Chapter on meat

Disclaimer

This chapter describes the background for setting recommendations for "meat and meat products" in the 6th edition of the Nordic Nutrition Recommendations (NNR2022). Jelena Meinilä and Jyrki K. Virtanen has been assigned as authors. The present version of the chapter has been peer reviewed by Liv Elin Torheim and Alicja Wolk, and considered by the NNR2022 Committee. The chapter is now open for public consultation. The hearing responses will be publicly available and carefully considered by the NNR2022 Committee. All input considered by NNR2022 Committee as scientifically valid and relevant will be forwarded to the authors for consideration. Please note that sustainability aspects and other issues such as obesity, physical activity, and burden of diseases will be integrated at a later stage, if relevant. The NNR Committee is responsible for setting the recommendations. The suggestion for setting of dietary reference values will be open for public consultation at a later stage, before the NNR2022 Committee reach the final conclusion, and are not included in the document now available for public consultation.

1. *ABSTRACT*

Meat is a source of several nutrients but also a proposed risk factor for several non-communicable diseases. Here we describe the totality of evidence for the role of meat intake for health-related outcomes, discuss potential mechanistic pathways, knowledge gaps and limitations of the literature, and advice for setting and updating the food-based dietary guidelines for meat. The chapter is based on a *de novo* systematic review (SR) and meta-analysis on the association between poultry intake and cardiovascular disease and type 2 diabetes (T2D), qualified SRs on meat intake and cancer by the World Cancer Research Fund (WCRF) and the International Agency for Research on Cancer (IARC), and on a systematic literature search of SRs and meta-analyses by the chapter authors. The quality of the SRs was evaluated using a modified AMSTAR-2 tool. The strength of evidence was evaluated based on a predefined criteria developed by the WCRF. The quality of the SRs was on average critically low. In the literature search (including the qualified SRs), the number of SRs on meat intake and health outcomes was 154, from which 23 were included in the chapter. Our findings indicate strong evidence that processed meat increases the risk of colorectal cancer (CRC) and probable evidence that red meat increases the risk. The evidence suggests red meat as a probable risk factor for type 2 diabetes (T2D) and red meat and processed meat as probable risk factors for cardiovascular disease (CVD) and stroke. There was also suggestive evidence that red and processed meat are risk factors for several other diseases and that poultry intake is associated with a lower risk of some diseases.

2. *INTRODUCTION*

Meat commonly refers to "red meat" from pork, beef, and lamb and to "white meat" from chicken and turkey. In Western countries, red meat is a major source of energy and several nutrients. Red meat is a good source of, e.g., protein and essential amino acids, vitamins B1 and B2, iron, and zinc but also a notable source of unfavorable saturated fatty acids. High intake of red meat has been linked to a higher risk of several major chronic diseases, such as some cancers, cardiovascular diseases, and T2D. Some proposed mechanisms for this include the saturated fat and heme iron content in red meat. The increased risks have been especially observed with high intake of processed meat. Although meat is usually processed before it is consumed (by at least adding salt and baking or frying), “processed meat” generally refers to a meat product that has been industrially processed by adding e.g., sodium, nitrites, or other preservatives or coloring agents, or by smoking, drying, curing, or fermenting. The added substances or substances formed during the meat processing (such as polycyclic aromatic hydrocarbons, advanced glycation end products, heterocyclic aromatic amines) are among the factors that have been suggested to contribute to the increased disease risk from high processed meat intake. Compared to red meat, poultry consumption is typically lower in Western countries. Less research data also exists on the impact of poultry intake on health.

The aim of this chapter is to describe the totality of evidence for the role of meat intake for health-related outcomes as a basis for setting and updating the food-based dietary guidelines.

3. *METHODS*

This review follows the protocol developed within the NNR2022 project (“The Nordic Nutrition Recommendations 2022 – Instructions to authors of chapter”). The protocol can be found on the official NNR2022 website. The sources of evidence used in this chapter follow the eligibility criteria described in the paper “The Nordic Nutrition Recommendations 2022 – Principles and methodologies” (Christensen et al. 2020).

The evidence on the associations of poultry consumption with CVD and T2D are based on the *de novo* SR conducted by NNR [to be included when ready]. Qualified SRs on the association between meat and the majority of the most common cancer sites were available by WCRF (red meat, processed meat, and poultry) and by IARC (red meat and processed meat) (WCRF 2018, IARC 2018). The results of the associations between meat and cancer sites that WCRF reviewed in 2018 but did not find sufficient evidence to make conclusions are not included in the table of included studies (Table 1). The results on the associations between meat and those cancer sites for which WCRF has concluded on the strength of evidence are presented in Table 1 along with other included studies. The conclusions of IARC are reported in the text but not in the table because of the narrative nature of the IARC monograph. To review the association between meat intake and other health outcomes we performed a literature search on 13 September 2021 in PubMed and 29 October 2021 in Web of Science. The search string for PubMed search was: (meat[MeSH Terms] OR meats[MeSH Terms]) AND ("2011"[Date - Publication] : "3000"[Date - Publication]) AND humans[Filter] AND (systematic review[Publication Type] OR meta-analysis[Publication Type]). The search string for Web of Science search was “(ALL=((meat OR meats OR beef OR lamb OR mutton OR pork OR poultry))) AND ALL=(systematic review OR meta-analysis) and Review Articles (Document Types)” in the following Web of Science categories: Respiratory System or Allergy or Gerontology or Integrative Complementary Medicine or Geriatrics Gerontology or Pediatrics or Behavioral Sciences or Obstetrics Gynecology or Clinical Neurology or Neurosciences or Rheumatology or Hematology or Peripheral Vascular Disease or Immunology or Orthopedics or Medicine Research Experimental or Surgery or Psychiatry or Cardiac Cardiovascular Systems or Gastroenterology Hepatology or Endocrinology Metabolism or Oncology or Medicine General Internal or Nutrition Dietetics. Additional relevant articles were found in PubMed “Similar articles” list and reference lists of umbrella SRs found in the PubMed and Web of Science searches.

Altogether 716 SRs were retrieved, whose titles and abstracts were reviewed for relevance. Altogether 154 SRs on meat intake and health outcomes were found. From the 154, the most recent and highest quality articles on each of the outcomes were referred to in this chapter (n=23, Table 1). Articles not included in the chapter are described in Table 2 (n=131).

The quality of the SRs included in the chapter and derived from the literature search were evaluated using a modified AMSTAR-2 tool (Shea et al. 2017). The modified AMSTAR-2 tool is available at the NNR2022 official webpage. The criteria for the rating were as follows (YES= meets the criteria, NO=does not meet the criteria): High confidence: all critical domains YES, ≤ 2 non-critical domains NO; Moderate confidence: all critical domains YES, ≥ 3 non-critical domains NO; Low confidence: 1 critical domain NO, ≤ 2 non-critical domains NO; Critically low: ≥ 2 or more critical domains NO independent of non-critical domains, OR 1 critical domains NO and > 2 non-critical domains NO..

The critical domains of the tool concerned protocol registration, comprehensiveness of literature search, adequacy of risk of bias assessment, appropriate statistical methods, accounting risk of bias in interpretation of the results, and investigation of publication bias. The strength of evidence per outcome (with positive or negative association with meat intake) was evaluated based on predefined criteria developed by WCRF described by Arnesen et al. (2020).

In the literature, categorization of meat types varies. The most common meat categories were unprocessed red meat, processed red meat, total red meat (including unprocessed and processed red meat), processed meat (including processed red meat and poultry), and poultry. When in a SR unprocessed red meat and processed red meat were analyzed separately, the possible combined results of total red meat were not considered unless the evidence was substantially stronger for total red meat. Similarly, combined red and processed meat results were reported only if results from more refined categories were unavailable.

The number of cases included in a SR / meta-analysis was reported (in text and in Table 1) for each analysis if it was traceable from the publication. Otherwise, instead the number of participants was reported.

4. *DIET INTAKE IN NORDIC AND BALTIC COUNTRIES*.

The average reported meat intake varies between the Nordic and Baltic countries, roughly between 100 and 200 g/day, with significant variation also in the within-country mean intakes (Warensjö Lemming & Pitsi. NNR report 2022). Of the total meat intake, red meat accounts for the majority of the intake, with poultry intake being several times lower. The mean intakes of any meat in all countries are higher in men than in women. However, the differences in reporting and definition of meat between the countries make comparisons difficult. There is also no data for comparing national average intake of processed meat separately from total red meat.

5. *HEALTH OUTCOMES RELEVANT FOR NORDIC AND BALTIC COUNTRIES*

Overall cardiovascular disease and coronary heart disease

One meta-analysis found that lower intakes of both unprocessed red meat and processed meat were associated with modestly lower risk of CVD mortality (unprocessed red meat: 8 studies / 389,528 participants; processed meat: 9 studies / 478,128 participants), when compared to higher intakes (Zeraatkar et al. 2019a). The associations were found only in the studies with low risk of bias. There was evidence of significant heterogeneity, but mainly in the studies with high risk of bias (unprocessed red meat: 4 studies / 301,788 participants; processed meat: 5 studies / 408,839 participants). No associations or evidence of heterogeneity were found with overall CVD risk (unprocessed red meat: 4 studies / 65,736 participants; processed meat: 4 studies / 69,186 participants).

Another meta-analysis found that higher intakes of both red meat (3 cohorts / 6,659 cases) (includes studies that reported associations with total red meat intake or with unprocessed red meat intake) and processed meat intake (5 cohorts / 7,038 cases) were associated with higher risk of CHD, without evidence of heterogeneity (Bechthold et al. 2019). Although Bechthold et al. (2019) found significant non-linearity for the association between red meat and CHD, that particular analysis was based only on two cohort studies. y . Processed meat increased the risk of CHD by 27% and of stroke by 17% per each 50 g/d increase in intake (Bechthold et al. 2019). Although not with significant non-linearity, the risk for CHD seemed to increase the most on lower intake levels (up to less than 15 g/d).
(*Based on the evidence from several cohort studies with low risk of bias, no evidence for significant heterogeneity and evidence for biological plausibility (please see section 6. Mechanisms),* the *strength of evidence is regarded as probable that higher red meat intake, whether processed or unprocessed, is a risk factor for CVD mortality and CHD. Based on the limited number of studies with low risk of bias, the strength of evidence is regarded as limited – no conclusion that high intake of unprocessed or processed meat is a risk factor for overall CVD.*)

Myocardial infarction

One meta-analysis investigated the association with lower intake of unprocessed red meat and processed meat and found one prospective cohort study (Zeraatkar et al. 2019a). The cohort study (55,171 participants) suggested lower intakes of both unprocessed red meat and processed meat were associated with modestly lower risk of myocardial infarction.
(*Based on the limited number of studies, the strength of evidence is regarded as limited – no conclusion that higher red meat intake, whether processed or unprocessed, is a risk factor for myocardial infarction.*)

Stroke

In the meta-analysis by Zeraatkar et al. (2019a), lower intake of unprocessed red meat (any stroke: 6 cohorts / 102,024 participants; fatal stroke 3 cohorts / 671,259 participants) and processed meat (any stroke: 6 cohorts / 101,861; fatal stroke: 2 studies / 571,378 participants) was associated with modestly lower risk of any stroke and fatal stroke. Most studies were considered having a high risk of bias. There was little evidence of heterogeneity.

Similar findings were observed in a meta-analysis by Bechthold et al. (2019), who found a higher risk of any stroke with higher intake of red meat (7 cohorts / 10,541 cases) or processed meat (6 cohorts / 9,492 cases). For the risk of stroke, each 100 g/d increase in total red meat intake increased the risk by 15% (Bechthold et al. 2019, Zeraatkar et al. 2019a). Most studies were considered to have a low risk of bias. There was heterogeneity only for processed meat and only in a dose-response analysis, not in the analysis of extreme categories. In the dose-response analysis the association with processed meat intake was mainly found in the studies conducted in the USA, with no significant heterogeneity, but not in the European studies.
(*Based on the moderate number of studies with low risk of bias, no evidence for unexplained heterogeneity and with evidence for biologic plausibility, the strength of*

evidence is regarded as probable that higher red meat intake, whether processed or unprocessed, is a risk factor for any stroke. Based on the limited number of studies with low risk of bias, the strength of evidence is regarded as limited - no conclusion for fatal stroke.)

Heart failure

Bechthold et al. (2019) observed a higher risk of heart failure with higher intake of red meat (all red meat or unprocessed red meat) (5 cohorts / 9,229 cases) and processed meat (3 cohorts / 7,077 cases), although there was evidence for non-linearity. No heterogeneity was observed for either of the meat types.

Another meta-analysis also found a higher risk of heart failure with higher intake of processed meat (5 cohorts) but did not find an association with unprocessed red meat intake (5 cohorts) (Cui et al., 2019). There was evidence of heterogeneity in the analyses with processed meat intake, which was mainly explained by the geographic location. The association with increased risk was stronger in the European studies than in the US studies.

(*Based on the moderate number of studies with little evidence for unexplained heterogeneity and with evidence for biological plausibility, the strength of evidence is regarded as limited - suggestive that higher intake of especially processed meat is a risk factor for heart failure*)

Hypertension

Meta-analyses of prospective cohort studies found an increased risk of hypertension with higher unprocessed red meat and processed red meat intakes (both meat types: 5 cohorts / 23,854 cases, Zhang & Zhang 2018), total red meat intake (7 cohorts / 97,745 cases, Schwingshackl et al. 2017a), and poultry intake (6 cohorts / 14,739 cases, Zhang & Zhang 2018). All the associations were with significant unexplained heterogeneity, and the directions of the associations were not always consistent (red meat and poultry).

(*Based on the significant unexplained heterogeneity and inconsistent findings, the strength of evidence is regarded as limited – no conclusion that red meat (whether unprocessed or processed), processed meat, or poultry increase the risk of hypertension*)

Type 2 diabetes

A meta-analyses of prospective cohort studies found a reduced risk of T2D with lower intake of unprocessed red meat (12 cohorts / >211,467 participants) and processed meat (19 cohorts / >25,032 participants) (Zeraatkar et al. 2019a). Zeraatkar et al. (2019a) found that reduction of unprocessed red meat by 3 serving/wk (1 serving = 120g) reduced the risk of T2D by approximately 10%, which equals to approximately 20% reduction in risk by 100g/d reduction in intake, assuming linear association between the intake and the risk. The association was stronger in low risk of bias studies (n=8) and with no heterogeneity for unprocessed red meat, but the association was weaker for processed red meat with unexplained between-study heterogeneity. Another meta-analysis (14 cohorts) also found a higher risk of T2D with higher combined unprocessed and processed red meat (45,702 cases) and processed meat (43,781 cases) intakes, but with significant unexplained between-study heterogeneity (Schwingshackl et al. 2017b). Schwingshackl et al. (2017b) found a 17% increase in risk of T2D for each 100g/d increase in total red meat intake.

(*Based on the existing evidence on several low-risk-of-bias cohort studies, dose-response association, lack of between-study heterogeneity, and evidence of biological plausibility, the strength of evidence is regarded as probable that unprocessed red meat increases the risk of T2D. Based on large number of studies with consistent results but significant* *unexplained heterogeneity, the strength of evidence is regarded as limited - suggestive that processed meat increases the risk of T2D.*)

Cancer

Colorectal cancer

Both, WCRF in their Continuous Update Project and IARC, reviewed the available evidence on meat intake and several cancer sites (WCRF 2018, IARC 2018). They found that, both, total red meat and processed meat consumption were associated with increased risk for CRC. The increase in the risk of CRC was 12% for each 100g increase in total red meat intake (WCRF 2018). The risk for CRC increased by 16% per each 50 g/d increase in intake of processed meat (WCRF 2018). In the meta-analyses by WCRF, there was no heterogeneity between the studies. IARC concluded based on the large amount of data, strength of association, and consistency across cohort studies in different populations, that there is sufficient evidence in humans that processed meat consumption is a cause of colorectal cancer. For unprocessed red meat, IARC concluded that the positive causal interpretation "is credible but chance, bias or confounding could not be ruled out". (*As assessed by both, WCRF and IARC, the strength of evidence is regarded as convincing that processed meat increases the risk of CRC. Based on the conclusions of the IARC, and WCRF, the strength of evidence is regarded as probable that red meat (unprocessed, processed or both) increases the risk of CRC.*)

Lung cancer

WCRF (2018) found that total red meat intake was associated with increased risk for lung cancer but there was significant between-study heterogeneity. Heterogeneity decreased in analyses by sex, although the number of studies with data available separately for both sexes was small. The association between red meat and risk of lung cancer persisted in men but not in women. Processed meat was also associated with increased risk of lung cancer with no apparent between-study heterogeneity but the association was statistically significant in only one of the primary studies. Poultry intake was associated with reduced risk for lung cancer, with no between-study heterogeneity but only one primary study showed a significant result. The findings of the IARC (2018) regarding red and processed meat were similar to the findings of WCRF but IARC did not express an evaluation of the strength of evidence.
(*As assessed by WCRF, strength of evidence is regarded as limited – suggestive that red meat and processed meat increase the risk of lung cancer and limited – no conclusion evidence that poultry intake decreases the risk of lung cancer.)*

Other cancers

WCRF (2018) found that total red meat was associated with pancreatic cancer and nasopharyngeal cancer (based on a meta-analysis by Li et al. 2016). Large unexplained between-study heterogeneity was present and the results were based on case-control studies only. WCRF (2018) also found that processed meat was associated with increased risk of pancreatic, nasopharyngeal, oesophageal, and stomach cancers. No heterogeneity was detected between the studies for any of the cancer types. However, as stated by IARC (2018) on pancreatic, oesophageal, and stomach cancers, modest number of studies prevented ruling out chance, bias, and confounding.
(*As assessed by WCRF, strength of evidence is regarded as limited – suggestive that red meat increases the risk of pancreatic and nasopharyngeal cancers, and that processed meat increases the risk of oesophageal, nasopharyngeal, stomach, and pancreatic cancers.)*

WCRF (2018) did not find sufficient evidence to conclude on the associations between different meat types and cancers of breast, skin, bladder, cervical, gallbladder, kidney, liver, endometrial, ovarian, prostate, mouth, pharynx and larynx. IARC (2018), in addition, did not find sufficient evidence to conclude on the associations between red meat (whether unprocessed or processed) or processed meat intake and cancers of non-Hodgin lymphoma, leukemia, and brain. No SRs other than those analyzed by WCRF (2018) with adequate quality were found regarding poultry intake and any cancer site. In addition to the cancer sites covered by WCRF and IARC, the literature search returned only a SR on thyroid cancer, which found no association with total meat intake (Lin & Liu 2014).

Total cancer incidence and mortality
A meta-analysis of prospective cohort studies found that lower intake of unprocessed red meat (3 cohorts, 875,290 participants) and processed meat (6 cohorts, 1,198,234 participants) were associated with decreased cancer mortality but not with cancer incidence (Han et al. 2019). For processed meat, between-study heterogeneity was large but not in studies with low risk of bias. For both, unprocessed red meat and processed meat, the result was significant in only one primary study. One meta-analysis on poultry and total cancer mortality with prospective cohort studies (8 cohorts / 257 - 9861 cases in the original studies) found a borderline decreased total cancer mortality in high versus low consumption of poultry with no dose-response association (Zhang et al. 2018).
(*Based on the limited number of studies with low risk of bias, and inconsistent findings, the strength of evidence is regarded as limited - no conclusion that red and processed meat increase the risk of total cancer mortality. Based on the weak association and lack of dose-response relationship the strength of evidence is regarded as limited – no conclusion that poultry decreases the risk of total cancer mortality.*)

Total mortality
In the meta-analysis by Zeraatkar et al (2019a), lower intakes of both unprocessed red meat (9 cohorts / 413,760 participants) and processed meat (10 cohorts / >696,822 participants) were associated with a modestly lower risk of all-cause mortality. The associations were observed mainly in the studies with low risk of bias. There was evidence of significant heterogeneity between the studies, but the sources of heterogeneity were not studied.

Another meta-analysis by Schwingshackl et al (2017c) found that higher total red meat intake (12 cohorts / 177,655 cases) and especially intake of processed meat (7 cohorts / 143,572 cases) were associated with higher risk of all-cause mortality. There was evidence of significant heterogeneity that also persisted in the subgroup analyses.
(*Based on the large number of studies and with evidence for biologic plausibility, but with significant unexplained heterogeneity, the strength of evidence is regarded as limited - suggestive that higher red meat intake and especially intake of processed meat increase the risk of all-cause mortality*)

Other health outcomes
Because of limited number of studies, no conclusion was possible regarding the association of meat intake with obesity, mental health, metabolic syndrome, chronic obstructive pulmonary disease, gout, chronic kidney disease, gestational diabetes, or anemia. However, the results of the SRs studying the association between meat intake and these outcomes are presented in Table 1 (Schlesinger et al. 2019, Zhang et al. 2017, Guo

et al. 2021, Salari-Moghaddam et al. 2018, Li et al. 2018, van Westing et al. 2020, Schoenaker et al. 2016, Zeraatkar et al. 2019a).

6. ***MECHANISMS***

Red meat is a source of nutrients, such as heme iron, carnitine and saturated fatty acids, which in large amounts may have harmful health effects. Furthermore, processing and cooking of red meat have the potential to produce potentially harmful compounds such as N-nitroso compounds (NOCs), heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), N-glycolylneuraminic acid (Neu5Gc) (Turesky 2018), and advanced glycation end products (AGE) (Huang et al. 2021). IARC (2018) has classified processed meat as carcinogenic and unprocessed red meat as probably carcinogenic to humans.

Etiology of colorectal cancer
Processing and cooking of meat produce potential carcinogens such as PAH, NOC, and HCA. NOCs cause tumors in a variety of animal species and could cause tumors in humans (Cross & Sinha 2004). Red meat increases the amount of NOCs in human feces suggesting also endogenous production, e.g. by bacterial activity or by the effect of heme iron of meat (Cross et al. 2003). Two recent meta-analyses concluded that consumption of HCA was positively associated with colorectal adenomas (Matinez Gongora et al. 2019, Chiavarini et al. 2017). Heme-iron mediates the formation of lipid peroxidation and NOC in the colon, which can cause DNA damage (Turesky 2018). WCRF has concluded, based on evaluation of the literature, that there is suggestive evidence on the association between heme iron and CRC (WCRF 2018). Long-term exposure of a compound Neu5Gc, rich in red meat, resulted in an increased incidence of carcinomas in mice (Samraj et al. 2015). Saturated fat in meat products is not a likely explanation for the increased CRC risk because in a recent meta-analysis saturated fat intake was not associated with CRC (Kim & Park et al. 2018).

Blood pressure
The potential effects of red and processed meat could be mediated by salt or heme iron because they both affect the vascular system (Tzoulaki et al. 2008, Sacks & Campos 2010). Recent SRs and meta-analyses of RCTs have not found an effect of replacing red meat with other food groups on blood pressure (Guasch-Ferre et al. 2019, Zeraatkar et al. 2019b). However, due to limitations of such RCTs, this does not necessarily exclude the possibility of an effect of red meat on blood pressure over a long period or an effect by processed meat (see *Limitations* in section *Food-based dietary guidelines*).

Glycemia
Several dietary components of red and processed meat, such as saturated fatty acids, advanced glycation end products, nitrites and nitrates, heme iron, TMAO, branched chain amino acids, or endocrine disruptors could enhance the development of glycemia. They can influence glucose and insulin metabolism through affecting adipocyte and muscle cell metabolism, by increasing inflammation and oxidative stress, or through effects on pancreatic β-cell and liver function (Kim et al. 2015). Meta-analyses of prospective studies suggest an association between serum ferritin and risk of T2D, and between heme iron intake and risk of T2D (Zhao et al. 2012, Kunutsor et al. 2013, Shahinfar et al. 2022). Iron causes oxidative stress, which could inhibit insulin binding (Fernandez-Real et al. 2002). Elevated iron concentrations can increase glucose production and output (Ferrannini 2000), and interfere with hepatic glucose utilization, and glucose metabolism of adipocytes (Green et al. 2006)

and muscle tissue (Tuomainen et al. 1997).
A meta-analysis of RCTs did not find any effect of red meat on blood glucose concentrations, blood insulin concentrations, HOMA-IR, HbA1c, CRP, IL-6, or TNF-alpha (O´Connor et al. 2021). However, due to limitations of such RCTs, this does not necessarily exclude the possibility of a long-term effect by red meat or an effect by processed meat (see *Limitations* in section *Food-based dietary guidelines*).

Inflammation
As mentioned above, RCTs do not support short-term effects of red meat on inflammation markers (O'Connor et al. 2021). Association between red meat and chronic inflammation in observational studies may be confounded by excess body weight (Chai et al. 2017) or mediated by visceral adiposity resulting from a high SFA diet (Mazidi et al. 2021). Other dietary factors such as fruits, vegetables, and whole grains may also interact with red meat in the association with inflammation (Schulze et al. 2005). If, however, in the future, a longer-term intervention was found to cause inflammation, one potential mechanism could be through a recently found compound Neu5Gc, which red meat contains high amounts, has been linked with systemic inflammation in mice (Samraj et al. 2015).

Serum lipid profile
Evidence from meta-analyses of RCTs have not found evidence that red meat would have an adverse impact on blood concentrations of total, low-density lipoprotein (LDL), or high-density lipoprotein cholesterol (LDL), apolipoproteins A1 and B (O'Connor et al. 2017, Guasch-Ferre et al 2019). Guasch-Ferre et al. (2019), however, found that substitution of red meat by plant foods (soy, nuts and legumes) had a favorable effect on total and LDL cholesterol concentrations. A meta-analysis of RCTs found that red meat had an adverse effect on LDL cholesterol but had no effect on total or HDL cholesterol or triglycerides (Schwingshackl et al. 2018). Processed meat intake is less frequently tested in RCTs. Processed meat often contains large amounts of saturated fat. The current evidence suggests that reducing SFA, especially when replaced with cis-PUFA or cis-MUFA, improves serum lipid profile, more specifically decreases total and LDL cholesterols (Mensink 2016). The results of a recent Cochrane systematic review suggest that reducing SFA for at least two years could reduce the risk of cardiovascular events (Hooper et al. 2020).

Trimethylamine-N-oxide (TMAO)
Meat contains high amounts of carnitine and choline, which are precursors of TMAO. Red meat intake seems to increase blood concentrations of TMAO (Wang et al. 2019). High TMAO levels have been associated with increased risk of atherosclerosis and major cardiovascular events (Wang et al. 2011, Tang et al. 2013). A recent cross-over RCT found that plant-based alternative meat products decreased TMAO levels compared to animal meat (Crimarco et al. 2020). TMAO has also been associated with cancer, potentially through promoting inflammation, oxidative stress, DNA damage and disruption in protein folding (Chan et al. 2019). However, it is difficult to interpret whether the effects of meat intake on TMAO have an impact on disease risk, because fish, which contains TMAO, increases circulating TMAO concentration more than red meat (Cho et al. 2017), but does not increase the risk of CVD.

7. ***FOOD-BASED DIETARY GUIDELINES***.

There is strong evidence that processed meat intake increases the risk of CRC and probable evidence that red meat (unprocessed, processed, or both) intake increases the risk of CRC. Although IARC concluded that unprocessed red meat is probably carcinogenic to humans, concerning the effects on CRC, there is not enough evidence to separate between unprocessed and processed red meat, Several potentially carcinogenic compounds are formed in processing and heating red meat. There is also probable evidence that unprocessed red meat increases the risk of T2D. Heme iron is a strong candidate to at least partially mediate the effect. There is probable evidence that red meat and processed meat intake are risk factors for CHD and stroke. For stroke, also unprocessed red meat is a probable risk factor. Based on the current evidence, sodium of processed meat through its effect on blood pressure and SFA of unprocessed and processed red meat through its effect on blood lipids, are potential candidates as mediators of the effect.

Data gaps for future research

One of the main issues is that in most meta-analyses of observational cohort studies there is little information on food substitution analyses with other protein sources, although this would be very relevant for public health guidelines. In other words, if the intake of meat is reduced, what (protein-containing) foods should be added to the diet. Meta-analyses of observational studies have not commonly addressed this important question, although some original studies have included substitution analyses. These kinds of analyses were, however, included in the *de novo* SR that investigated the association of poultry intake with disease risk [these results will be included when the de novo SR is ready].

Although cognitive decline shares many of the same risk factors as cardiometabolic diseases and especially processed meat intake has been associated with higher risk of these diseases, currently there is insufficient data on the impact of meat intake on the risk of cognitive decline. Some observational studies suggest that consumption of unprocessed meat may have a favorable and processed meat an unfavorable relationship with cognitive performance (Yeh, et al., AJCN 2021), but the findings are inconsistent and a comprehensive synthesis of the longitudinal relationship between intake of different types of red and white meat and risk of cognitive decline is lacking.

There are also several other outstanding questions, for which comprehensive research data is lacking. These include (in no particular order): Is red meat from game or grass-fed animals healthier than the red meat from animals raised by conventional intensive agriculture ? What is the health impact of organ meat intake? What is the health impact of the different cooking methods of meat? What is the impact of lean vs. fatty meat on the risk of diseases?

Limitations

One of the main limitations is that, as with most dietary factors, there are no long-term RCTs that would have investigated the effects of consuming different kinds of meat on disease outcomes. Such studies would provide the highest quality of evidence, but will likely never be conducted due to financial, practical, and logistic reasons. Therefore, the evidence is based on short-term RCT with disease risk factors or on observational studies. The interpretation of findings from RCTs can be challenging, because the results may depend on the comparison food that replaces meat in the diet. Most RCTs last only a few weeks or months, which may be too short a time to observe significant effects on disease risk factors. It is possible that, for example, high blood pressure or glycaemia develop over a period of as long as years or decades. Even in short-term RCTs the attrition may be high, especially if the participants are required to make large changes to their typical diets. In RCTs the meat is also often minimally processed lean meat, and therefore the evidence of processed meat on, for example, blood pressure and glycaemia is limited (Zeraatkar et al. 2019, O'Connor et al.

2021). On the other hand, observational studies do not provide evidence for causality and may be biased due to residual confounding, reverse causation, and difficulty in estimating dietary intakes accurately and repeatedly. The significant heterogeneity in many meta-analyses of observational studies of meat intake and risk of diseases may partly be explained by these issues. A limitation is also that very few cohort studies collect information on long-term diet.

Another limitation is that the definition of red meat is not always the same. In some studies red meat refers to only unprocessed red meat whereas in other studies red meat refers to a mixture of unprocessed and processed red meat. This may be one cause for the heterogeneity often observed in meta-analyses. Many studies have combined intakes of processed red and processed white meat, when they have analyzed the relationships between processed meat intake and risk of disease. Therefore, there is not sufficient data to conclude whether processed white meat intake is as harmful as intake of processed red meat.

The quality of the majority of the SR articles on the association between meat and health outcomes were rated as critically low (according to AMSTAR-2 evaluation). The main limitations that led to the rating "critically low" were failure to preregister the plan for the SR , and restricting the literature search to articles written in English. Addressing these issues in future SRs would improve the quality with relatively little additional effort from the authors.

8. *INTEGRATION*

To be included at a later timepoint.

References

Ahmad MI, Zou X, Ijaz MU, Hussain M, Liu C, Xu X, Zhou G, Li C. Processed Meat Protein Promoted Inflammation and Hepatic Lipogenesis by Upregulating Nrf2/Keap1 Signaling Pathway in Glrx-Deficient Mice. J Agric Food Chem. 2019 Aug 14;67(32):8794-8809. doi: 10.1021/acs.jafc.9b03136. Epub 2019 Aug 6.

Arnesen EK, Christensen JJ, Andersen R, Eneroth H, Erkkola M, Høyer A, Lemming EW, Meltzer HM, Halldórsson ÞI, Þórsdóttir I, Schwab U, Trolle E, Blomhoff R. The Nordic Nutrition Recommendations 2022 - handbook for qualified systematic reviews. Food Nutr Res. 2020 Jun 18;64.

Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, De Henauw S, Michels N, Devleesschauwer B, Schlesinger S, Schwingshackl L. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr. 2019;59(7):1071-1090.

Chai W, Morimoto Y, Cooney RV, Franke AA, Shvetsov YB, Le Marchand L, Haiman CA, Kolonel LN, Goodman MT, Maskarinec G. Dietary red and processed meat intake and markers of adiposity and inflammation: the multiethnic cohort study. J Am Coll Nutr. 2017;36(5):378–85.chan

Chan CWH, Law BMH, Waye MMY, Chan JYW, So WKW, Chow KM. Trimethylamine-N-oxide as One Hypothetical Link for the Relationship between Intestinal Microbiota and Cancer - Where We Are and Where Shall We Go? J Cancer. 2019 Oct 8;10(23):5874-5882.

Chiavarini M, Bertarelli G, Minelli L, Fabiani R. Dietary Intake of Meat Cooking-Related

Mutagens (HCAs) and Risk of Colorectal Adenoma and Cancer: A Systematic Review and Meta-Analysis. Nutrients. 2017 May 18;9(5):514.

Cho CE, Taesuwan S, Malysheva OV, Bender E, Tulchinsky NF, Yan J, Sutter JL, Caudill MA. Trimethylamine-N-oxide (TMAO) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition: A randomized controlled trial. Mol Nutr Food Res. 2017;61:10.1002/mnfr.201600324.

Crimarco A, Springfield S, Petlura C, Streaty T, Cunanan K, Lee J, Fielding-Singh P, Carter MM, Topf MA, Wastyk HC, Sonnenburg ED, Sonnenburg JL, Gardner CD. A randomized crossover trial on the effect of plant-based compared with animal-based meat on trimethylamine-N-oxide and cardiovascular disease risk factors in generally healthy adults: Study With Appetizing Plantfood-Meat Eating Alternative Trial (SWAP-MEAT). Am J Clin Nutr. 2020 Nov 11;112(5):1188-1199.

Christensen JJ, Arnesen EK, Andersen R, Eneroth H, Erkkola M, Høyer A, Lemming EW, Meltzer HM, Halldórsson ÞI, Þórsdóttir I, Schwab U, Trolle E, Blomhoff R. The Nordic Nutrition Recommendations 2022 - principles and methodologies. Food Nutr Res. 2020 Jun 18;64.

Cross AJ, Pollock JR, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. Cancer Res. 2003 May 15;63(10):2358-60.

Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. Environ Mol Mutagen. 2004;44(1):44-55. doi: 10.1002/em.20030. PMID: 15199546.

Cui K, Liu Y, Zhu L, Mei X, Jin P, Luo Y. Association between intake of red and processed meat and the risk of heart failure: a meta-analysis. BMC Public Health. 2019 Mar 29;19(1):354.

Fernández-Real JM, Peñarroja G, Castro A, García-Bragado F, Hernández-Aguado I, Ricart W. Blood letting in high-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function. Diabetes. 2002 Apr;51(4):1000-4. doi: 10.2337/diabetes.51.4.1000. PMID: 11916918.

Ferrannini E. Insulin resistance, iron, and the liver. Lancet. 2000 Jun 24;355(9222):2181-2. doi: 10.1016/S0140-6736(00)02397-7. PMID: 10881887.

Green A, Basile R, Rumberger JM. Transferrin and iron induce insulin resistance of glucose transport in adipocytes. Metabolism. 2006 Aug;55(8):1042-5. doi: 10.1016/j.metabol.2006.03.015. PMID: 16839839.

Guasch-Ferré M, Satija A, Blondin SA, Janiszewski M, Emlen E, O'Connor LE, Campbell WW, Hu FB, Willett WC, Stampfer MJ. Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular Risk Factors. Circulation. 2019 Apr 9;139(15):1828-1845.

Guo H, Ding J, Liang J, Zhang Y. Association of Red Meat and Poultry Consumption With the Risk of Metabolic Syndrome: A Meta-Analysis of Prospective Cohort Studies. Front Nutr. 2021 Jul 8;8:691848.

Han MA, Zeraatkar D, Guyatt GH, Vernooij RWM, El Dib R, Zhang Y, Algarni A, Leung G, Storman D, Valli C, Rabassa M, Rehman N, Parvizian MK, Zworth M, Bartoszko JJ, Lopes LC, Sit D, Bala MM, Alonso-Coello P, Johnston BC. Reduction of Red and Processed Meat Intake and Cancer Mortality and Incidence: A Systematic Review and Meta-analysis of Cohort Studies. Ann Intern Med. 2019 Nov 19;171(10):711-720.

Haring B, Selvin E, Liang M, Coresh J, Grams ME, Petruski-Ivleva N, Steffen LM, Rebholz CM. Dietary Protein Sources and Risk for Incident Chronic Kidney Disease: Results From the Atherosclerosis Risk in Communities (ARIC) Study. J Ren Nutr. 2017 Jul;27(4):233-242.

Hooper L, Martin N, Jimoh OF, Kirk C, Foster E, Abdelhamid AS. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev. 2020 May 19;5(5):CD011737.

Huang S, Huang M, Dong X. Advanced Glycation End Products in Meat during Processing and Storage: A Review. Food Reviews International. 2021 Jun 24;1–17.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Red Meat and Processed Meat. Lyon (FR): International Agency for Research on Cancer; 2018. PMID: 29949327.

Kim M, Park K. Dietary Fat Intake and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis of Prospective Studies. Nutrients. 2018; 10(12):1963.

Kim Y, Keogh J, Clifton P. A review of potential metabolic etiologies of the observed association between red meat consumption and development of type 2 diabetes mellitus. Metabolism. 2015 Jul;64(7):768-79.

Kunutsor SK, Apekey TA, Walley J, Kain K. Ferritin levels and risk of type 2 diabetes mellitus: an updated systematic review and meta-analysis of prospective evidence. Diabetes Metab Res Rev. 2013 May;29(4):308-18. doi: 10.1002/dmrr.2394. PMID: 23381919.

Li F, Duan F, Zhao X, Song C, Cui S, Dai L. Red Meat and Processed Meat Consumption and Nasopharyngeal Carcinoma Risk: A Dose-response Meta-analysis of Observational Studies. Nutr Cancer. 2016 Aug-Sep;68(6):1034-43.

Li R, Yu K, Li C. Dietary factors and risk of gout and hyperuricemia: a meta-analysis and systematic review. Asia Pac J Clin Nutr. 2018;27(6):1344-1356.

Liu ZT, Lin AH. Dietary factors and thyroid cancer risk: a meta-analysis of observational studies. Nutr Cancer. 2014;66(7):1165-78.

Martínez Góngora V, Matthes KL, Castaño PR, Linseisen J, Rohrmann S. Dietary Heterocyclic Amine Intake and Colorectal Adenoma Risk: A Systematic Review and Meta-analysis. Cancer Epidemiol Biomarkers Prev. 2019 Jan;28(1):99-109.

Mazidi M, Kengne AP, George ES, Siervo M. The association of red meat intake with inflammation and circulating intermediate biomarkers of type 2 diabetes is mediated by central adiposity. Br J Nutr. 2021 May 14;125(9):1043-1050.

Mensink, Ronald P. & World Health Organization. (2016). Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. World Health

Organization. https://apps.who.int/iris/handle/10665/246104

Mirmiran P, Yuzbashian E, Aghayan M, Mahdavi M, Asghari G, Azizi F. A Prospective Study of Dietary Meat Intake and Risk of Incident Chronic Kidney Disease. J Ren Nutr. 2020 Mar;30(2):111-118. Erratum in: J Ren Nutr. 2021 Mar;31(2):227.

O'Connor LE, Kim JE, Campbell WW. Total red meat intake of ≥0.5 servings/d does not negatively influence cardiovascular disease risk factors: a systemically searched meta-analysis of randomized controlled trials. Am J Clin Nutr. 2017 Jan;105(1):57-69.

O'Connor LE, Kim JE, Clark CM, Zhu W, Campbell WW. Effects of Total Red Meat Intake on Glycemic Control and Inflammatory Biomarkers: A Meta-Analysis of Randomized Controlled Trials. Adv Nutr. 2021 Feb 1;12(1):115-127.

Sacks FM, Campos H. Dietary therapy in hypertension. N Engl J Med. 2010 Jun 3;362(22):2102-12.

Salari-Moghaddam A, Milajerdi A, Larijani B, Esmaillzadeh A. Processed red meat intake and risk of COPD: A systematic review and dose-response meta-analysis of prospective cohort studies. Clin Nutr. 2019 Jun;38(3):1109-1116.

Samraj AN, Pearce OM, Läubli H, Crittenden AN, Bergfeld AK, Banda K, Gregg CJ, Bingman AE, Secrest P, Diaz SL, Varki NM, Varki A. A red meat-derived glycan promotes inflammation and cancer progression. Proc Natl Acad Sci U S A. 2015 Jan 13;112(2):542-7.

Schlesinger S, Neuenschwander M, Schwedhelm C, Hoffmann G, Bechthold A, Boeing H, Schwingshackl L. Food Groups and Risk of Overweight, Obesity, and Weight Gain: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Adv Nutr. 2019 Mar 1;10(2):205-218.

Schulze MB, Hoffmann K, Manson JE, Willett WC, Meigs JB, Weikert C, Heidemann C, Colditz GA, Hu FB. Dietary pattern, inflammation, and incidence of type 2 diabetes in women. Am J Clin Nutr. 2005;82(3):675–84.; quiz 714–5.

Schoenaker DA, Mishra GD, Callaway LK, Soedamah-Muthu SS. The Role of Energy, Nutrients, Foods, and Dietary Patterns in the Development of Gestational Diabetes Mellitus: A Systematic Review of Observational Studies. Diabetes Care. 2016 Jan;39(1):16-23.

Schwingshackl L, Hoffmann G, Iqbal K, Schwedhelm C, Boeing H. Food groups and intermediate disease markers: a systematic review and network meta-analysis of randomized trials. Am J Clin Nutr. 2018 Sep 1;108(3):576-586. doi:10.1093/ajcn/nqy151. PMID: 30535089; PMCID: PMC6134288.

Schwingshackl L, Hoffmann G, Lampousi AM, Knüppel S, Iqbal K, Schwedhelm C, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol. 2017b May;32(5):363-375.

Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, Andriolo V, Bechthold A, Schlesinger S, Boeing H. Food Groups and Risk of Hypertension: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies. Adv Nutr. 2017a Nov 15;8(6):793-803. Erratum in: Adv Nutr. 2018 Mar 1;9(2):163-164.

Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi AM, Knüppel S, Iqbal K, Bechthold A, Schlesinger S, Boeing H. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr. 2017c Jun;105(6):1462-1473.

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, Wu Y, Hazen SL. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med. 2013 Apr 25;368(17):1575-84.

Thomson CA, Stanaway JD, Neuhouser ML, Snetselaar LG, Stefanick ML, Arendell L, et al. Nutrient intake and anemia risk in the women's health initiative observational study. Journal of the American Dietetic Association. 2011;111(4):532-41.

Tuomainen TP, Nyyssönen K, Salonen R, Tervahauta A, Korpela H, Lakka T, Kaplan GA, Salonen JT. Body iron stores are associated with serum insulin and blood glucose concentrations. Population study in 1,013 eastern Finnish men. Diabetes Care. 1997 Mar;20(3):426-8. doi: 10.2337/diacare.20.3.426. PMID: 9051399.

Shahinfar H, Jayedi A, Shab-Bidar S. Dietary iron intake and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of prospective cohort studies. Eur J Nutr. 2022 Aug;61(5):2279-2296. doi: 10.1007/s00394-022-02813-2. Epub 2022 Feb 2. PMID: 35107626.

Turesky RJ. Mechanistic Evidence for Red Meat and Processed Meat Intake and Cancer Risk: A Follow-up on the International Agency for Research on Cancer Evaluation of 2015. Chimia (Aarau). 2018 Oct 31;72(10):718-724.

Tzoulaki I, Brown IJ, Chan Q, Van Horn L, Ueshima H, Zhao L, Stamler J, Elliott P; International Collaborative Research Group on Macro-/Micronutrients and Blood Pressure. Relation of iron and red meat intake to blood pressure: cross sectional epidemiological study. BMJ. 2008 Jul 15;337:a258.

Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM, Wu Y, Schauer P, Smith JD, Allayee H, Tang WH, DiDonato JA, Lusis AJ, Hazen SL. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011 Apr 7;472(7341):57-63.

Wang Z, Bergeron N, Levison BS, Li XS, Chiu S, Jia X, Koeth RA, Li L, Wu Y, Tang WHW, Krauss RM, Hazen SL. Impact of chronic dietary red meat, white meat, or non-meat protein on trimethylamine N-oxide metabolism and renal excretion in healthy men and women. Eur Heart J. 2019 Feb 14;40(7):583-594.

van Westing AC, Küpers LK, Geleijnse JM. Diet and Kidney Function: a Literature Review. Curr Hypertens Rep. 2020 Feb 3;22(2):14.

World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and colorectal cancer. Available at dietandcancerreport.org.

World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Meat, fish, and dairy products and the risk of cancer. Availables at dietandcancerreport.org

Zeraatkar D, Han MA, Guyatt GH, Vernooij RWM, El Dib R, Cheung K, Milio K, Zworth M, Bartoszko JJ, Valli C, Rabassa M, Lee Y, Zajac J, Prokop-Dorner A, Lo C, Bala MM, Alonso-Coello P, Hanna SE, Johnston BC. Red and Processed Meat Consumption and Risk for All-Cause Mortality and Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Cohort Studies. Ann Intern Med. 2019a Nov 19;171(10):703-710.

Zeraatkar D, Johnston BC, Bartoszko J, Cheung K, Bala MM, Valli C, Rabassa M, Sit D, Milio K, Sadeghirad B, Agarwal A, Zea AM, Lee Y, Han MA, Vernooij RWM, Alonso-Coello P, Guyatt GH, El Dib R. Effect of Lower Versus Higher Red Meat Intake on Cardiometabolic and Cancer Outcomes: A Systematic Review of Randomized Trials. Ann Intern Med. 2019b Nov 19;171(10):721-731.

Zhang Z, Chen GC, Qin ZZ, Tong X, Li DP, Qin LQ. Poultry and Fish Consumption in Relation to Total Cancer Mortality: A Meta-Analysis of Prospective Studies. Nutr Cancer. 2018 Feb-Mar;70(2):204-212.

Zhang Y, Yang Y, Xie MS, Ding X, Li H, Liu ZC, Peng SF. Is meat consumption associated with depression? A meta-analysis of observational studies. BMC Psychiatry. 2017 Dec 28;17(1):409.

Zhang Y, Zhang DZ. Red meat, poultry, and egg consumption with the risk of hypertension: a meta-analysis of prospective cohort studies. J Hum Hypertens. 2018 Jul;32(7):507-517.

Zhao Z, Li S, Liu G, Yan F, Ma X, Huang Z, Tian H. Body iron stores and heme-iron intake in relation to risk of type 2 diabetes: a systematic review and meta-analyses. PLoS ONE. 2012;7:e41641.

Table 1. List of included 23systematic reviews and meta-analyses (one SR can contribute to several outcomes) in setting the Nordic Nutrition Recommendations 2022 for intake of meat and meat products

1st author (year), (reference)	**Outcome(s)**	**Design of included primary studies**	**Definition of exposure**	**Exposure categories**	**Main findings (after RR or OR, 95% confidence interval in the parenthesis)**	**Evidence for heterogeneity (I^2 >40% or p>0.10)? xMentioned if heterogeneity explained**	**Evidence for publication bias?**	**AMSTAR-2 rating †**
Cardiovascular diseases								
Zeraatkar et al. (2019a)	CVD mortality, CVD, fatal or non-fatal stroke, fatal or nonfatal MI	Prospective cohorts (N of cases not reported) *N of studies / participants:* **Unprocessed red meat**: *Highest vs. lowest* CVD mortality: 8 / 389,528; CVD: 4 / 65,736; stroke: 6 / 102,024; fatal stroke: 3 / 268,504; MI: 1 / 55,171	**Red meat**: mammalian meat; **Processed meat**: white or red meat preserved by smoking, curing, salting, or adding chemical compounds (for example, hot dogs, charcuterie, sausage, ham, and deli meats)	Reduction of 3 servings/wk Lowest vs. highest	**Unprocessed red meat** *Highest vs. lowest* CVD mortality: RR 0.88 (0.77-1.01); CVD: 0.92 (0.80-1.06); stroke: 0.90 (0.83-0.97); fatal stroke: 0.89 (0.76-1.05); MI: 0.85 (0.73-0.98) *Reduction of 3 servings/wk* CVD mortality: 0.90 (0.88-0.91); CVD: 0.95 (0.85-1.06); stroke: 0.94 (0.90-0.98); fatal stroke: 0.94 (0.89-0.99); MI: 0.93 (0.87-0.99) **Processed meat** *Highest vs. lowest* CVD mortality: 0.88 (0.77-1.00); CVD:0.97 (0.88-1.05); stroke: 0.85 (0.80-0.93); fatal	**Unprocessed red meat**: *Highest vs. lowest* Yes, CVD mortality: I^2=83.4% (p=0.001), also in studies with LoR*: I^2=54.4% (p=0.099) *Reduction of 3 servings/wk* Yes, CVD mortality: I^2=86.9% (P<0.01, HiR*). NA for MI **Processed meat:** *Highest vs. lowest* Yes, CVD mortality: I^2=79.1% (P=0.001), no heterogeneity in low risk of bias studies. *Reduction of 3 servings/wk* Yes, CVD mortality: I^2=98.2% (P<0.001, HiR); CVD: I^2=75.1 (P<0.01, LoR).	Not done because <10 studies	Moder-ate quality

		Reduction of 3 servings/wk CVD mortality: 7 / 874,896; CVD: 3 / 191,803; stroke: 6 / 254,742; fatal stroke: 3 / 671,259; MI: 1 / 55,171 **Processed meat:** *Highest vs. lowest* CVD mortality: 9 / >472,128 (the numbers in extreme categories unknown in some studies); CVD: 4 / 69,186; stroke: 6 / 101,861; fatal stroke: 2 / 231,992; MI: 1 / 55,171			stroke: 0.92 (0.84-1.00); MI: 0.87 (0.79-0.95). *Reduction of 3 servings/wk* CVD mortality: 0.90 (0.84-0.97); CVD:0.97 (0.87-1.09); stroke: 0.94 (0.90-0.98); fatal stroke: 0.95 (0.92-0.98); MI: 0.94 (0.91-0.98).	NA for MI		

		Reduction of 3 servings/wk CVD mortality: 7 / 1,240,634; CVD: 3 / 200,421; stroke: 6 / 254,742; fatal stroke: 2 / 571,378 MI: 1 / 55,171 *Follow-up time in the original studies:* **Unprocessed red meat:** 5.5-28 **Processed meat:** 8-28						
Bechthold et al (2019)	Fatal or non-fatal CHD, fatal or non-fatal stroke, heart failure	Prospective cohorts *N of studies / cases* Highest vs. lowest comparisons:	**Processed and unprocessed red meat, processed meat**. No detailed definition.	Highest vs. lowest category Increase of 100 g/d of total red meat or 50 g/d of	**Total red meat** *highest vs. lowest category* CHD: RR=1.16 (95% CI 1.08-1.24); stroke: 1.16 (1.08-1.25); heart	**Total red meat:** no **Processed meat**: yes, for stroke when assessed per 50 g/d higher intake (I^2=56%, P=0.05), mainly explained by the	Not done because <10 studies	High quality

		Total red meat: CHD: 3 / 6,659; stroke: 7 / 10,541; heart failure: 5 / 9,229 **Processed meat**: CHD: 5 / 7,038 cases; stroke: 6 / 9,492; heart failure: 3 / 7,077 *Follow-up time in the original studies:* **Total red meat:** 6-26 **Processed meat:** 4-26		processed meat	failure: 1.12 (1.04-1.21) *per 100 g/d increase* CHD: 1.15 (1.08-1.23); stroke: 1.12 (1.06-1.17); heart failure: 1.08 (1.02-1.12) Evidence for non-linear dose-response between red meat intake and heart failure (3 studies). **Processed meat** *highest vs. lowest category* CHD: 1.15 (0.99-1.33); stroke: 1.16 (1.07-1.26); heart failure: 1.27 (1.14-1.41) *Per 50 g/d increase* CHD: 1.27 (1.09-1.49); stroke: 1.17 (1.02-1.34); heart failure: 1.12 (1.05-1.19). The association with stroke was stronger in US studies (1.47, 1.16-1.85) than in European	geographical location (USA vs. Europe)		

					studies (1.08, 0.96-1.22)			
Cui et al (2019)	Heart failure	Prospective cohorts *N of studies / cases:* **Unprocessed red meat**: 5/8281 **Processed red meat:** 5/15,567 *Follow-up period:* **Unprocessed red meat**: 11.9 -21.5 y. **Processed meat:** 8.2-21.5 y.	**Unprocessed red meat, processed meat.** No detailed definition.	Highest vs. lowest category	**Unprocessed red meat** RR=1.04 (95% CI 0.96-1.12) **Processed meat** 1.23 (1.07-1.41). In the stratified analyses, the association with increased risk was stronger in the European studies (1.33, 1.15-1.54) than in the US studies (1.08, 0.99-1.18).	**Unprocessed red meat:** no. **Processed meat:** yes (I^2=58.9%, P=0.05), which was mainly explained by the geographical location (USA vs Europe)	No	Critically low
All-cause mortality								
Zeraatkar et al. (2019a)	All-cause mortality	Prospective cohorts (N of cases not reported) *N of studies / participants:* **Unprocessed red meat:**	**Unprocessed red meat**: unprocessed mammalian meat; **Processed meat**: white or red meat preserved by smoking, curing, salting, or adding chemical compounds (for example, hot dogs, charcuterie,	Reduction of 3 servings/wk Lowest vs. highest category	**Unprocessed red meat** *Reduction of 3 servings/wk* 0.93 (0.87-1.00) *Lowest vs. highest category* 0.90 (0.80-1.01) **Processed meat** *Reduction of 3 servings/wk*	**Unprocessed red meat:** *Reduction of 3 servings/wk* yes, I^2=96.0% (P<0.001, 8 LoR studies) *Highest vs. lowest category* yes, I^2=94.6% (P<0.001, 9 LoR studies)	Not done because <10 studies	Moder-ate quality

		Reduction of 3 servings/wk 8 / 893,436 *Highest vs. lowest* 9 / 413,760 **Processed meat:** *Reduction of 3 servings/wk* 8 / 1,241,900 *Highest vs. lowest* 10 / >696,822 (some studies did not report the n in extreme categories) *Follow-up time:* **Unprocessed red meat:** 5.5-28 y. **Processed meat:** 9-28 y.	sausage, ham, and deli meats)		0.92 (0.87-0.96) *Lowest vs. highest category* 0.88 (0.85-0.90)	**Processed meat:** yes, *Reduction of 3 servings/wk* I^2=86.0% (P<0.001, 7 LoR studies) *Highest vs. lowest category* no		
Schwingshackl et al (2017c)	All-cause mortality	Prospective cohorts *N of studies / cases:*	**Total red meat, processed meat**. No detailed definition.	Highest vs. lowest category	**Total red meat** *highest vs. lowest category* RR=1.10 (95% CI 1.00-1.22)	**Total red meat:** yes *highest vs. lowest category:* I^2=93%, P<0.001)	**Total red meat:** yes **Processed meat:** no	Critically low

		Total red meat: *Highest vs. lowest category* 12 / 177,655 *Dose-response* 10 / not reported **Processed meat**: *Highest vs. lowest category* 7 / 143,572 *Dose-response* 7 / not reported *Follow-up time:* **Total red meat:** 5.5-28 y. **Processed meat:** 9-28 y.		Increase of 100 g/d of total red meat or 50 g/d of processed meat	*Per 100 g/d increase* 1.10 (1.04-1.18) In stratified analyses, the positive association was observed mainly in studies with only men, with a longer follow-up, with a larger number of participants, with a validated dietary assessment method, and in the US vs. European or Asian studies. **Processed meat** *highest vs. lowest category* 1.21 (1.16-1.26) *Per 50 g/d increas* 1.23 (1.12-1.36). In stratified analyses the positive association was observed mainly in studies with a longer follow-up, with a larger number of participants, with a validated dietary assessment method,	*per 100 g/d increase:* I^2=92%, P<0.001). There was significant heterogeneity also in the stratified analyses (I^2=56-95%). **Processed meat:** yes *highest vs. lowest category:* I^2=56%, P=0.03) *Per 50 g/d increase:* I^2=94%, P<0.001). There was significant heterogeneity also in the stratified analyses (I^2=85-95%), except for the studies conducted in Europe (I^2=0%).		

					and in the US. vs European studies.			
Hypertension								
Zhang & Zhang (2018)	Hypertension	Prospective cohorts *N of studies / cases:* **Unprocessed red meat**: 5 / 23,854 **Processed red meat**: 5 / 23,854 **Poultry:** 6 / 14,739	**Unprocessed red meat**, **processed red meat, poultry.** No detailed definition.	Highest vs. lowest category	**Unprocessed red meat** RR 1.19 (1.04-1.36) **Processed red meat:** RR 1.12 (1.02-1.23) **Poultry** RR 1.15 (1.03-1.28)	**Unprocessed red meat:** yes, I^2=91%, p<0.001 **Processed red meat:** yes, I^2=79.8%, p=0.001 **Poultry:** yes, I^2=63.3%, p=0.02	No (for all meat types)	Critically low

Schwingshackl et al. (2017a)	Hypertension	Prospective cohort studies *N of studies / cases:* **Total red meat:** 7 / 97,745 **Processed meat:** 4 / 97,441 *Follow-up time:* Total red meat: 3-14 y. and 564247-1396062 person years Processed meat: 10-14 y. and 564247-1396062 person years	**Total red meat, processed meat**. No detailed definition.	**Total red meat:** Increase of 100 g/d **Processed meat:** Increase of 50 g/d	**Total red meat** RR: 1.14 (1.02, 1.28); **Processed meat** RR: 1.12 (1.00, 1.26)	**Total red meat:** yes, I^2 = 88%, p < 0.001 **Processed meat:** yes, I^2 = 82%, P < 0.001	Not done because <10 studies	Critically low

Type 2 diabetes

Zeraatkar et al. (2019a)	T2D	Prospective cohorts (N of cases not reported) *N of studies / participants* **Unprocessed red meat:** *Dose-response analyses:* 11 / 531,843 *Lowest vs. highest* 12 / >211,467 (some studies did not report n in extreme categories) **Processed red meat:** *Dose-response analyses:* 17 / 758,540 *Lowest vs. highest* 19 / >25,032 (some studies did	**Unprocessed red meat**: mammalian meat; **Processed meat:** white or red meat preserved by smoking, curing, salting, or adding chemical compounds (for example, hot dogs, charcuterie, sausage, ham, and deli meats);	Reduction of 3 servings/wk Lowest vs. highest category	**Unprocessed red meat:** *Per 3 servings/wk reduction (1 serving equals 120 g)* RR 0.94 (95% CI 0.89-0.98,) *Lowest vs. highest* RR 0.91 (0.84 to 0.98) Association stronger in low risk of bias studies **Processed meat:** *Per 3 servings/wk reduction (1 serving equals 50 g)* RR 0.85 (0.79-0.92,), non-linear association *Lowest vs. highest* RR 0.83 (0.79-0.88)	**Unprocessed red meat:** yes, *Per 3 servings/wk reduction* I^2=64.9%, p<0.01 No heterogeneity between studies with low risk of bias: I^2=0.1%, p=0.27 *Lowest vs. highest* I^2=61.8%, p<0.01 heterogeneity also in analysis including only low risk of bias studies (I^2=64.8, p=0.016) **Processed meat:** yes,	No (for all analyses)	Moder-ate quality

		not report n in extreme categories) *Follow-up time:* **Unprocessed red meat:** 4.6-28 **Processed red meat:** 4.3-28			Association was weaker in low risk of bias studies	*Per 3 servings/wk reduction* I^2=92%, p<0.001 heterogeneity also in analysis including only low risk of bias studies (I^2=83.4, p<0.001) *Lowest vs. highest* I^2=56.9%, p<0.01 heterogeneity also in analysis including only low risk of bias studies (I^2=64.4, p=0.004)		

Schwingshackl et al. (2017b)	T2D	Prospective cohort studies *N of studies / cases:* **Total red meat:** 14 / 45,702 **Processed meat:** 14 / 43,781 *Follow-up time:* 4.6-28 y. for both meat types	**Total red meat, processed meat.** No detailed definition.	**Total red meat**: 100g/d increase; **Processed meat**: 50 g/d increase	**Total red meat** RR 1.17 (1.08–1.26) The results were unchanged in the subgroups of low risk of bias studies. The association was stronger in studies with longer follow-up (≥10 years), in the US, higher number of cases (≥1000), and when outcome was self-reported or from registry (vs. diagnosed by physician). **Processed meat:** RR 1.37 (1.22-1.55) Evidence of a non-linear dose–response association; the risk of T2D increased by 30% with increasing intakes up to 50 g/day. Moderate additional detrimental effects for increasing intake above this value were observed The association was stronger in low risk of bias studies, studies with women,	**Total red meat:** yes, I^2 = 83%, p<0.001 Heterogeneity persisted in stratified analyses. **Processed meat:** yes, I^2=88%, p<0.001 The observed heterogeneity persisted in stratified analyses	**Total red meat**: No **Processed meat:** Yes. Visual inspection of the funnel plot suggests that small studies showing inverse or null association may be missing	Critically low

					individuals above 50 years, in US, in studies with FFQ as a dietary intake method, and in studies with self-reported outcome measures			
Cancers								
WCRF (2018)	Colorectal cancer	cohort, nested case-control and case-cohort designs *N of studies / cases* **Total red meat:** 8 / 6662 **Processed meat:** 10 / 10,738 **Poultry**: 6 / 3429 *Follow-up time:* **Total red meat**: 6- 24 y. and 105044-2279075 person years	**Total red meat; Processed meat:** generally described as processed meat, preserved meat or cured meat, but individual items included in the meat group could vary between the studies; **Poultry**: chicken, turkey, ground poultry, and the processed poultry components of turkey or chicken cold cuts and low-fat versions of hot dogs and sausage	**Total red meat** 100 g increase **Processed meat:** 50 g increase **Poultry:** 100 g	**Total red meat** RR 1.12 (1.00-1.25), **Processed meat:** RR1.16 (1.08-1.26) **Poultry:** RR 0.81(0.53-1.25), From individual studies, only one study observed a significant inverse association.	**Total red meat:** no **Processed meat:** no **Poultry:** yes, I^2=48.0%, p=0.05	No (for all meat types)	Qualified systematic review - No AMSTAR evaluation

		Processed meat: 3.3 – 24 y. and 105044-2279075 person years Poultry: 3.3 – 16 years and 105044-286731 person years						

WCRF (2018, based on systematic review by Li et al. 2016)	Nasopharyngeal cancer	case-control studies *N of studies / cases:* **Total red meat:** 6 / 911; **Processed meat:** 10 / 3154 Follow-up time not reported.	**Total red meat, processed meat.** No detailed definition.	**Total red meat** <100g/week vs. never, 100-300 g/week vs. never, >300 g/week vs. never **Processed meat** <30 g/week vs. never, 30-60 g/week vs. never, >60 g/week vs. never	**Total red meat** *<100g/week vs. never* RR 1.35 (95% CI = 1.21-1.51) *100-300 g/week vs. never* RR 1.54 (95% CI = 1.35-1.76) *>300 g/week vs. never* RR 1.71 (95% CI = 1.14-2.55) **Processed meat** *<30 g/week vs. never* RR 1.46 (95% CI = 1.31-1.64) *30-60 g/week vs. never* RR 1.59 (95% CI = 1.33- 1.90) *>60 g/week vs. never* RR 2.11 (95% CI = 1.31-3.42)	**Total red meat** *<100g/week vs. never* No *100-300 g/week vs. never*: yes, I^2=57%, p=0.05 *>300 g/week vs. never*: yes, I^2=77%, p=0.01 **Processed meat** *<30 g/week vs. never*: yes, I^2=76%, p<0.01 *30-60 g/week vs. never*: yes, I^2=82%, p<0.01 *>60 g/week vs. never*: yes, I^2=85%, p<0.01	No (for all analyses)	Qualified systematic review - No AMSTAR evaluation

WCRF (2016) no relevant new studies were found during the continuous updating processed in 2018	Lung cancer	cohort, nested case-control and case-cohort *N of studies / cases* **Total red meat:** 7 / 9765 **Processed meat:** 7 / 10,292 **Poultry:** 6 / 11,707 *Follow-up time:* 7-11.4 y. for Total red meat, and for processed meat Poultry: 9.1-11.4 y.	**Total red meat**, **processed meat, poultry**. No detailed definition.	**Total red meat** 100 g/d increase **Processed meat** 50 g/d **Poultry** 100 g/d	**Total red meat** RR 1.22 (1.02-1.46) **Processed meat** RR 1.14 (1.05-1.24) **Poultry** RR 0.91 (0.85-0.97) Only one study showed a significant inverse association	**Total red meat:** yes, I^2=66%, p<0.01 Heterogeneity probably explained by two studies that reported stronger associations than the average (concluded from funnel plot). **Processed meat:** no **Poultry:** no	**Total red meat** No **Processed meat** Yes (p=0.04) **Poultry** No	Qualified systematic review - No AMSTAR evaluation

WCRF (2011) no relevant new studies were found during the continuous updating processed in 2018	Pancreatic cancer (combined incidence and mortality)	prospective cohort studies *N of studies / cases* **Total red meat:** 8 / 2761 **Processed meat:** 6 / 2748 *Follow-up time:* (reported only for studies found for the update of 2011) Processed meat: 5-13.3 Red meat:5-16.3	**Total red meat, Processed meat.** No detailed definition.	**Total red meat** 100 g/d **Processed meat** 50 g /d increase	**Total red meat** RR 1.19 (0.98-1.45) In the analysis stratified by sex Men RR 1.43 (1.10-1.86, 3 studies) Women RR = 1.06 (0.86-1.31, 4 studies) **Processed meat** RR 1.17 (1.91-1.34) In subgroup analyses by sex a positive association of processed meat was found in men, but not in women. Study results in women were inconsistent, showing associations to both directions.	**Total red meat:** yes, I^2=52%, p=0.04 Heterogeneity decreased in subgroups of men and women: Men (3 studies): no Women (4 studies):no **Processed meat:** no	No for both meat types	Qualified systematic review - No AMSTAR evaluation

WCRF (2018)	Oesophageal cancer	cohort, nested case-control and case-cohort *N of studies / cases* Mixed red meat and processed meat: 3 / 1234 Processed meat: 4 / 1388 N of cases not reported for beef, lamb, pork, or poultry *N of studies* Beef: 2 Pork: 3 Lamb: 1 Poultry: 3 *Follow-up time* Red and processed meat: 6.8-9.7 y.	**Mixed red meat and processed meat, processed meat**. Processed meat definitions in the primary studies: ham, sausages, bacon, sausages, processed meat, processed meat and fish; **Beef, pork, lam1b, poultry**	**Mixed red meat and processed meat** 100 g/d **Processed meat** 50 g /d **Beef, pork, lamb, poultry** No meta-analysis	**Mixed red meat and processed meat** RR 1.22 (0.95-1.56) **Processed meat** RR 1.39 (1.09-1.77) association significant only in a subgroup of European studies. Association was not significant when only those studies were analysed that adjusted for alcohol and physical activity. **Beef:** no association (Iso 2007) and borderline significant association (Kjaerheim et al. 1998) **Pork:** Borderline significant association in men (Iso et al. 2007); no association (Kjaerheim et al. 1998), significant positive association (Yu et al. 1993) **Lamb**: No association (Kjaerheim et al. 1998) **Poultry:** No association in analysed comparing the highest vs. lowest analysis	Mixed red meat and processed meat, and processed meat: no Beef, pork, lamb, poultry: NA because no meta-analysis	Not assessed because <10 studies Beef, pork, lamb, poultry: NA	Qualified systematic review - No AMSTAR evaluation

		Processed meat: 6.8-25 y. Not reported for other meat types.			intake categories (Iso et al 2007, Jakszyn et al. 2013, Daniel et al. 2011)			

WCRF (2018)	Stomach cancer	cohort, nested case-control and case-cohort designs *N of studies / cases* **Total red meat:** 4 / 2408; **Processed meat:** 10 / 4728; **Poultry:** 5 / 3708 *Follow-up time:* Total red meat: 6.5-19 y. Processed meat: 6.3-21 y. Poultry: 6.5-19 y.	**Total red meat, processed meat, mixed red and processed meat, poultry.** No detailed definition.	**Total red meat** 100 g/d **Processed meat** 50 g/d **Poultry** 100 g/d	**Total red meat** RR 1.12 (0.95-1.32) **Processed meat** RR 1.19 (1.06-1.34), In a stratified analysis by geographical location the result was significant only in subgroup of European studies. The results not significant when only those included that adjusted for physical activity. **Poultry** RR 0.98 (0.82-1.17)	no (for all meat types)	**Total red meat** NA **Processed meat** Yes. 0.05 Asymmetry mainly driven by a small study that reported a very strong positive association. **Poultry** No	Qualified systematic review - No AMSTAR evaluation

Liu & Lin 2014	Thyroid cancer	Case-control studies *N of studies / cases:* 5 / 831 *Follow-up time:* 2-9 y.	**Total meat**	Highest vs. lowest category	OR 0.96 (0.70-1.34, 5 studies)	no	No	Critically low
Han et al. (2019)	Total cancer mortality and incidence	Prospective cohort studies (N of cases not reported) *N of participants:* **Unprocessed red meat**: cancer mortality: 3 / 875,290 cancer incidence: 2 / 71,858	**Red meat:** meat from mammals **Processed meat**: meat that has been preserved by smoking, curing, salting, or adding preservatives (for example, hot dogs, charcuterie, sausage, ham, and cold-cut deli meats).	3 serving / wk reduction	**Unprocessed red meat** Cancer mortality: RR 0.93 (0.91-0.94) The result was similar in low-risk of bias studies () with no heterogeneity. The result significant in only 1 primary study Cancer incidence: RR 0.93 (0.83-1.04) The results was significant in the 1 low-risk of bias study **Processed meat**	**Unprocessed red meat** Cancer mortality**:** no Cancer incidence: yes, I^2=50.9%, p=0.15 **Processed meat** Cancer mortality**:** yes, I^2=53.9%, p=0.04 Cancer incidence**:** yes, I2=69.7%, p=0.07	Not done because n of studies <10	Critically low

		Processed red meat cancer mortality: 6 / 1,198,234 cancer incidence: 2 / 71,858 *Follow-up time:* Unprocessed red meat: on a range 5-28 y. Processed meat: range 5-28 y.			Cancer mortality: RR 0.93 (0.90-0.96), The result was similar in subgroup of low-risk of bias studies (3) with no evidence of heterogeneity. The result significant in only 1 primary study Cancer incidence: RR 0.99 (0.89-1.09) The result was similar in the one low risk of bias study.			
Zhang et al. (2018)	Total cancer mortality	Prospective cohort studies *N of cases in original studies* 257-9861 *N of studies* Highest vs. lowest: 8 Dose-response: 5 *Follow-up time* 5.5-22 y.	**Poultry**	Highest vs. lowest category; 100g/d	*Highest vs. lowest* RR 0.96 (0.93-1.00), Subgroup analysis showed a statistically significant inverse association in the subgroups of Asian studies, studies with shorter follow-up duration, high-quality studies and studies with large number of participants *Per 100g/d increase* RR 0.97 (0.88-1.07)	no (for both analyses)	No (for both analyses)	Critically low

Obesity								
Schlesinger et al. (2019)	Obesity	Prospective cohort studies *N of studies / cases* 1 / 7183 *Follow-up time:* Total red meat: 1-16 y.	**Unprocessed and processed red meat**: Pork, veal, lamb, beef, mutton, processed red meat (sausages, salami, ham), hamburger, meatloaf; processed meat: Salami, cold-cut sausage, ham, fried sausage, liver sausage.	Highest vs. lowest category	**Total red meat:** No meta-analysis. Result of the individual study: RR 1.23 (1.07-1.41)	NA because no meta-analysis	NA	Not assessed
	Abdominal obesity	Prospective cohort studies *N of studies / cases:* **Total red meat:** 2 / 1500 **Processed meat:** 1 / 36 *Follow-up time:* Total red meat: 1->10 y. Processed meat: 1 y.	**Red meat**: Pork, veal, lamb, beef, mutton, processed red meat (sausages, salami, ham), hamburger, meatloaf; **Processed meat**: Salami, cold-cut sausage, ham, fried sausage, liver sausage.	**Total red meat** Highest vs. lowest category Increase of 100 g/d **Processed meat** Highest vs. lowest category	**Total red meat** *Highest vs. lowest* RR 1.18 (95% CI: 1.06, 1.32) *Increase of 100 g/d* 1.10 (1.04, 1.16) **Processed meat** No meta-analysis. Result of an individual study RR 8.80 (95% CI: 1.20-64.28)	**Total red meat:** no **Processed meat:** NA because no meta-analysis	NA	
Mental health								

Zhang et al. (2017)	Depression	Prospective cohort studies (N of cases not reported) *N of studies / participants* 3 / 20,072 *Follow-up time not reported.*	**Total meat**	Highest vs. lowest	RR = 1.13, 95% CI: 1.03 to 1.24)	no	No	Not assessed
Other health outcomes								
Schoenaker et al. (2016)	Gestational diabetes	Prospective cohort study *N of studies / cases:* 1 / 870 *Follow-up time* 10 y.	**Totalunprocessed, processed red meat**: beef, lamb, pork, hamburger, bacon, beef hot dogs and sausages, salami and bologna	1 serving /d increase	No meta-analysis. Individual study: **Total red meat:** RR 2.05 (1.55–2.73), **Unprocessed red meat**: 1.60 (1.21–2.12) **Processed red meat:** 1.36 (1.03–1.80)	NA because no meta-analysis	NA	Not assessed
van Westing et al. (2020)	Chronic kidney disease	prospective cohort study (Haring et al. 2017) *N of studies / cases:* 1 / 2632 *Follow-up time:* 23 y.	**Red meat (not clear whether unprocessed or total), processed meat, poultry.** No detailed definition.	Q5 vs. Q1	**Red meat (not clear whether unprocessed or total)** HR 1.19 (1.03-1.36) **Processed meat** HR 1.12 (0.98-1.29) **Poultry** HR 0.94 (0.84-1.06)	NA because no meta-analysis	NA	Not assessed

		prospective cohort study (Mirmiran et al. 2019) *N of studies / cases:* 1 / 613 *Follow-up time:* 3.12 y.	**Total red meat, processed red meat.** No detailed definition.	Q4 vs. Q1	**Total red meat** OR 1.73 (1.33-2.24) **Processed red meat** OR 1.99 (1.54-2.56)	NA because no meta-analysis	NA	
Guo et al. (2021)	Metabolic syndrome	Prospective cohorts (N of cases not reported) *N of studies / participants:* **Total red meat**: 8 / 16,121 **Unprocessed red meat**: 3 / 5535 **Processed red meat**: 4 / 5959 **Poultry:** 3 / 7270 *Follow-up time:* Unprocessed red meat: 1-6 y.	**Red meat:** beef, pork, horse, veal, deer, and lamb. **Processed red meat:** red meat products with ingredients (sausages, cold cuts, and others)	Highest vs. lowest category	**Total red meat** 1.35 (1.13-1.62) **Unprocessed red meat** 1.32 (1.14-1.54) **Processed red meat** 1.48 (1.11-1.97) **Poultry:** 0.85 (0.75, 0.97)	**Total red meat**: yes, I^2=54.4%, P=0.03) No heterogeneity between studies with only non-Asian populations (4 studies) and between studies adjusting for physical activity (5 studies) **Unprocessed red meat:** no **Processed red meat**: yes, I^2=64.7%; P=0.04) **Poultry:** no	No	Not assessed

		Processed red meat: 1-6 y.						
Salari-Moghaddam et al. (2018)	Chronic obstructive pulmonary disease (COPD)	Prospective cohorts *N of studies / cases:* Highest vs. lowest category: 5 / 8338 Dose-response: 5 / 8338 *Follow-up time:* 11.6-17 y.	**Processed red meat:** sausages, cold cuts, ham, salami, blood pudding, liver pate, cured meat, bacon, hot dogs, bologna	Highest vs. lowest category Increase of 50 g/wk	*Highest vs. lowest category* HR=1.40 (95% CI 1.21-1.62) *Increase of 50 g/wk* 1.08 (1.03-1.13)	*Highest vs. lowest category:* No *Increase of 50 g/wk:* yes, I^2=90.6%, P<0.001)	No	Not assessed
Li et al (2018)	Gout	Prospective cohorts *N of studies / cases:* 2 / 2897 Follow-up time: 11-12 y.	**Red meat.** No detailed definition.	Highest vs. lowest category	Gout: OR=1.29 (95% CI 1.16-1.44)	no	No	Not assessed
Zeraatkar et al. (2019a, based on one primary study: Thomson et al. 2011)	Anemia	Prospective cohort study *N studies / cases:* 1 / 3979	**Red meat (unclear whether unprocessed or total red meat)**	incident anemia (defined as anemia developed from at 3	Incident anemia: OR 0.98 (0.90-1.06) Persistent anemia: OR 0.89 (0.79-1.01)	NA because no meta-analysis.	NA	Not assessed

		Follow-up: 3 y.		years from the baseline) vs. no anemia persistent anemia (defined as anemia detected at baseline and at 3 years) vs. no anemia	At baseline mean intake of red meat 0.6 servings/d with no differences between those with anemia and those without anemia			

NA, not applicable. *In the study heterogeneity was investigated separately for high-risk (HR) and low-risk (LR) studies. Risk was based on Clinical Advances through Research and Information Translation (CLARITY) risk-of-bias instrument for cohort studies.

CVD=cardiovascular disease, CHD=coronary heart disease, CI=confidence interval, HF=heart failure, OR=odds ratio, RR=relative risk

†One weakness in the critical domains of the AMSTAR-2 tool led to rating of “low” and 2 or more weaknesses in the critical domains led to rating “critically low”.