⁵ Associations tended to be different between subgroups of geographic region (Europe+USA versus Asia; P-heterogeneity=0.051): a statistically significantly unfavourable association was observed in the Western cohorts (HR (95%CI): 1.36 (1.20, 1.54); $I^2=86\%$), whereas no association was observed among the Asian cohorts (HR (95%CI): 0.98 (0.72, 1.33); $I^2=92\%$). However, the extent of heterogeneity did not reduce in any of these subgroups. The committee noted that all except one study included in the MA adjusted for BMI in their models, which may have resulted in attenuation of the association. This assumption could, however, not be assessed, because no analyses without BMI adjustment are available in this MA.

The individual-participant federated MA by Li et al. (2024)⁵⁴ comprises of 38 cohorts from 20 countries that participated in the InterConnect project. Participating cohorts originated from Europe (n=16), the America's (North and South America; n=12), Asia (n=7) and Australia (n=3). The MA includes nearly 2 million adult participants in total, and 107,721 incident cases of type 2 diabetes were reported. The exposure examined was unprocessed red meat. The median consumption level of unprocessed red meat across the cohorts ranged between 9 and 110 g/d. Individual-participant data were harmonized and pooled relative risks were estimated using a random-effects meta-analysis. All analyses were adjusted for the following potential confounders: age, sex, education level, smoking, physical activity, alcohol intake, BMI, total energy intake and consumption of multiple food groups including poultry and processed meat. Based on the fully adjusted model including BMI, higher unprocessed red meat consumption was found to be associated with a higher risk of incident type 2 diabetes (HR (95%CI) per +50 g/d: 1.10 (1.06, 1.15)). Substantial between-study heterogeneity was observed ($I^2=61\%$), mainly in magnitude of the association, not in direction of the association. The association was slightly weaker in the European cohorts than in the American cohorts (HRs (95%CI): 1.06 (1.04, 1.09) and 1.13 (1.06, 1.20), respectively), but in both subgroups was the association statistically significant unfavourable. In sensitivity analyses, models not adjusted for BMI were fitted. This resulted in a considerable increase in size of the association: the HR (95%CI) per 50 g/d higher intake became 1.18 (1.07, 1.29). Substantial between-study heterogeneity was still observed ($I^2=77\%$). Overall, the committee considered that those findings based on the current state of science are in line with the conclusion drawn in the DDG2015.

3.3.3 Processed meat

The DDG2015 committee concluded that consumption of 50 grams of processed (red) meat per day is associated with an approximately 20% higher risk of type 2 diabetes. The level of evidence was judged as strong. This conclusion was based on 4 MAs of 7 to 21 cohorts per MA.

According to the committee's method for updating the DDG, the starting point for DDG2015 conclusions with strong evidence is that these will not be evaluated in detail. An exception was made for the association between processed meat consumption and risk of type 2 diabetes, because the committee noticed on the basis of its less extensive evaluation that processed meat might be more strongly related to the risk of type 2 diabetes than the DDG2015 conclusion suggests. Therefore, it considered an extensive evaluation of the relationship with type 2 diabetes necessary.

For the evaluation of the association between processed meat consumption and risk of type 2 diabetes the committee selected two MAs: Schwingshackl et al. (2017)⁵³ and Zeraatkar et al. (2019).⁴⁹ Compared to the studies on which the DDG2015 conclusion was based, the MA by Zeraatkar et al. includes six additional (more recent) cohorts and the MA by Schwingshackl et al. just one. The committee, however, considered the MA by Schwingshackl et al. also relevant to take into account since non-linear dose-response analyses and relevant subgroup analyses were performed. Moreover, Schwingshackl et al. included the pooled analysis of 8 EPIC cohorts by Bendinelli et al. (2013),³⁴ whereas Zeraatkar et al. did not (but did include a few individual EPIC cohorts). The committee decided to present the results of the pooled analysis of EPIC cohorts by Bendinelli et al. also separately, since it – in contrast to the two MAs – gives more insight in the impact of BMI-adjustment on the overall findings. The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the association between processed meat consumption and risk of type 2 diabetes

Aspect	Explanation
Available studies	<ul style="list-style-type: none"> • 1 meta-analyses of 21 cohorts^{53,a} • 1 meta-analysis of 19 cohorts⁴⁹ • 1 pooled analysis of 8 EPIC cohorts³⁴
Heterogeneity	<ul style="list-style-type: none"> • Yes (in magnitude)^{49,53} • No³⁴
Strength of the association	<ul style="list-style-type: none"> • RR (95%CI) for 35 versus 0 g/d: 1.29 (1.25, 1.33)⁵³ • RR (95%CI) for 21 versus 0 g/d: 1.18 (1.09, 1.27)⁴⁹ • HR (95%CI) per 50 g/d higher intake: 1.24 (1.18, 1.31)³⁴ • HR (95%CI) for Q5 versus Q1: 1.51 (1.37, 1.65)³⁴
Consumption level examined	<ul style="list-style-type: none"> • Range: 0 to 142 g/d⁵³ • NR⁴⁹ • Median Q1 to median Q5: ♀ 4 to 61 g/d, ♂ 9 to 94 g/d³⁴
Study population	Europe ^{34,49,53} , North America ^{49,53} , Asia ^{49,53}

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; NR: not reported; Q: quintile; RR: relative risk.

^a Including the pooled analysis of 8 EPIC cohorts by Bendinelli et al. (2013).³⁴

Conclusion: Consumption of 50 gram of processed meat per day is associated with an approximately 30% higher risk of type 2 diabetes

Evidence level: Strong

Additional remark: The magnitude of the association applies to European populations, but might be stronger among American populations

Explanation

The MA by Schwingshackl et al.⁵³ comprises of 21 cohort studies, including 8 cohorts of the European EPIC consortium. The other cohorts were from Europe (n=5), the USA (n=6) or Asia (n=2). Over 550,000 male and female participants were involved in total, and nearly 44,000 cases were reported over a follow-up of 5 to 28 years (Table 16). The consumption level of processed meat across the cohorts ranged between 0 and 142 g/d. Both the high-low analysis and the dose-response analysis showed that a higher consumption of processed meat is associated with a higher risk of type 2 diabetes. There was, however, evidence of a non-linear relationship: the non-linear dose-response analysis (Table 16) indicated that the risk of type 2 diabetes increases most strongly up to a consumption level of approximately 35 g/d (~1 serving), at which the risk is about 30%. Above this consumption level, the risk increases further, but more moderately, to approximately 43% at an intake of 140 g/d (~4 servings). The committee noted substantial between-study heterogeneity ($I^2 = 55-87\%$), predominantly in magnitude of the association, not in direction. This may be due to, amongst others, the geographic location: the magnitude of the association tended to be smaller, but still statistically significant, in European studies (RR (95%CI) per +50 g/d:

1.13 (1.09, 1.18); $I^2=0\%$) compared to American studies (1.65 (1.47, 1.85), $I^2=54\%$). Subgroup analyses also indicated heterogeneity due to outcome assessment: the magnitude of the associations tended to be larger among studies in which the outcome was self-reported compared to studies in which the disease was diagnosed by a physician or via a registry. Sex and age were not found to be sources of heterogeneity. The committee considered that the type of meat (white versus red processed meat or lean versus fatty processed meat) might also be an explanation, but this could not be verified based on the data available.

The committee noted that all studies included in the MA adjusted for BMI in their models, which is considered a mediator in the relationship between processed meat consumption and type 2 diabetes risk. Adjustment for a potential mediator could be interpreted as over-adjustment and may result in attenuation of the association. The committee considered it plausible that this is the case in the MA by Schwingshackl et al. since the pooled analysis of EPIC cohorts by Bendinelli et al. showed that the risk ratios for the association between processed meat consumption and type 2 diabetes were substantially smaller (more towards 1) in the multivariable model with BMI compared to the multivariable model without BMI (Table 16). Although such adjustments could give insight in whether processed meat consumption might be associated with the risk of type 2 diabetes via BMI or via other mechanisms, the committee believes that preferably no adjustment should be made for a moderator. Therefore, it assumed that the risk estimates from the MA by Schwingshackl et al. may have been underestimated.

At least 10 of the studies were judged by Schwingshackl et al. as having a low risk of bias. The quality of the studies did not appear to have a substantial impact on the results. Schwingshackl et al. reported that there was significant evidence for small study effects in the dose-response analysis, but not in the high versus low analysis. Visual inspection of the funnel plot suggests that small studies showing inverse or null association may be missing. Schwingshackl et al. did not report on the funding sources of the individual studies or their own MA. One author received funding by an NHS BCR grant. None of the authors had a conflict of interest to declare.

The MA by Zeraatkar et al.⁴⁹ includes 20 cohort studies from Europe (n=9), the USA (n=7) or Asia (n=4) with a follow-up ranging from 5 to 28 years (Table 16).

The consumption level of processed meat across the cohorts was not reported in the MA. Based on 17 cohorts including over 750,000 participants, this MA shows that consuming 3 servings per week (~21 g/d) of processed meat more is associated with an 18% higher risk of type 2 diabetes. Similar findings were obtained from the high-low analysis, based on 19 cohorts. There was, however, evidence of a non-linear relationship (P-nonlinearity <0.001). From the non-linear dose-response curve, the committee understood that the relative risk increases most quickly up to approximately 5 servings/week (= 250 g/wk = 36 g/d), at which the risk is about 40%. Above this

consumption level, the relative risk increases further, but more moderately, to approximately 68% at a consumption level of 20 servings/week (~142 g/d). The committee noted substantial between-study heterogeneity ($I^2 = 57-92\%$). In the absence of a forest plot, it is unknown if this reflects heterogeneity in magnitude or in direction of the association. The heterogeneity was not explored by Zeraatkar et al. Only subgroup analyses based on risk of bias were performed. Nine of the 20 studies were judged by Zeraatkar et al. as having a low risk of bias and 11 as having a high risk of bias. High risk of bias was mostly due to a lack of repeated measurement of dietary intake and/or inadequate adjustment for potential confounders.

The confounders that the individual studies adjusted for were, unfortunately, not reported in the MA. Therefore, the committee could not assess what influence the failure to correct for certain confounders may have had on the overall result, nor whether and to what extent the associations might have been over-adjusted (e.g. by correcting for the potential mediator BMI). The risk of bias did, however, not appear to have a substantial impact on the results. Based on the Egger's test, there was no indication of small-study effects.

All studies were funded by government agencies, some with additional support from non-profit organisations. The authors reported that no external funding or other support was received for the MA. Two authors of the MA received funding. One author received funding from a government agency and university. The other author received a grant from a government agency and a federation of entities consisting of non-profit organisations with public and private sector members (International Life Science Institute). The other authors disclosed no conflicts of interest.

The pooled analysis of EPIC cohorts by Bendinelli et al.³⁴ comprises of cohorts from 8 European countries, including a total of 26,088 participants and 11,559 cases (Table 16). The results are generally in line with the two MAs described above. A substantial harmful association between processed meat consumption and type 2 diabetes risk was observed. There was, however, no clear indication of a non-linear dose-response relationship (P -linear trend < 0.001). At least not within the consumption range examined in the EPIC cohorts, which is approximately 0 to 94 g/d. The relative risks increase gradually over the quintiles. The committee noted a substantial difference in risk estimates between models with and without adjustment for BMI, which may suggest that at least part of the association is explained by BMI. In the quintile analysis, Q5 compared to Q1 of processed meat consumption (approximately 77 compared to 7 g/d) is associated with a 16% and 51% higher type 2 diabetes risk in models with and without adjustment for BMI, respectively. A 50 g/d higher consumption of processed meat is associated with a 12% and 24% higher risk of type 2 diabetes in models with and without adjustment for BMI, respectively. Moderate heterogeneity was observed between the cohorts ($I^2 = 38\%$).

The general picture based on the two MAs and the pooled analysis of EPIC cohorts, is that a higher consumption of processed meat is associated with a higher risk of type 2 diabetes. Based on the decision tree, the committee considered the evidence for this association to be strong: there are more than 5 studies in total, more than 500 cases, there is no obvious evidence of heterogeneity in direction of the association, the association is statistically significant, and there are no other major considerations that would weaken the evidence level. The committee noted substantial between-study heterogeneity in magnitude of the association in both MAs. This may be, at least partially, due to the geographic location (the size of the associations tended to be smaller, but still statistically significant, in European studies compared to American studies). For the magnitude of the association, the committee therefore relied mainly on the risk estimates from the pooled EPIC analysis. Furthermore, as explained above, the committee believed that no adjustment should be made for a mediator (BMI), thus based the quantification of its conclusion on the models without BMI adjustment. Although there was no clear indication of a non-linear relationship, the committee observed that the risk estimate based on the dose-response analysis substantially differs from the risk estimate based on the quintile analyses (when converted to an equal amount of processed meat). Therefore, it used the average of both. The dose-response analysis shows that a 50 g/d higher consumption of processed meat is associated with a 24% higher risk of type 2 diabetes. In the quintile analysis, Q5 compared to Q1 of processed meat consumption (contrast: 70 g/d) is associated with a 51% higher risk. Taken together, it concluded that a 50 g/d higher consumption of processed (red or white) meat is associated with an approximately 30% higher risk of type 2 diabetes. This association applies (at least) to the consumption range examined in this study, which is approximately 5 to 95 g/d.

Table 16 Main characteristics and results of the meta-analyses and pooled analysis of cohort studies on the association between processed meat consumption and risk of type 2 diabetes

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: RR/HR (95%CI)	I ²	Study population (n)	Risk of bias (n)
Schwingshackl 2017 ⁵³ MA	Processed meat: 0 to 142 g/d (range)	High vs. low	21	550,347; 43,781	1.27 (1.20, 1.35)	55%	Europe (13), USA (6), Asia (2)	Low (≥10), high (≤11)
Schwingshackl 2017 ⁵³ MA	Processed meat: 0 to 142 g/d (range)	Per +50 g/d	21	550,347; 43,781	1.37 (1.22, 1.55) ^{a,b} P-nonlinearity <0.001	87%	Europe (13), USA (6), Asia (2)	Low (≥10), high (≤11)

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: RR/HR (95%CI)	I^2	Study population (n)	Risk of bias (n)
Schwingshackl 2017 ⁵³ MA	Processed meat: 0 to 142 g/d (range)	Per number of servings/d ^c	21	NR; NR	1 vs. 0 servings/d ^c : 1.29 (1.25, 1.33) 2 vs. 0 servings/d ^c : 1.35 (1.28, 1.42) 3 vs. 0 servings/d ^c : 1.39 (1.27, 1.54) 4 vs. 0 servings/d ^c : 1.43 (1.26, 1.63)	NA	Europe (13), USA (6), Asia (2)	Low (≥ 10), high (≤ 11)
Zeraatkar 2019 ⁴⁹ MA	Processed meat: NR	High vs. low	20	>25,032; NR	1.20 (1.14, 1.27)	57%	Europe (9), USA (7), Asia (4)	Low (11), high (9)
Zeraatkar 2019 ⁴⁹ MA	Processed meat: NR	Per +3 servings/wk (= 21 g/d) ^d	18	758,540; NR	1.18 (1.09, 1.27) ^e P-nonlinearity <0.001	92%	Europe (8), USA (6), Asia (4)	Low (10), high (8)
Bendinelli 2013 ³⁴ Pooled EPIC analysis	Processed meat: Median Q1 to median Q5: ♀ 4 to 61 g/d ♂ 9 to 94 g/d	Per + 50 g/d	8	26,088; 11,559	Model excl. BMI ^{f,g} : 1.24 (1.18, 1.31)	NA	Europe (all)	NR
Bendinelli 2013 ³⁴ Pooled EPIC analysis	Processed meat: Median Q1 to median Q5: ♀ 4 to 61 g/d ♂ 9 to 94 g/d	Per quintile of intake ^h	8	26,088; 11,559	Model excl. BMI ^{f,i} : Q2 vs. Q1 ^h : 1.13 (1.04, 1.23) Q3 vs. Q1 ^h : 1.18 (1.08, 1.28) Q4 vs. Q1 ^h : 1.31 (1.20, 1.43) Q5 vs. Q1 ^h : 1.51 (1.37, 1.65) P-linear trend <0.001	NA	Europe (all)	NR

Abbreviations: BMI: body mass index; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; MA: meta-analysis; n: number; NA: not applicable; NR: not reported; PCS: Prospective cohort study; Q: quintile; RR: relative risk.

^a RR (95%CI) among the studies with a low risk of bias (n=10): 1.39 (1.21, 1.60), $I^2=92\%$.

^b RR (85%CI) among the studies conducted in Europe (n=6): 1.13 (1.09, 1.18), $I^2=0\%$; America (n=6): 1.65 (1.47, 1.85), $I^2=54\%$; and Asia/Australia (n=2): 1.35 (1.01, 1.79), $I^2=0\%$.

^c 1 serving of processed meat is ~35 g/d.

^d According to Zeraatkar et al., 1 serving of processed meat is 50 g, so 3 servings/week is approximately 21 g/d.

^e Based on the non-linear dose-response curve, the risk increases most quickly up to 5 servings/week (= 250 g/wk = 36 g/d). The RR (95%CI) at 5 servings/week is approximately 1.40 (1.25, 1.55).

^f Based on the fully adjusted model: HRs were stratified by EPIC centre and adjusted for sex, energy intake, smoking status, alcohol consumption, physical activity and educational level.

^g HR (95%CI) based on the fully adjusted model plus BMI: 1.12 (1.05, 1.19).

^h Quintile cut-offs (and median) observed intakes per quintile of processed meat consumption were ≤ 17 (9), >17 to ≤ 30 (23), >30 to ≤ 45 (37), >45 to ≤ 70 (56), >70 (94) g/d in men and ≤ 9 (4), >9 to ≤ 17 (13), >17 to ≤ 27 (22), >27 to ≤ 44 (34) and >44 (61) g/d in women, respectively.

ⁱ HRs (95%CI) based on the fully-adjusted model plus BMI: Q2 vs. Q1: 1.08 (0.98, 1.19), Q3 vs. Q1: 1.03 (0.94, 1.14), Q4 vs. Q1: 1.14 (1.04, 1.26) and Q5 vs. Q1: 1.16 (1.04, 1.31), respectively; P-linear trend=0.006.

After evaluation of this exposure-health outcome relationship, the committee became aware of another relevant and more recent MA of prospective cohort studies on the association between processed meat consumption and risk of type 2 diabetes: Li et al. (2024).⁵⁴ The committee noted that this MA included 19 cohorts that were not included in the MAs by either Schwingshackl et al., Zeraatkar et al. or Bendinelli et al. It therefore considered it important to evaluate if the findings of this MA are in line with the committee's conclusion.

The individual-participant federated MA by Li et al. (2024)⁵⁴ comprises of 36 cohorts from 18 countries that participated in the InterConnect project. Cohorts originated from Europe (n=16), the America's (North and South; n=12), Asia (n=5) and Australia (n=3). The MA includes nearly 2 million adult participants in total, and 90,512 incident cases of type 2 diabetes. The exposure examined was processed meat. Median consumption of processed meat across the cohorts ranged between 0 and 49 g/d. Generally, reported processed meat consumption tended to be higher in the European and American cohorts than in the Asian cohorts. Individual-participant data were harmonised and pooled relative risks were estimated using random-effects models. All analyses were adjusted for the following potential confounders: age, sex, education level, smoking, physical activity, alcohol intake, BMI, total energy intake and consumption of multiple food groups including red meat and poultry. Based on the fully adjusted model including BMI, higher processed meat consumption was associated with a higher risk of incident type 2 diabetes (HR (95%CI) per +50 g/d: 1.15 (1.11, 1.20)). Substantial between-study heterogeneity was observed ($I^2=59\%$), mainly in magnitude of the association, not in direction. Results were essentially unchanged in subgroups of geographic region. In sensitivity analyses, models not adjusted for BMI were fitted. This resulted in a considerable increase in size of the association: the HR (95%CI) per 50 g/d higher intake became 1.23 (1.14, 1.34). Substantial between-study heterogeneity remained ($I^2=74\%$). It is unknown if this reflects heterogeneity in direction and/or magnitude of the association as no forest plot for this sensitivity analysis was available.

Overall, the committee considered that the findings from this more recent MA are in line with the committee's conclusion that there is strong evidence for an unfavourable association between processed meat consumption and risk of type 2 diabetes.

3.3.4 Unprocessed red and processed meat combined

In the DDG2015, total red meat, unprocessed red meat and processed meat were evaluated in relation to the risk of type 2 diabetes, but not unprocessed red and processed meat combined. The committee now selected one MA for its evaluation of the association between red and processed meat consumption combined and risk of type 2 diabetes: Zeraatkar et al. (2019).⁴⁹ In addition, it took into account the pooled analysis of EPIC cohorts by Bendinelli et al. (2013).³⁴ This analysis was not included in

the MA by Zeraatkar et al. (which included a few but not all individual EPIC cohorts). The results are summarised in Table 17 and briefly described below.

The general picture of the MA of 19 cohorts by Zeraatkar et al.⁴⁹ and the pooled analysis of EPIC cohorts from 8 European countries by Bendinelli et al.³⁴ is that a higher intake of red and processed meat combined is associated with a higher risk of type 2 diabetes. In the MA by Zeraatkar et al., a 3 servings/week higher intake of unprocessed red and processed meat combined (which equals approximately 43 g/d) was statistically significantly associated with a 12% higher risk of type 2 diabetes. There was no evidence of a non-linear relationship (P-nonlinearity=0.12). Substantial heterogeneity in magnitude of the association between the studies was observed. This might be (partially) explained by the quality of the studies. Zeraatkar et al. reported a statistically significant difference between studies with high and low risk of bias (P-interaction=0.027): the size of the association was slightly smaller, but in the same direction and still statistically significant, among the studies with a low risk of bias (n=7), and no heterogeneity was observed. In the pooled analysis of EPIC cohorts, based on the calibrated intake data, it was observed that a 50 g/d higher intake of unprocessed red and processed meat combined was associated with a 20% higher risk. This association was found based on the fully adjusted model without BMI. The committee noted attenuation of the association when BMI was added to the model. There were indications of a linear dose-response relationship (P-linear trend<0.0001).

Altogether, the overall picture based on the current state of science for red and processed meat combined is generally in line with the DDG2015 conclusions on total red meat, unprocessed red meat and processed meat with type 2 diabetes risk.

Table 17 Main characteristics and results of the meta-analysis and pooled analysis of cohort studies on the association between consumption of unprocessed red meat and processed meat combined and risk of type 2 diabetes

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR/HR (95%CI)	I ²
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red and/or processed meat: NR	High vs. low	19: NR ^a	1.28 (1.20, 1.39)	71%
Zeraatkar 2019 ⁴⁹ MA	Unprocessed red and/or processed meat: NR	Per +3 servings/wk (= 43 g/d) ^p	12: NR ^c	1.12 (1.09, 1.16) ^d	77%
Bendinelli 2013 ³⁴ Pooled EPIC analysis	Unprocessed red and/or processed meat: Median Q1 to median Q5: ♀ 22 to 120 g/d ♂ 38 to 182 g/d	Per + 50 g/d	8; 11,559	Model excl. BMI ^{e,f} : 1.20 (1.16, 1.24)	NA
Bendinelli 2013 ³⁴ Pooled EPIC analysis	Unprocessed red and/or processed meat; Median Q1 to median Q5: ♀ 22 to 120 g/d ♂ 38 to 182 g/d	Per quintile of intake ^g	8; 11,559	Model excl. BMI ^{e,h} : Q2 vs. Q1 ^g : 1.11 (1.01, 1.21) Q3 vs. Q1 ^g : 1.28 (1.17, 1.40) Q4 vs. Q1 ^g : 1.39 (1.26, 1.52) Q5 vs. Q1 ^g : 1.70 (1.54, 1.88) P-linear trend<0.0001	NA

Abbreviations: BMI: body mass index; CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; MA: meta-analysis; n: number; NA: not applicable; NR: not reported; PCS: prospective cohort study; Q: quintile; RR: relative risk.

^a n cases = NR; n participants >760,824.

^b According to Zeraatkar et al., 1 serving of unprocessed red and processed meat combined is 100 g, so 3 servings/week is approximately 43 g/d.

^c n cases = NR; n participants = 555,717.

^d The authors of the MA reported a statistically significant difference between studies with high and low risk of bias (P-interaction=0.027). The RR (95%CI) for the studies with a low risk of bias (n=7) is 1.09 (1.08, 1.10), I²=0%.

^e Based on the fully adjusted model: HRs were stratified by centre and adjusted for sex, energy intake, smoking status, alcohol consumption, physical activity and educational level.

^f HR (95%CI) based on the fully adjusted model plus BMI: 1.09 (1.05, 1.13).

^g Quintile cut-offs (and median) observed intakes per quintile of red and processed meat consumption combined were ≤56 (38), >56 to ≤84 (71), >84 to ≤112 (97), >112 to ≤149 (129) and >149 (182) g/d in men and ≤35 (22), >35 to ≤54 (45), >54 to ≤74 (64), >74 to ≤99 (85) and >99 (120) g/d in women, respectively.

^h HRs (95%CI) based on the fully adjusted model plus BMI: Q2 vs. Q1: 0.97 (0.88, 1.08), Q3 vs. Q1: 1.08 (0.97, 1.20), Q4 vs. Q1: 1.18 (1.06, 1.31) and Q5 vs. Q1: 1.18 (1.04, 1.33); P-linear trend<0.0001.

3.3.5 White meat

In the DDG2015 it was concluded that the evidence for an association between white meat and type 2 diabetes was ambiguous (inconclusive). This was based on one MA of 10 cohorts, and 2 individual cohort studies. Main reasons for the conclusion of inconclusive was the unexplained heterogeneity in the MA and the divergent findings in the two individual cohort studies.

The committee now selected two MAs, of 7 and 38 cohorts, for its evaluation of the association between white meat consumption and risk of type 2 diabetes: Ramel et al. (2023)⁴⁷ and Li et al. (2024).⁵⁴ The committee is also aware of the pooled analysis of EPIC cohorts by Bendinelli et al. (2013),³⁴ but it was not taken into account in the evaluation because the 8 cohorts in the pooled analysis by Bendinelli et al. are also part of the MA by Li et al. There was no full overlap between Ramel et al. and Li et al. (Ramel et al. included three cohorts not included in Li et al.) and therefore both MAs were considered by the committee. The evidence from these MAs is summarised below, followed by the committee’s conclusion and explanation.

Summary of evidence for the association between white meat consumption and risk of type 2 diabetes

Aspect	Explanation
Available studies	<ul style="list-style-type: none"> • 1 meta-analysis of 7 cohorts⁴⁷ • 1 meta-analysis of 38 cohorts^{54,a}
Heterogeneity	<ul style="list-style-type: none"> • Yes, in direction, not explained⁴⁷ • Yes, in direction and magnitude, not explained⁵⁴
Strength of the association	<ul style="list-style-type: none"> • RR (95%CI) for highest versus lowest intake category: 0.98 (0.87, 1.11)⁴⁷ • HR (95%CI) per +50 g/d: 1.21 (1.12, 1.31)⁵⁴
Consumption level examined	<ul style="list-style-type: none"> • Lowest median intake in lowest intake category and highest median intake in highest intake category: 0 to 40 g/d⁴⁷ • Range of median consumption across cohorts: 0 to 70 g/d⁵⁴
Study population	<ul style="list-style-type: none"> • Europe^{47,54}, USA^{47,54}, Asia^{47,54}, Australia⁵⁴

Abbreviations: CI: confidence interval; interval; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; RR: relative risk.

^a Including the pooled analysis of 8 EPIC cohorts by Bendinelli et al. (2013).³⁴

Conclusion: The evidence for an association between white meat consumption and risk of type 2 diabetes is inconclusive

Evidence level: Not applicable

Explanation

The MA by Ramel et al.⁴⁷ comprises of 7 cohort studies originating from Europe (n=3), Asia (n=3) and the USA (n=1). In total, over 388,000 adult participants were included (Table 18). The number of incident cases of type 2 diabetes was not reported. The mean/median follow-up time across the cohorts ranged between approximately 5 and 23 years. The exposure examined was white meat, defined as poultry, chicken, turkey, duck and goose, but not white fish. The median intake of white meat ranged roughly between 0 and 4 g/d in the lowest intake categories and between 14 and 41 g/d in the highest intake categories of the individual studies. The committee calculated that the difference in white meat consumption between the lowest and highest intake category in the included studies ranged between approximately 12 and 37 g/d.

In the high-low analysis, no association was observed with risk of type 2 diabetes (RR (95%CI): 0.98 (0.87, 1.11)). There was evidence of substantial between-study heterogeneity ($I^2=82\%$), both in direction and in size of the association. This was not further explored by meta-regression, subgroup or sensitivity analyses. Based on visual inspection of the forest plot, the committee noted that white meat consumption was statistically significantly associated with a lower risk of type 2 diabetes in two studies, whereas three other studies showed a (nearly) statistically significant increased risk. The committee identified some potential explanatory factors: geographic location, degree of processing and consumption level. It is possible that the background diet or the way the meat is prepared is different among American, European or Asian populations, which may explain differences according to geographic region. Furthermore, subgroup analyses showed that processed poultry consumption was associated with a higher risk of type 2 diabetes, whereas unprocessed poultry consumption was not associated with diabetes risk. However, too few data were available to draw any conclusions on whether or not the degree of processing might affect the relationship between white meat consumption and risk of type 2 diabetes. Last, the committee noted that the consumption level of white meat in the two studies showing an unfavourable association was somewhat higher than in most other studies. By using the USDA's Risk of Bias for Nutrition Observational Studies tool, the authors of the MA judged 5 of the 7 studies as having a high risk of bias (mainly related to confounding and exposure assessment), which limits the certainty of the evidence. With regard to confounding adjustment, the committee noted that 6 of the 7 studies adjusted for BMI. BMI might be on the causal pathway and can thus be considered a mediator of the relationship between white meat consumption and type 2 diabetes risk. Adjustment for a potential mediator could be interpreted as over-adjustment and may result in attenuation of the association. Indications for this come, amongst others, from the pooled analysis of EPIC cohorts by Bendinelli et al. (2013),³⁴ which showed that the RRs for white meat and type 2 diabetes were substantially weaker (more towards 1) in the multivariable model with BMI compared to the multivariable model without BMI (e.g. the HRs (95%CI) for the highest versus lowest intake of poultry consumption were 1.02 (0.91, 1.13) and 1.12 (1.02, 1.24), respectively). A similar picture was seen in the MA by Li et al. 2024 (see below). Although such adjustments could give insight in whether white meat consumption might be associated with the risk of type 2 diabetes via BMI or via other mechanisms, the committee believes that preferably no adjustment should be made for a mediator. Considering these findings, the committee assumed that the risk estimates from the MA by Ramel et al. may have been underestimated. The authors reported that risk of publication bias could not be assessed due to the low number of included studies. Funding for the MA was received from government agencies, but no information has been reported on possible funding of the individual studies in the MA. Ramel et al. declared no potential conflicts of interest.

The individual-participant federated MA by Li et al.⁵⁴ comprises of 38 cohorts from 20 countries that participated in the InterConnect project (Table 18). Participating cohorts originated from Europe (n=16), the America's (North and South America; n=12), Asia (n=7) and Australia (n=3). The MA includes nearly 2 million adult participants in total, and 107,721 incident cases of type 2 diabetes were reported over a median follow-up time of 10 years (interquartile range: 7-15 years). The exposure examined was poultry, defined as chicken, turkey, duck and goose. Median consumption of poultry across the cohorts ranged between 0 and 72 g/d. Generally, reported poultry consumption was higher in the cohorts from the America's then in the European, Asian and Australian cohorts. A very rough estimation of the committee based on the medians and ranges reported for the individual cohorts is that the intake of poultry in the American cohorts might be about twice as high as in the other regions.

Individual-participant data were harmonized and pooled relative risks were estimated using a random-effects meta-analysis. All analyses were adjusted for the following potential confounders: age, sex, education level, smoking, physical activity, alcohol intake, BMI, total energy intake and consumption of multiple food groups including red meat and processed meat. Based on the fully adjusted model including BMI, higher poultry consumption was found to be associated with a higher risk of incident type 2 diabetes (HR (95%CI) per +100 g/d: 1.08 (1.02, 1.14)). Substantial between-study heterogeneity was observed ($I^2=68\%$), both in direction and in magnitude of the association. In sensitivity analyses, models not adjusted for BMI were fitted. This resulted in a considerable increase in size of the association: the HR (95%CI) became 1.21 (1.12, 1.31). Substantial between-study heterogeneity was still observed ($I^2=63\%$). It is, however, unknown if this reflects heterogeneity in direction and/or magnitude of the association since no forest plot for this sensitivity analysis was available.

As mentioned before, the committee attaches more value to the analyses without BMI adjustment. Unfortunately, all analyses that were performed to check the robustness of the findings, such as meta-regression, subgroup and sensitivity analyses, were only performed in the BMI-adjusted models. The findings from the meta-regression, subgroup and sensitivity analyses in the BMI-adjusted models, are as follows.

Subgroup analyses according to geographical region showed that the unfavourable association between poultry consumption and risk of type 2 diabetes was statistically significant in the European cohorts (HR (95%CI) per +100 g/d: 1.10 (1.01, 1.21); $I^2=24\%$), but not in the other regions (Table 18), although the direction of the association was similar (HR>1.0). Based on meta-regression analyses, there was no evidence that the heterogeneity was explained by age, sex or BMI. Sensitivity analyses in which individuals with comorbidities (e.g. dyslipidaemia or stroke) at baseline were excluded or in which those who developed type 2 diabetes in the first 2 years of follow-up were excluded did not essentially change the pooled estimate. Also, results were essentially unchanged when models were additional adjusted for other potential

confounding factors, including waist circumference, comorbidities at baseline or family history of diabetes. Associations became slightly weaker (non-significant, but still in the same direction) after excluding meat non-consumers or when models were additionally adjusted for cooking methods. Regarding the shape of the association, the authors reported that log-linear associations were observed (based on $n=17$), without any obvious threshold or ceiling effect.

By using the NutriGrade scoring system (possible score: 0 to 10 points), the authors concluded that the certainty of the meta-evidence for the association between poultry consumption and risk of type 2 diabetes was moderate (7 points). This was largely due to the heterogeneity by population and because the strength of the association was not always robust in sensitivity analyses. Publication bias was not assessed, but the authors reported that although only 31 of the 115 cohorts approached agreed to participate in this study, 18 had not previously published on this topic, which likely reduced the risk of publication bias. The authors did not report on the funding sources of the individual studies. Funding for the MA was provided by governmental agencies and by research institutes, some of which were (partially) affiliated to the pharmaceutical industry. The authors reported that the funders had no role in the study design, data collection, data analysis, data interpretation or writing of the report. Two authors reported that they received grants from the dairy industry.

Based on the above and taking into account the decision tree, the committee concluded that the evidence for an association between consumption of white meat and risk of type 2 diabetes is inconclusive. This is because substantial heterogeneity between studies was observed, both before and after adjustment for BMI. The committee saw mostly indications for neutral and unfavourable associations, and hardly any evidence for beneficial associations between white meat consumption and type 2 diabetes, especially when looking at the European studies, which are considered the most relevant for the Dutch context. Also, the available data were not sufficient to properly investigate the robustness of the findings.

Table 18 Main characteristics and results of the meta-analyses of prospective cohort studies on the association between white meat consumption and risk of type 2 diabetes

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: RR/HR (95%CI)	I ²	Study population (n)	Risk of bias (n)
Ramel 2023 ⁴⁷ MA	White meat ^a : 0 to 40 g/d ^b	High vs. low	7	388,273; NR	0.98 (0.87, 1.11)	82%	Europe (3), Asia (3), USA (1)	Serious (5), moderate (2)
Li 2024 ⁵⁴ MA	White meat ^a : 0 to 72 g/d ^c	Per +100 g/d	38 ^d	1,966,444; 107,271	Model excl. BMI: 1.21 (1.12, 1.31) Model incl. BMI: 1.08 (1.02, 1.14) ^e	63% 68%	Europe (16), North and South America (12), Asia (7), Australia (3)	NR

Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio; MA: meta-analysis; n: number; NR: not reported; PCS: prospective cohort study; RR: relative risk.

^a Poultry, chicken, turkey, duck, and goose.

^b Lowest median intake in lowest intake category and highest median intake in highest intake category.

^c Range of median consumption across the cohorts.

^d Including the pooled analysis of EPIC cohorts from 8 European countries by Bendinelli et al. (2013).

^e HRs (95%CI) and I² according to geographic region in the (fully-adjusted) model with BMI: Europe: 1.10 (1.01, 1.21), I²=24%; North and South America: 1.03 (0.98, 1.09), I²=72%; Western Pacific and east Asia: 1.18 (0.95, 1.47), I²=39%.

3.4 Colorectal cancer

3.4.1 Total red meat

In the DDG2015 it was concluded that consumption of 100 grams of total red meat per day is associated with a 10% higher risk of colorectal cancer. The level of evidence was judged as strong. This conclusion was based on 4 MAs of 8 to 25 cohorts and 3 individual cohort studies.

The committee identified the WCRF report (2018),² which is based on the WCRF systematic literature review (2016),⁵⁶ in which the association between processed meat consumption and risk of colorectal cancer was evaluated. The WCRF panel concluded that consumption of red meat is probably a cause of colorectal cancer. The committee, however, noted that all studies included in the WCRF report were published before 2015. This means that this WCRF report provides no new evidence as compared to the evidence that informed the DDG2015 conclusion. Via publication alerts, the committee became aware of a more recent MA on this exposure-health outcome relationship, which included at least 12 studies that were published after 2015: Di et al. (2023).⁵⁷ Based on this MA, the committee evaluated whether the findings based on the current state of science are in line with the conclusion from 2015.

The MA by Di et al.⁵⁷ includes a total of 33 cohorts, of which 16 originated from Europe, 8 from the USA/Canada, 8 from Asia and 1 from Australia (Table 19). Among these, is the pooled analysis of EPIC cohorts from 10 European countries by Norat et al. (2005).³⁵ The committee counted this as 10 cohorts. The MA involved a total of nearly 2.5 million participants. Follow-up ranged from 4 to 18 years. The number of cases and consumption level of total red meat across the cohorts was not reported. The MA showed that higher consumption of total red meat was associated with a higher risk of colorectal cancer (RR (95%CI) for the highest versus lowest intake category: 1.09 (1.02, 1.16)). The observed moderate level of heterogeneity between studies reflects heterogeneity in magnitude of the association, not in direction. Subgroup analyses according to geographic region showed that the size of the association was greater in Western countries compared to Eastern countries, but this difference was not statistically significant. Results were essentially unchanged in the subgroup of cohorts that adjusted for a higher number of potential confounding factors and in sensitivity analysis in which one study was excluded at a time. Overall, the committee considered that these findings based on the current state of science seem to be in line with the DDG2015 conclusion.

Table 19 Main characteristics and results of the meta-analysis of cohort studies on the association between total red meat consumption and risk of colorectal cancer

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR (95%CI)	I ²
Di 2023 ⁵⁷ MA	Total red meat: NR	High vs. low	33 ^a ; NR ^b	1.09 (1.02, 1.16) ^c	27%

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; MA: meta-analysis; n: number; NR: not reported; PCS: prospective cohort study; RR: relative risk.

^a Including the pooled analysis of 10 EPIC cohorts by Norat et al. (2005).³⁵

^b n cases = NR; n participants = 2,476,938.

^c RR (95%CI) among Western countries: 1.12 (1.04, 1.19).

3.4.2 Unprocessed red meat

In the DDG2015 it was concluded that an association between moderate consumption of unprocessed red meat and risk of colorectal cancer is unlikely. This was based on 1 pooled analysis of 7 British cohorts and 2 individual cohort studies, all showing no association between unprocessed red meat consumption and risk of colorectal cancer. In the pooled analysis, high consumption of unprocessed red meat was defined as at least 50 g/d and low consumption as less than 5 g/d.

The most recent WCRF report (2018)² on meat consumption and colorectal cancer does not address unprocessed red meat, so could not be taken into account for the committee's current evaluation. In the NNR2023 advisory report²⁹ and background

paper,³³ no other MAs on this topic were mentioned. Via publication alerts, the committee became aware of a more recent MA on this exposure-health outcome relationship, which included multiple recent studies: Farvid et al. (2021).⁵⁸ Based on this MA, the committee evaluated whether the findings based on the current state of science are in line with the conclusion from 2015. The evidence is summarised below, followed by the committee’s conclusion and explanation.

Summary of evidence for the association between consumption of unprocessed red meat and risk of colorectal cancer

Aspect	Explanation
Available studies	1 meta-analysis of 34 cohorts ^{58,a}
Heterogeneity	Yes
Strength of the association	RR (95%CI) for highest versus lowest intake category: 1.10 (1.03, 1.17)
Consumption level examined	Range: 10 to ~120 g/d ^b
Study population	Europe, USA/Canada, Asia, Australia

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; RR: relative risk.

^a Including the pooled analysis of 10 EPIC cohorts by Norat et al. (2005).³⁵

^b In one study the highest intake category was defined as >120 g, without specification of the mean, median or maximum of that intake category.

Conclusion: A higher consumption level of unprocessed red meat is associated with a higher risk of colorectal cancer

Evidence level: Limited

Evaluation

The MA by Farvid et al.⁵⁸ includes a total of 34 cohorts, of which 16 originated from Europe, 10 from the USA/Canada, 7 from Asia and 1 from Australia (Table 20). Farvid et al. included the pooled analysis of EPIC cohorts from 10 European countries by Norat et al. (2005).³⁵ The committee counted this as 10 cohorts. In total, 2.3 million participants were involved in the MA and nearly 28,000 cases of colorectal cancer were reported during a follow-up of 4 to 28 years. A rough estimation by the committee, based on the data of the individual studies as reported in the MA, is that the consumption level of unprocessed red meat across the cohorts ranged from approximately 0 to <65 g/d in the lowest intake categories and from >40 to >120 g/d in the highest intake categories. The MA shows that higher consumption of unprocessed red meat was associated with a higher risk of colorectal cancer (RR (95%CI) for the highest versus lowest intake category: 1.10 (1.03, 1.17), and per +100 g/d: 1.14 (1.04, 1.25)). Associations for colon cancer and rectal cancer were comparable. The observed moderate to high level of heterogeneity between studies reflects heterogeneity in magnitude of the association, not in direction. The committee noted that most studies adjusted for important potential confounding factors including age,

sex, BMI, physical activity, smoking, alcohol intake, education and energy intake. Some studies additionally adjusted for calcium and/or fibre intake, or family history of colorectal cancer. No subgroup analyses or sensitivity analyses were performed. Also, the risk of bias of the individual studies was not assessed. These latter shortcomings in combination with the moderate to high level of heterogeneity limited the committee in assessing the robustness and validity of the findings. The authors reported that they did not receive any funding for the MA, that they have no conflicts of interest to declare, and that they have no financial disclosures to make.

Based on the above and considering the decision tree, the committee concluded that a higher consumption of unprocessed red meat is associated with a higher risk of colorectal cancer. The committee judged the evidence for this association as limited. This is because the committee considered the lack of subgroup analyses, sensitivity analyses and risk of bias assessment in combination with the moderate to high level of heterogeneity important limitations to the MA, and therefore downgraded the evidence level from strong to limited. Limited evidence was considered appropriate, because there are many studies with many cases, a statistically significant association was found and there is no heterogeneity in the direction of the association. This conclusion is different from the conclusion drawn in the DDG2015.

Table 20 Main characteristics and results of the meta-analysis of cohort studies on the association between unprocessed red meat consumption and risk of colorectal cancer

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS	n participants; n cases	Strength of the association: RR (95%CI)	I ²	Study population (n)	Risk of bias
Farvid 2021 ⁵⁸ MA	Unprocessed red meat: 0 to >120 g/d ^a	High vs. low	34 ^b	2,317,000; 27,708	1.10 (1.03, 1.17)	28%	Europe (16), USA/Canada (10), Asia (7), Australia (1)	NR
Farvid 2021 ⁵⁸ MA	Unprocessed red meat: 0 to >120 g/d ^a	Per +100 g/d	NR	NR; NR	1.14 (1.04, 1.25)	56%	NR	NR

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; MA: meta-analysis; n: number; NR: not reported; PCS: prospective cohort study; RR: relative risk.

^a Numbers reflect the lowest intake reported across cohorts in the lowest intake category and the highest intake reported across cohorts in the highest intake category. In one study the highest intake category was defined as >120 g, without specification of the mean, median or maximum of that intake category.

^b Including the pooled analysis of 10 EPIC cohorts by Norat et al. (2005).³⁵

3.4.3 Processed meat

In the DDG2015 it was concluded that consumption of 50 grams of processed (red) meat per day is associated with a 15% higher risk of colorectal cancer. The level of evidence was judged as strong. This conclusion was based on 4 MAs of 5 to 26 cohorts, 1 pooled analysis of 7 British cohorts, and 3 individual cohort studies.

The committee identified the WCRF report (2018),² which is based on the WCRF systematic literature review (2016),⁵⁶ addressing the association between processed meat consumption and risk of colorectal cancer. The WCRF panel concluded that consumption of processed meat is a convincing cause of colorectal cancer.

The committee, however, noted that all studies included in this report were published before 2015. This means that this WCRF report provides no new evidence as compared to the evidence that informed the DDG2015 conclusion. The committee, therefore, did not select the WCRF report for its evaluation.

Via publication alerts, the committee became aware of two more recent MAs on this exposure-health outcome relationship, which both included 11 studies that were published after 2015: Farvid et al. (2021)⁵⁸ and Di et al. (2023).⁵⁷ Although there is almost complete overlap in included studies between the two MAs, the committee chose to present them both, for the reason that one MA performed a dose-response analysis but did not perform sensitivity or subgroup analyses, whereas the other MA did not perform a dose-response analysis but did perform several sensitivity and subgroup analyses. Based on these MAs, the committee evaluated whether the findings based on the current state of science are in line with the conclusion from 2015.

The MA by Farvid et al.⁵⁸ includes a total of 36 cohorts, of which 17 originated from Europe, 11 from the USA/Canada, 7 from Asia and 1 from Australia (Table 21). Farvid et al. included the pooled analysis of EPIC cohorts from 10 European countries by Norat et al. (2005).³⁵ The committee counted this as 10 cohorts. In total, approximately 2.3 million participants were involved in the MA and over 28,000 cases of colorectal cancer were reported during a follow-up of 4 to 28 years. A rough estimation by the committee, based on the data of the individual studies as reported in the MA, is that the consumption level of processed meat across the cohorts ranged from approximately 0 to 26 g/d in the lowest intake categories and from >14 to 122 g/d in the highest intake categories. The MA showed that higher consumption of processed meat was associated with a higher risk of colorectal cancer (RR (95%CI) for the highest versus lowest intake category: 1.18 (1.13, 1.24), and per +50 g/d: 1.16 (1.09, 1.24)). There was little heterogeneity between studies. The heterogeneity that was observed, was in magnitude of the association, not in direction. No subgroup analyses or sensitivity analyses were performed.

The MA by Di et al.⁵⁷ includes a total of 34 cohorts, of which 17 originated from Europe, 9 from the USA/Canada, 7 from Asia and 1 from Australia (Table 21). Di et al. included the pooled analysis of EPIC cohorts from 10 European countries by Norat et al. (2005).³⁵ The committee counted this as 10 cohorts. The MA involved a total of nearly 2.5 million participants. Follow-up ranged from 4 to 24 years. The number of cases and consumption level of processed meat across the cohorts was not reported. The MA showed that higher consumption of processed meat was associated with a higher risk

of colorectal cancer (RR (95%CI) for the highest versus lowest intake category: 1.19 (1.13, 1.26)). There was very little heterogeneity between studies. Subgroup analyses according to geographic region showed no essential difference in association between Western countries and Eastern countries. Also, results were essentially unchanged in the subgroup of cohorts that adjusted for a higher number of potential confounding factors and in sensitivity analysis in which one study was excluded at a time.

Based on the above, the committee considered that these findings based on the current state of science seem to be in line with the DDG2015 conclusion.

Table 21 Main characteristics and results of the meta-analyses of cohort studies on the association between processed meat consumption and risk of colorectal cancer

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR (95%CI)	I ²
Farvid 2021 ⁵⁸ MA	Processed meat: 0 to 122 g/d ^a	High vs. low	36 ^b ; 28,129	1.18 (1.13, 1.24)	2%
Farvid 2021 ⁵⁸ MA	Processed meat: 0 to 122 g/d ^a	Per +50 g/d	NR; NR	1.16 (1.09, 1.24)	24%
Di 2023 ⁵⁷ MA	Processed meat: NR	High vs. low	34 ^b ; NR ^c	1.19 (1.13, 1.26) ^d	6%

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; MA: meta-analysis; n: number; NR: not reported; PCS: prospective cohort study; RR: relative risk.

^a Numbers reflect the lowest intake reported across cohorts in the lowest intake category and the highest intake reported across cohorts in the highest intake category.

^b Including the pooled analysis of 10 EPIC cohorts by Norat et al. (2005).³⁵

^c n cases = NR; n participants = 2,477,419.

^d RR (95%CI) among Western countries: 1.20 (1.13, 1.29).

3.5 LDL cholesterol

In the DDG2015, it was concluded that there is strong evidence that an effect of replacing lean red meat with lean white meat on the LDL cholesterol is unlikely. The committee now found no MAs of RCTs on lean red meat compared to lean white meat, but did find MAs on total red meat compared to white meat (poultry; 3.5.4), and on total red meat compared to plant-based food sources of protein (3.5.1) and animal-based food sources of protein (3.5.2). MAs of RCTs on effects of processed meat on LDL cholesterol were not available in 2015 and have not been found now either.

It was also concluded in the DDG2015 that it is unlikely that consuming fatty fish as compared to meat (both red and white) affects the LDL cholesterol level. The current committee is not aware of MAs of RCTs evaluating the specific comparison of fatty fish with total meat, but did find MAs on the effect of total fish compared to red meat (3.5.3).

3.5.1 Total red meat compared to plant protein foods

The committee selected one MA for its evaluation of the effect of consumption of red meat compared to plant-based food sources of protein on the LDL cholesterol: Guasch-Ferré et al. (2019).⁵⁹ The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the effect of consumption of red meat (intervention) compared to plant-based food sources of protein (control) on LDL cholesterol

Aspect	Explanation
Available studies	1 meta-analysis of 7 RCTs ⁵⁹
Heterogeneity	No
Strength of the effect	MD (95%CI) for red meat vs. plant protein foods: +0.198 (0.065, 0.330) mmol/L ^a
Consumption level examined	Unweighted average (range) of red meat ^b : 220 (75 to 500) g/d
Study population	NR

Abbreviations: CI: confidence interval; LDL: low-density lipoprotein; MD: mean difference; NR: not reported; RCT: randomised controlled trial.

^a A positive value indicates a higher LDL cholesterol level, on average, in the red meat group than in the control group.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

Conclusion: Consumption of red meat compared to plant-based food sources of protein increases the LDL cholesterol level

Evidence level: Strong

Explanation

The MA by Guasch-Ferré et al.⁵⁹ comprises of 7 RCTs that examined the effect of substitution of red meat with plant-based food sources of protein (hereafter referred to as plant protein foods; Table 22) on the LDL cholesterol. In total, approximately 171 participants were included. Four of the seven studies examined the effect of minimally processed red meat (Guasch-Ferré et al. used the term minimally processed meat instead of unprocessed meat since all meat available for purchase is processed to some extent, for example via slaughtering and packaging). For the other studies it is unknown whether the meat concerned unprocessed red meat, processed red meat or a combination of both. Plant protein foods included legumes (beans, soy, tofu), seeds, peanuts and plant-based alternatives for meat. The difference in red meat intake between the intervention group and the control group ranged substantially across the individual studies: from approximately 75 to 500 g/d (calculated by the committee). This is approximately 220 g/d on average (unweighted). It was not reported if the intervention diets and control diets were isocaloric.

The MA shows that the participants who consumed red meat had, on average, a 0.20 mmol/L higher LDL cholesterol level after 2 to 12 weeks as compared to the participants consuming plant protein foods. Little heterogeneity was observed between

studies.

Four of the 7 RCTs were categorised as high-quality by Guasch-Ferré et al. The funding sources of the RCTs (red meat industry or other funding sources) were not reported on an individual-study level. One of the ten authors of the MA received support from an organisation affiliated to the meat industry. Some other authors received support from or had connections with government agencies, non-profit research organisations or an economic consultancy firm. The funders had no role in the work for the MA.

Based on the above and considering the decision tree, the committee concluded that consumption of red meat compared to plant protein foods increases the LDL cholesterol level. Based on the decision tree, the committee considered the evidence for this effect to be strong: there are more than five RCTs and more than 150 participants, there is no obvious heterogeneity in direction of the effect, the effect is statistically significant and there are no other major considerations.

The committee noted large variation between the RCTs in the type of plant protein foods (e.g. legumes, nuts, plant-based meat alternatives) and especially in the consumption level of red meat and plant protein foods. Also, there is no dose-response analysis performed. Therefore, the committee considered that the data do not allow quantification of the conclusion.

Table 22 Main characteristics and results of the meta-analysis of RCTs on the effect of consumption of red meat compared to plant protein foods on LDL cholesterol

Author, year, study design	Intervention (n); comparison (n)	n RCTs; n participants	Strength of the effect: MD (95%CI)	I ²	Study population (n)	Study quality (n)
Guasch-Ferré 2019 ⁵⁹ MA	i: minimally processed red meat ^a (4), red meat, not further specified (3): ~75-500 g/d ^b ; c: high-quality plant protein foods (7)	7; 171	+0.198 (0.065, 0.330) mmol/L ^c	7%	Geographic region NR	High (4), low (3)

Abbreviations: c: control group; CI: confidence interval; i: intervention group; LDL: low-density lipoprotein; MA: meta-analysis; MD: mean difference; n: number; NR: not reported; RCT: randomised controlled trial.

^a Guasch-Ferré et al. used the term minimally processed meat instead of unprocessed meat since all meat available for purchase is processed to some extent, for example via slaughtering and packaging.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

^c A positive value indicates that the LDL cholesterol level was higher, on average, in the red meat group than in the control group.

3.5.2 Total red meat compared to animal protein foods

The committee selected one MA for its evaluation of the effect of consumption of red meat compared to animal-based food sources of protein on the LDL cholesterol: Guasch-Ferré et al. (2019).⁵⁹ The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the effect of consumption of red meat (intervention) compared to animal-based food sources of protein (control) on LDL cholesterol

Aspect	Explanation
Available studies	1 meta-analysis of 5 RCTs ⁵⁹
Heterogeneity	No
Strength of the effect	MD (95%CI) for red meat vs. animal protein foods: -0.073 (-0.161, 0.035) mmol/L ^a
Consumption level examined	Unweighted average (range) of red meat ^b : 140 (60 to 320) g/d
Study population	NR

Abbreviations: CI: confidence interval; LDL: low-density lipoprotein; MD: mean difference; NR: not reported; RCT: randomised controlled trial.

^a A negative value indicates a lower LDL cholesterol level, on average, in the red meat group than in the control group.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

Conclusion: An effect of consumption of red meat compared to animal protein foods other than red meat on the LDL cholesterol level is unlikely

Evidence level: Strong

Explanation

The MA by Guasch-Ferré et al.⁵⁹ comprises of 5 RCTs that examined the effect of substitution of red meat with animal-based food sources of protein other than red meat (hereafter referred to as animal protein foods; Table 23) on the LDL cholesterol. In total, approximately 165 participants were included. Four of the 5 RCTs examined the effect of minimally processed red meat, and in the other study, the intervention group received both processed and unprocessed red meat. Animal protein foods included dairy, poultry, fish or a combination of these. The difference in red meat intake between the intervention group and the control group ranged substantially across the individual studies: from approximately 60 to 320 g/d (calculated by the committee). This is approximately 140 g/d on average (unweighted). It was not reported if the intervention diets and control diets were isocaloric.

The MA does not show an effect of consumption of red meat as compared to other animal protein foods on the LDL cholesterol level after 2 to 14 weeks. There was no evidence of between-study heterogeneity.

Four of the 5 RCTs were categorised as high-quality by Guasch-Ferré et al. The funding sources of the RCTs (red meat industry or other funding sources) were not reported on an individual-study level. One of the ten MA authors received support from an organisation affiliated to the meat industry. Some other authors received support from or had connections with government agencies, non-profit research organisations or an economic consultancy firm. The funders had no role in the work for the MA.

Based on the above and considering the decision tree, the committee concluded that an effect of consuming red meat compared to other animal protein foods (fish, poultry and/or dairy) on the LDL cholesterol level is unlikely. This is because there are more than 5 RCTs and more than 150 participants (which allows a conclusion with strong evidence), there is no substantial heterogeneity in direction or size of the effect, there is no statistically significant effect observed and there are no other major considerations.

Table 23 Main characteristics and results of the meta-analysis of RCTs on the effect of consumption of red meat compared to other animal protein foods on LDL cholesterol

Author, year, study design	Intervention (n); comparison (n)	n RCTs; n participants	Strength of the effect: MD (95%CI)	I ²	Study population (n)	Study quality (n)
Guasch-Ferré 2019 ⁵⁹ MA	i: minimally processed red meat ^a (4), processed and unprocessed red meat (1): ~60-320 g/d ^b ; c: animal protein foods ^c (5)	5; 165	-0.073 (-0.161, 0.035) mmol/L ^d	0%	Geographic region NR	High (4), low (1)

Abbreviations: c: control group; CI: confidence interval; i: intervention group; LDL: low-density lipoprotein; MA: meta-analysis; MD: mean difference; n: number; NR: not reported; RCT: randomised controlled trial.

^a Guasch-Ferré et al. used the term minimally processed meat instead of unprocessed meat since all meat available for purchase is processed to some extent, for example via slaughtering and packaging.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

^c Animal protein sources could be either dairy, poultry or fish or a combination of these.

^d A negative value indicates a lower LDL cholesterol level, on average, in the red meat group than in the control group.

3.5.3 Total red meat compared to fish

The committee selected one MA for its evaluation of the effect of consumption of red meat compared to fish on the LDL cholesterol: Guasch-Ferré et al. (2019).⁵⁹

The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the effect of consumption of red meat (intervention) compared to fish (control) on LDL cholesterol

Aspect	Explanation
Available studies	1 meta-analysis of 10 RCTs ⁵⁹
Heterogeneity	No
Strength of the effect	MD (95%CI) for red meat vs. fish: -0.173 (-0.260, -0.086) mmol/L ^a
Consumption level examined	Unweighted average (range) of red meat ^b : 220 (50-500) g/d
Study population	NR

Abbreviations: CI: confidence interval; LDL: low-density lipoprotein; MD: mean difference; NR: not reported; RCT: randomised controlled trial.

^a A negative value indicates a lower LDL cholesterol level, on average, in the red meat group than in the control group.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

Conclusion: Consumption of red meat compared to fish decreases the LDL cholesterol level

Evidence level: Strong

Explanation

The MA by Guasch-Ferré et al.⁵⁹ comprises of 10 RCTs with 12 comparisons that examined the effect of substituting red meat with fish (Table 24). In total, approximately 340 participants were included. Seven of the 10 RCTs examined the effect of minimally processed red meat; for the other studies it is unknown whether the meat concerned unprocessed red meat, processed red meat or a combination of both. Regarding the control interventions, half of the studies used fatty fish and the other half of the studies used lean fish as the comparison food. The difference in red meat intake between the intervention group and the control group ranged substantially across the individual studies: from 50 to 500 g/d (calculated by the committee). This is approximately 220 g/d on average (unweighted). It was not reported if the intervention diets and control diets were isocaloric.

The MA shows that the participants who consumed red meat had, on average, a 17 mmol/L lower LDL cholesterol level after 2 to 8 weeks as compared to the participants consuming fish. There was no evidence of between-study heterogeneity.

Six of the 10 RCTs were categorised as high-quality by Guasch-Ferré et al.

The funding sources of the RCTs (red meat industry or other funding sources) were not reported on an individual-study level. One of the ten MA authors received support from an organisation affiliated to the meat industry. Some other authors received support from or had connections with government agencies, non-profit research organisations or an economic consultancy firm. The funders had no role in the work for the MA.

Based on the above, the committee concluded that consumption of red meat compared to fish decreases the LDL cholesterol level. Based on the decision tree, the committee considered the evidence for this effect to be strong: there are more than 5 RCTs and more than 150 participants, there is no obvious heterogeneity in direction of the effect, the effect is statistically significant and there are no other major considerations.

The committee noted large variation in the consumption level of both red meat and fish between the RCTs, and no dose-response analysis was performed. Therefore, the committee considered that the data do not allow quantification of the conclusion.

The committee additionally notes that it considered this conclusion of little relevance for the Dutch situation, because the consumption level of fish in the RCTs (approximately 60 to 500 g/d) deviates considerably from the Dutch recommendation to consume fish weekly (1 serving of fish per week is ~15 g/d)³² and the current consumption level of fish in the Netherlands (15 g/d on average; only 30% complies with the fish recommendation⁶⁰).

Table 24 Main characteristics and results of the meta-analysis of RCTs on the effect of consumption of red meat compared to fish on LDL cholesterol

Author, year, study design	Intervention (n); comparison (n)	n RCTs; n participants	Strength of the effect: MD (95%CI)	I ²	Study population (n)	Study quality (n)
Guasch-Ferré 2019 ⁵⁹ MA	i: minimally processed red meat ^a (7), red meat, not further specified (3): ~50-500 g/d ^b ; c: fatty fish (5), lean fish (5)	10; 342	-0.173 (-0.260, -0.086) mmol/L ^c	0%	Geographic region NR	High (6), low (4)

Abbreviations: c: control group; CI: confidence interval; i: intervention group; LDL: low-density lipoprotein; MA: meta-analysis; MD: mean difference; n: number; NR: not reported; RCT: randomised controlled trial.

^a Guasch-Ferré et al. used the term minimally processed meat instead of unprocessed meat since all meat available for purchase is processed to some extent, for example via slaughtering and packaging.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

^c A negative value indicates a lower LDL cholesterol level, on average, in the red meat group than in the control group.

3.5.4 Total red meat compared to white meat (poultry)

The committee selected 2 recent MAs for its evaluation of the effect of consumption of red meat compared to white meat (poultry) on the LDL cholesterol: Guasch-Ferré et al. (2019)⁵⁹ and Ramel et al. (2023).⁴⁷ Guasch-Ferré et al. included most RCTs, but Ramel et al. included 2 more recent RCTs that were not included by Guasch-Ferré et al: Bergeron et al. (2019)⁶¹ and Mateo-Gallego et al. (2012).⁶² Moreover, Ramel et al. did not pool the data because of the limited number of studies. Therefore, these two individual RCTs from the MA by Ramel et al. are described separately, in addition to the MA by Guasch-Ferré et al. The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the effect of consumption of red meat (intervention) compared to white meat (control) on LDL cholesterol

Aspect	Explanation
Available studies	<ul style="list-style-type: none"> • 1 meta-analysis of 6 RCTs⁵⁹ • 2 individual RCTs^{61,62}
Heterogeneity	<ul style="list-style-type: none"> • No⁵⁹ • NA^{61,62}
Strength of the association	<ul style="list-style-type: none"> • MD (95%CI) for red meat vs. poultry: -0.040 (-0.105, 0.024) mmol/L^{59,a} • MD ± SD for red meat vs. poultry: 0.001 ± 0.03 mmol/L⁶¹; NR⁶²
Consumption level examined	<ul style="list-style-type: none"> • Unweighted average (range) of red meat: 180 (70 to 380) g/d^{59,b} • NR⁶¹; average of red meat and of poultry: ~55 g/d⁶²
Study population	<ul style="list-style-type: none"> • NR • USA⁶¹, Europe⁶²

Abbreviations: CI: confidence interval; LDL: low-density lipoprotein; MD: mean difference; NA: not applicable; NR: not reported; RCT: randomised controlled trial; SD: standard deviation.

^a A negative value indicates a lower LDL cholesterol level, on average, in the red meat group than in the control group.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

Conclusion: An effect of consumption of red meat compared to poultry on the LDL cholesterol level is unlikely
Evidence level: Strong

Explanation

The MA by Guasch-Ferré et al.⁵⁹ comprises of 6 RCTs that examined the effect of substitution of red meat with poultry (white meat; Table 25). In total, approximately 200 participants were included. Four of the 6 studies examined the effect of minimally processed red meat; for the other studies it is unknown whether the meat concerned unprocessed red meat, processed red meat or a combination of both. The difference in red meat intake between the intervention group and the control group ranged substantially across the individual studies: from 70 to 380 g/d (calculated by the committee). This is approximately 180 g/d on average (unweighted). It was not reported if the intervention diets and control diets were isocaloric.

The MA does not show an effect of consumption of red meat compared to poultry on the LDL cholesterol after 4 to 12 weeks. There was no evidence of between-study heterogeneity.

Half of the studies had a relatively high quality and half had a relatively low quality, according to Guasch-Ferré et al., but the study quality seemed not to have substantially affected the overall result. The funding sources of the RCTs (red meat industry or other funding sources) were not reported on an individual-study level. One of the 10 MA authors received support from an organisation affiliated to the meat industry. Some other authors received support from or had connections with government

agencies, non-profit research organisations or an economic consultancy firm. The funders had no role in the work for the MA.

The individual RCT by Bergeron et al.⁶¹ included 177 adult men and women from the USA (Table 25). The RCT had a cross-over design and each diet lasted 1 month. The intervention group received a diet providing approximately 12 energy percentage (E%) from lean red meat (11 E% from beef and 1 E% from pork), and the control group received a diet providing approximately 12 E% lean white meat (8 E% from chicken and 4 E% from turkey). Both diets did not contain any processed meat. Intervention and control diets were matched for fat content. The RCT did not show an effect of consumption of red meat compared with white meat on the LDL cholesterol. Ramel et al. judged the RCT by Bergeron et al. as having a low risk of bias. The RCT was not supported by the industry. Two authors received a grant from a non-profit trade organisation affiliated to the dairy industry, but they mentioned that this grant was not for this publication. The other authors reported no conflicts of interest.

The individual RCT by Mateo-Gallego et al.⁶² included 36 women from Europe (Table 25). This open-label RCT had a cross-over design and each diet lasted 5 weeks. Two interventions were provided (in addition to the participants' usual diet): lean lamb (red meat) and chicken (white meat). The participants were instructed to consume 125 g/d of the meat on 3 days per week. This amounts to approximately 55 g/d. Intervention and control diets were matched for fat content. The RCT did not show any differences in LDL cholesterol between the diets after the intervention period. Ramel et al. judged the RCT by Mateo-Gallego et al. as having some concerns because of bias due to deviations from the intended intervention and missing outcome data. The RCT was supported in part by a government agency; no funding was received from the industry. None of the authors reported conflicts of interest.

Based on the above and considering the decision tree, the committee concluded that an effect of replacing red meat with poultry on the LDL cholesterol is unlikely. This is because there is no statistically significant effect observed, the number of RCTs (≥ 5) and the number of participants (≥ 150) are sufficient for a conclusion with strong evidence, there is no substantial heterogeneity in direction or size of the effect, and there are no other major considerations. The committee noted that in the MA by Guasch-Ferré et al. the intervention concerned lean red meat in half of the RCTs, but the committee saw no clear indication, based on the forest plot, that the fat content affected the overall result.

Table 25 Main characteristics and results of the meta-analysis of RCTs and individual RCTs on the effect of consumption of red meat compared to white meat on LDL cholesterol

Author, year, study design	Intervention (n); comparison (n)	n RCTs; n participants	Strength of the effect	<i>I</i> ²	Study population (n)	Study quality (n)
Guasch-Ferré 2019 ⁵⁹ <i>MA</i>	i: minimally processed red meat ^a (4), red meat, not further specified (2); ~70-380 g/d ^b ; c: poultry (6)	6; 202	MD (95%CI): -0.040 (-0.105, 0.024) mmol/L ^c	0%	Geographic region NR	High (3), low (3)
Bergeron 2019 ⁶¹ <i>individual RCT</i>	i: poultry: ~12 E%; c: red meat: ~12 E%	1; 177	MD ± SD: 0.001 ± 0.03 mmol/L, P=0.98	NA	USA	RoB: Low
Mateo-Gallego 2012 ⁶² <i>individual RCT</i>	i: ~55 g/d of lamb (red meat) on average; c: ~55 g/d of poultry (white meat) on average	1; 36	Mean ± SD baseline vs. lamb vs. poultry: 116 ± 58 vs. 119 ± 64 vs. 119 ± 54 mg/L, P=0.463	NA	Europe	RoB: Moderate

Abbreviations: c: control group; CI: confidence interval; E%: energy percentage; i: intervention group; LDL: low-density lipoprotein; MA: meta-analysis; MD: mean difference; NA: not applicable; NR: not reported; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation.

^a Guasch-Ferré et al. used the term minimally processed meat instead of unprocessed meat since all meat available for purchase is processed to some extent, for example via slaughtering and packaging.

^b This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

^c A negative value indicates a lower LDL cholesterol level, on average, in the red meat group than in the control group.

3.6 Blood pressure

In the DDG2015, no conclusions were drawn regarding effects of red meat or processed meat consumption on blood pressure, because no literature was found on this topic. Unfortunately, MAs of RCTs on effects of processed meat on blood pressure have not been found now either. For red meat, however, the committee identified three MAs investigating the effect on blood pressure, as described below.

3.6.1 Total red meat compared to various control foods

The committee selected 1 MA of RCTs on the effect of total red meat consumption on blood pressure: Guasch-Ferré et al. (2019).⁵⁹ The evidence is summarised below, followed by the committee's conclusion and explanation.

Summary of evidence for the effect of consumption of red meat (intervention) compared to animal-based or plant-based foods (control) on blood pressure

Aspect	Explanation
Available studies	1 meta-analysis of 11 RCTs
Heterogeneity	No
Strength of the effect	MD (95%CI) for red meat vs. animal-based or plant-based foods: systolic blood pressure: -1.148 (-2.661, 0.365) mmHg diastolic blood pressure: -0.001 (-1.098, 1.095) mmHg
Consumption level examined	Unweighted average (range) of red meat: 100 (30 to 185) g/d ^a
Study population	NR

Abbreviations: CI: confidence interval; MD: mean difference; NR: not reported; RCT: randomised controlled trial.

^a This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

Conclusion: The evidence for an effect of consumption of red meat compared to other animal-based or plant-based food sources of protein on systolic blood pressure is inconclusive

Evidence level: Not applicable

Conclusion: An effect of consumption of red meat compared to other animal-based or plant-based food sources of protein on diastolic blood pressure is unlikely

Evidence level: Strong

Explanation

The MA of Guasch-Ferré et al.⁵⁹ comprises of 11 RCTs involving a total of 654 participants. Four of the 11 RCTs involved minimally processed red meat (Guasch-Ferré et al. used the term minimally processed meat instead of unprocessed meat since all meat available for purchase is processed to some extent, for example via slaughtering and packaging), 1 RCT processed meat and 1 RCT a combination of processed and unprocessed red meat. For the other RCTs, it was unknown if the meat was unprocessed or processed. The control interventions concerned either plant-based food sources of protein (e.g. legumes), non-meat animal-based food sources of protein (e.g. fish) or usual diet. The difference in red meat intake between the intervention group and the control group ranged substantially across the individual studies: from approximately 30 to 185 g/d (calculated by the committee). This is approximately 100 g/d on average (unweighted). It was not reported if the intervention diets and control diets were isocaloric.

The MA did not show an effect of consuming total red meat for at least 2 weeks as compared to animal-based or plant-based control foods on systolic or diastolic blood pressure in adults (Table 26). No stratified analyses by subtype of the comparison diet were conducted. Although the control interventions were heterogeneous, no hetero-

ogeneity between studies was observed ($I^2=0\%$ for both systolic and diastolic blood pressure).

Nine of 11 RCTs were categorised as high-quality by Guasch-Ferré et al. One of the 10 MA authors received support from an organisation affiliated to the meat industry. Some other authors received support from or had connections with government agencies, non-profit research organisations or an economic consultancy firm. The funders had no role in the work for the MA.

Based on the above and considering the decision tree, the committee concluded that an effect of replacing red meat with other animal-based or plant-based food sources on diastolic blood pressure is unlikely. This is because there is no statistically significant effect observed, there are more than 5 RCTs and more than 150 participants (which allows a conclusion with strong evidence), there is no substantial heterogeneity in direction or magnitude of the effect, and there are no other major considerations. The committee considered the evidence for an effect on systolic blood pressure to be inconclusive. Although there is no statistically significant effect observed and there is no evidence of heterogeneity in direction of the association, the committee considered that the effect estimate is not close to 0 (-1.15 mmHg) and the confidence interval is relatively broad, which precludes the conclusion that the association is 'unlikely'. Therefore, the evidence is considered inconclusive.

Table 26 Main characteristics and results of the meta-analysis of RCTs on the effect of consumption of red meat compared to other animal- or plant-based protein foods on systolic and diastolic blood pressure

Author, year, study design	Intervention (n); comparison (n)	n RCTs; n participants	Strength of the effect: MD (95% CI)	I^2	Study population (n)	Study quality (n)
Guasch-Ferré 2019 ⁵⁹ MA	i: red meat (11): 30 to 185 g/d ^a ; c: high-quality plant protein sources (4); mixed animal protein sources ^b (4); fish (2); usual diet (1) ^c	11; 654	SBP: -1.148 (-2.661, 0.365) mmHg DBP: -0.001 (-1.098, 1.095) mmHg	0% 0%	Geographic region NR	High (9), low (2)

Abbreviations: c: control group; CI: confidence interval; DBP: diastolic blood pressure; i: intervention group; MA: meta-analysis; MD: mean difference; n: number; NR: not reported; RCT: randomised controlled trial; SBP: systolic blood pressure.

^a This reflects the difference in red meat intake between the intervention group and the control group across the studies, as estimated by the committee based on the data provided in the MA.

^b Animal protein sources could be either dairy, poultry or fish or a combination of these.

^c No stratified analyses by subtype of the comparison diet were conducted.

3.7 Body weight

In the DDG2015, no conclusion was drawn regarding effects of red meat or processed meat consumption on body weight, because no literature on this topic was found.

The committee now aimed to perform a comprehensive evaluation of these relationships to consider if the current state of science does allow conclusions with strong evidence, and whether or not any of these conclusions are supportive to the conclusions on type 2 diabetes. Unfortunately, MAs of RCTs on effects of processed meat on body weight were not available in 2015 and have not been found now either. The evaluation is thus focused on red meat.

3.7.1 Total red meat compared to various control foods

The committee selected one recent MA for its evaluation of the effect of red meat consumption on body weight: Zeraatkar et al. (2019).⁵² This MA comprises of 8 RCTs and includes 3 RCTs published after 2015. In total, 42,271 participants were involved. It was not specified whether the exposure concerned total red meat, unprocessed red meat or processed red meat. The MA showed no effect of a lower intake of red meat (of at least 1 serving per week as compared to control) for 6 months or more on body weight (Table 27). Substantial heterogeneity between studies was observed ($I^2=87\%$), which may be due to the heterogeneous control interventions. It is unclear (i.e. it is not reported, and no effect estimates of individual studies or forest plot are shown) whether this reflects heterogeneity in direction and/or magnitude of the effect. The committee furthermore noted that 4 of the 8 RCTs compared different dietary patterns (e.g. a high-carbohydrate diet versus a high-protein diet), meaning that there was variation in multiple food groups and not only in red meat plus one other food group the meat is replaced with. The committee considered these comparisons less relevant for its evaluation of the effect of a relatively higher red meat intake on body weight. Excluding these RCTs on dietary patterns, would leave 4 RCTs relevant for the committee's evaluation. Based on 4 studies, the committee could not conclude that an effect is unlikely (for this, at least 5 studies are needed, according to the decision tree). The committee could also not conclude that the results are contradictory, since it is unknown whether there is heterogeneity in direction of the effect. Because of these considerations, the committee concluded that there is insufficient data on the effect of consumption of red meat compared to other animal- and plant-based foods on body weight to draw any conclusions.

Table 27 Main characteristics and results of the meta-analysis of RCTs on the effect of consumption of red meat compared to various control foods on body weight

Author, year, study design	Intervention (n); comparison (n)	n RCTs; n participants	Strength of the effect: MD (95%CI)	I ²
Zeraatkar 2019 ⁵² MA	i: red meat (4), dietary pattern (4 ^a); c: no/less meat (2), white meat (1), mushrooms (1), dietary pattern (4 ^b)	8; 42,271 (total)	-1.02 (-2.47, 0.43) kg	87%

Abbreviations: c: control group; CI: confidence interval; i: intervention group; MA: meta-analysis; MD: mean difference; n: number; RCT: randomised controlled trial.

^a For example, prudent diet or high-protein diet.

^b For example, Mediterranean diet or high-carbohydrate diet.

3.8 Additional topics

3.8.1 White meat and fatal cardiovascular disease

No conclusion on the association between white meat consumption and risk of CVD mortality was drawn in the DDG2015, since (total) CVD was not selected as a health outcome to be evaluated.

The committee now selected one recent MA for its evaluation of the association between white meat consumption and fatal CVD: Ramel et al. (2023).⁴⁷

The MA by Ramel et al.⁴⁷ comprises of 15 cohort studies from Europe, Asia and the USA, and includes over 1 million participants. This MA includes the pooled analysis of EPIC cohorts from 10 European countries by Rohrmann et al. (2013).⁶³ The median or mean intake of white meat in the studies in the MA ranged roughly between 0 and 12 g/d in the lowest intake categories and between 20 to 133 g/d in the highest intake categories. In high-low analyses, no association between white meat consumption and risk of fatal CVD was observed (Table 28). There was moderate between-study heterogeneity ($I^2=25\%$), in magnitude of the association, not in direction. Mostly neutral associations were observed, also in the pooled analysis of EPIC cohorts. Because on the one hand no statistically significant association was observed and on the other hand the point estimate is not close to 1.0 and the confidence interval is relatively broad, the committee considered that it is unlikely that a conclusion with strong evidence will be drawn (more plausible is the conclusion of inconclusive evidence). Therefore, the committee did not evaluate this relationship in more detail.

Table 28 Main characteristics and results of the meta-analysis of cohort studies on the association between white meat consumption and risk of fatal cardiovascular disease

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR (95%CI)	I ²
Ramel 2023 ⁴⁷ MA	White meat ^a : 0 to 135 g/d ^b	High vs. low	15 ^c ; NR ^d	0.95 (0.87, 1.02)	25%

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; MA: meta-analysis; n: number; NR: not reported; PCS: prospective cohort study; RR: relative risk.

^a Defined by the authors of the MA as poultry, chicken, turkey, duck and goose.

^b Numbers reflect the lowest median intake in the lowest intake category to the highest median intake in the highest intake category.

^c The MA includes the pooled analysis of EPIC cohorts from 10 European countries by Rohrmann et al. (2013),⁶³ which was counted as 10 individual cohorts by the committee.

^d n cases = NR; n participants = 1,158,411.

3.8.2 White meat and fatal (total) cancer

No conclusion on the association between white meat consumption and risk of fatal cancer was drawn in the DDG2015, since (total) cancer was not selected as a health outcome to be evaluated at the time.

The committee selected one MA for its evaluation of the association between white meat consumption and mortality due to cancer: Zhang et al. (2018).⁶⁴

The MA by Zhang et al.⁶⁴ comprises of 18 prospective cohort studies from Europe (n=11), Asia (n=5) and the USA (2). In total, 1 million participants were involved and 38,668 deaths due to cancer were reported. Ten of the 11 European cohorts were from the pooled analysis of EPIC cohorts by Rohrmann et al.⁶³ The MA shows a borderline statistically significant inverse association between poultry consumption and total cancer mortality in the high-low analysis (RR (95%CI): 0.96 (0.93, 1.00)), with no evidence of between-study heterogeneity (Table 29). Subgroup analyses suggest heterogeneity by geographic region. However, these subgroup analyses deemed the committee not reliable, because the committee noted that the countries/continents assigned by Zhang et al. to the different studies/cohorts (as described in the baseline table of the MA) seemed not always correct. So, whether there is actual variation in associations between continents remains uncertain. The dose-response analysis, based on 15 cohorts, did not show an association and there was no evidence of between-study heterogeneity. According to Zhang et al. and based on the Newcastle-Ottawa Scale, 14 studies were of high quality and three studies of low quality. A statistically significant association was observed when only the high-quality studies were considered (RR (95%CI): 0.92 (0.86, 0.97)).

Because the risk estimates differ between the analyses within this MA, indicating both beneficial associations (i.e. for the main high-low analysis as well as for the sensitivity analysis based on high-quality studies) and neutral associations (for the dose-response

analysis), which the committee could not explain, the committee considered the evidence too uncertain to conclude that there is strong evidence for a protective association between white meat consumption and risk of cancer mortality (rather, it considered the evidence to be inconclusive). Therefore, the committee did not evaluate this relationship in more detail.

Table 29 Main characteristics and results of the meta-analysis of cohort studies on the association between white meat consumption and risk of mortality due to cancer

Author, year, study design	Exposure: consumption level examined	Type of analysis	n PCS; n cases	Strength of the association: RR (95%CI)	I²
Zhang 2018 ⁶⁴ MA	Poultry: 0 to ~135 g/d ^a	High vs. low	18 ^b ; 38,668	0.96 (0.93, 1.00)	0%
Zhang 2018 ⁶⁴ MA	Poultry: 0 to ~135 g/d ^a	Per +100 g/d	15 ^b ; 21,632	0.97 (0.88, 1.07)	0%

Abbreviations: CI: confidence interval; EPIC: European Prospective Investigation into Cancer and Nutrition; MA: meta-analysis; n: number; NR: not reported; PCS: prospective cohort study; RR: relative risk.

^a Numbers reflect the lowest intake reported across cohorts in the lowest intake category and the highest intake reported across cohorts in the highest intake category. It is a rough estimation by the committee based on the data provided in the MA.

^b Including the pooled analysis of 10 EPIC cohorts by Rohrmann et al. (2013),⁶³ counted by the committee as 10 individual cohorts.

3.9 Translation of conclusions to the dietary guidelines

In the advisory document, the translation of conclusions into dietary guidelines is explained. In that document, it is also explained that the conclusions with strong evidence on red and processed meat and CHD and stroke risk were used as leading evidence for deriving and quantifying the dietary guideline on red and processed meat (evidence on colorectal cancer and type 2 diabetes were used as supportive evidence).¹ Because most above described conclusions suggest that these relationships are linear, an additional step was needed to determine the consumption level at which the risk of red and processed meat consumption is noteworthy for health. The committee considered a 5% increased relative risk as noteworthy. Regarding CHD risk, the committee estimated that the consumption levels associated with a 5% increase in risk were 25 g/d for unprocessed red meat, 17 g/d for processed meat and 25 g/d for unprocessed red and processed meat combined. Regarding stroke, the consumption levels associated with a 5% increase in risk were 55 g/d for unprocessed red meat, 25 g/d for processed meat and 55 g/d for total red meat. Based on this, the consumption level of 25 g/d was considered as the upper limit for the guideline (further explained in the advisory report¹). Finally, as a precaution, the committee checked whether consumption of 25 g/d was associated with a noteworthy increase of the risks of the supporting endpoints. For the supporting endpoints, due to the lower evidential value, a 10% increased relative risk was considered noteworthy. The conclusion was

that consumption of 25 g/d was not associated with a noteworthy increase in the risks of the supporting endpoints.

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Annexes

A Working group

The following working group prepared this background document:

Working group on meat and legumes and chronic diseases

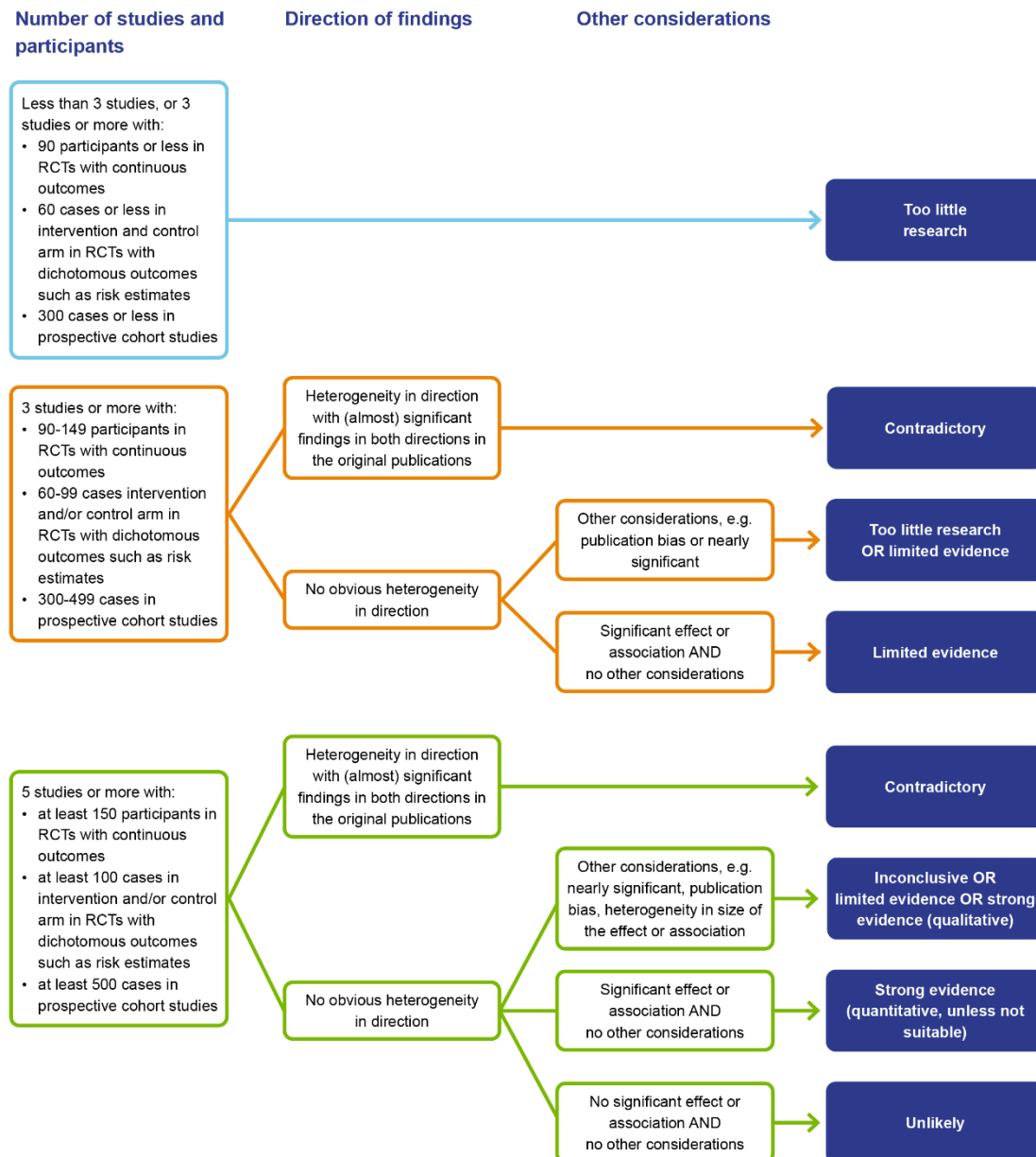
- Dr K.A.C. Berk, Registered Dietitian and Assistant Professor Department of Internal Medicine at Erasmus MC, Rotterdam, *chair of the working group*
- Prof. J.W.J. Beulens, Professor of lifestyle and cardiometabolic disease epidemiology, Amsterdam UMC
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Scientific Secretary

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B Decision tree

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



De Gezondheidsraad, ingesteld in 1902, is een adviesorgaan met als taak de regering en het parlement 'voor te lichten over de stand der wetenschap ten aanzien van vraagstukken op het gebied van de volksgezondheid en het gezondheids(zorg)onderzoek' (art. 22 Gezondheidswet). De Gezondheidsraad ontvangt de meeste adviesvragen van de bewindslieden van Volksgezondheid, Welzijn en Sport; Infrastructuur en Waterstaat; Sociale Zaken en Werkgelegenheid en Landbouw, Visserij, Voedselzekerheid en Natuur. De raad kan ook op eigen initiatief adviezen uitbrengen, en ontwikkelingen of trends signaleren die van belang zijn voor het overheidsbeleid. De adviezen van de Gezondheidsraad zijn openbaar en worden als regel opgesteld door multidisciplinaire commissies van – op persoonlijke titel benoemde – Nederlandse en soms buitenlandse deskundigen.

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