Evidence Check

Animal sourced protein (meat and poultry) and heart health

An **Evidence Check** rapid review brokered by the Sax Institute for the National Heart Foundation of Australia. December 2018.

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This report was prepared by:

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Disclaimer:

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Contents

Glossary

BOLD	Beef in an Optimal Lean Diet
CHD	Coronary heart disease
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
GI	Glycaemic index
GL	Glycaemic load
HDL-C	High density lipoprotein cholesterol
HF	Heart failure
LDL-C	Low density lipoprotein cholesterol
MI	Myocardial infarction
RCT	Randomised controlled trial
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglycerides

Executive summary

Background / Purpose of the review

Cardiovascular disease (CVD) is the leading cause of disease burden and death in Australia accounting for 32% of all deaths in 2017. There are a number of critical modifiable risk factors that alter the risk of CVD, including poor quality diets. It is therefore of crucial scientific and public health importance to understand how dietary components individually, and as part of different dietary patterns, impact on cardiovascular health.

Most current dietary guidelines for healthy eating recommend a focus on healthy dietary patterns that aim to increase intake of a variety of healthy foods and reduce intake of unhealthy foods. Specifically with regards to meats, the Australian Dietary Guidelines suggest that lean red meats and poultry are core foods that can be part of a healthy diet, and also set a quantitative recommendation for red meat (less than 455 grams per week), but not for poultry. The aim of this Evidence Check is to review and synthesize relevant literature on the relationship between unprocessed meat intake and CVD.

Review questions

This review aimed to address the following questions:

Question 1:

Is unprocessed meat and poultry consumption in adult populations (similar to Australia) associated with risk of cardiovascular disease?

Question 2:

Is there a level of unprocessed meat and poultry consumption in adult populations (similar to Australia) at which risk of cardiovascular disease increases?

Question 3:

What is the effect on risk of cardiovascular disease when unprocessed meat and poultry is added to healthy eating patterns in adult populations (similar to Australia)?

Summary of methods

Peer review literature was searched using electronic databases including Medline, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. Studies were restricted to those published from January 2010 to October 2018 and published in English. For Questions 1 and 2, eligible studies included meta-analyses of prospective cohort studies and randomised controlled trials (RCT) that assessed association of unprocessed meat intake and relevant CVD outcomes. In addition, prospective cohort studies and RCTs not included in prior systematic reviews and meta-analyses were included. Outcomes of interest included CVD, coronary heart disease (CHD), atrial fibrillation, heart failure, stroke, incidence of hypertension, change in blood pressure, change in lipid profile and weight gain. For Question 3, RCTs were included. Specifically, we searched for RCTs that randomised participants to healthy dietary patterns, with at least one of the randomised groups consuming the standard ‘healthy dietary pattern’ (for example, Mediterranean diet), and with those in the intervention group consuming a modified version of the healthy dietary pattern that includes additional servings of unprocessed meat.

Previous systematic reviews and meta-analyses included all relevant studies, regardless of where the studies were conducted. To manage scope and maximize applicability to the Australian population, newly published individual prospective cohort studies and RCTs were eligible if they were conducted among adult populations similar to Australia's. These were defined to include US, Western and Northern Europe, Canada and New Zealand. Data from eligible studies were extracted into summary tables. The results summary statistics (effect sizes and confidence intervals) from included studies were summarised as forest plots. Quality assessment was conducted for both new prospective cohort studies, as well as each individual study included in prior meta-analyses. Quality of RCTs was assessed using the Cochrane risk-of-bias assessment tool. All included studies were further separated into primary studies, which are those that reported results separately for unprocessed and processed meat and are thus of direct interest to our overall data synthesis, and secondary studies, which did not differentiate between processed and unprocessed meat.

Key findings and discussion

Questions 1 and 2:

For Questions 1 and 2, 19 studies were identified; three systematic reviews and meta-analysis of prospective cohort studies, one systematic review and meta-analysis of RCTs, 14 prospective cohort studies not included in the meta-analyses, and one new RCT. Evidence identified in this report indicates that red meat intake does not appear to be associated with the risk of CHD. However, higher intake is associated with higher risk of incident stroke and CVD. The association of unprocessed red meat intake appears to be specific for ischemic stroke, rather than haemorrhagic stroke. Moreover, increased risk of stroke could contribute to moderately elevated risk of incident CVD. Results from RCTs indicated that a total red meat intake of 50 grams or more per day in the intervention group compared to the control group did not significantly affect any of the CVD risk factors.

For poultry intake, the evidence reviewed suggests that they have a largely neutral association with CVD risk. There was less evidence available for poultry than unprocessed red meat, but findings were generally consistent across studies. Regarding dose-response, none of the studies were formally tested for potential non-linear relationships. There is very little evidence that higher intake of unprocessed meat intake is related to risk of heart failure (HF), at least within the exposure ranges studied (up to 80 grams per day). Recent prospective cohorts' data appears to generally indicate higher unprocessed red meat and poultry consumption are associated with moderate weight gain. Several 'secondary papers' were also identified that suggested higher total red meat consumption related to elevated risk of CVD and CHD. Such relations could be driven by processed meats, which prior studies suggest may be more harmful than red meat (due to higher levels of sodium and other preservatives).

Question 3:

Five RCTs met eligibility criteria. The studies investigated the effect of incorporating unprocessed red meat or chicken as part of two healthy dietary patterns: Dietary Approaches to Stop Hypertension (DASH) or the Mediterranean diet. Overall, the limited body of evidence suggested that replacement of a moderate amount of poultry or fish with lean pork and beef within the DASH and the Mediterranean dietary pattern can still lead to improved cardiovascular risk factors including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and systolic blood pressure (SBP) in the short-term. A limitation that may affect interpretation of these findings was that only one study specified that unprocessed red meat replaced chicken, whereas in the others the relative proportions of fish and poultry that were replaced by red meat was not clear.

Quality and gaps in the evidence

The quality of prospective cohort studies based on our appraisal was mostly good, with most studies having a score of equal to or more than 4 (n=12, 86%) out of a highest possible score of 5. Though most studies adjusted for confounders, residual confounding cannot be excluded. In some of the cohort studies, covariates that could be either confounders or mediators (e.g. blood pressure, which could itself be influenced by unprocessed meat intake and lie on the causal pathway to CVD) were adjusted for, which raises potential concerns of over-adjustment. For the RCTs, several potential sources of bias were reported. For instance, a lack of reporting for allocation concealment methods and whether the researchers were blinded with regards to which intervention a participant received, which could lead to significant selection and performance bias. In addition, many of the studies received funding from meat industry organisations, which could also be a source of bias.

Several gaps in research are apparent. Though meat intake may be part of various dietary patterns, evidence in this review pertains to DASH and Mediterranean dietary patterns only, and the effect of incorporating unprocessed meat for other healthy dietary patterns is unclear for addressing Question 3 in this review. RCTs have assessed only limited set of CVD risk factors. Given the emerging link between unprocessed red meat intake and the risk of type 2 diabetes in prospective cohort studies, RCTs powered to study markers of glucose-insulin homeostasis are needed. Future studies funded by independent government and non-governmental organizations with improved study design (for instance, incorporating the blinding of assessors/investigators) are needed to strengthen the evidence base and minimize concerns over selective and biased reporting. In addition, cooking methods may modify the effect of unprocessed meat and this warrants further investigation.

Applicability

Findings from this review are likely to be relevant to the Australian population. Our selection strategy likely captured all key recent studies with demographic and dietary characteristics relatively similar to Australians'.

Conclusion

The findings of this review raise the possibility of considering specific dietary recommendations for different populations. For the general population, emphasis should be on healthy dietary patterns, with preference for plant protein sources and fish rather than unprocessed poultry and red meat. Evidence from prospective cohort studies suggests limiting unprocessed red meat to up to 50 grams per day. For poultry, there is no strong evidence for recommending a limit on intake level, although this should not be interpreted as suggesting poultry is beneficial for CVD health; other healthy sources of protein such as fish and legumes should be preferred choices. In clinical populations assisted by dietitians or in other instances where individuals are already achieving dietary patterns highly consistent with the DASH or Mediterranean diet, up to one serve per day (100 grams of unprocessed red meat or poultry) is reasonable to include if it enables individuals to achieve greater adherence to the healthy dietary pattern since at such levels the unprocessed meats are unlikely to materially diminish the cardiovascular benefits of such diets.

Background

Cardiovascular disease (CVD) is the leading cause of disease burden and death in Australia accounting for 32% of all deaths in 2017.[1] There are a number of critical modifiable risk factors of CVD, including dietary patterns of poor nutritional quality.[2] It is therefore of crucial scientific and public health importance to understand how dietary components individually, and as part of different dietary patterns, impact on risk of cardiovascular disease (CVD).

Many national and international guidelines currently recommend the public focus on healthy dietary patterns that aim to lower risk of CVD by increasing intake of a variety of healthy foods and reducing intake of unhealthy foods.[3] Specifically, such recommendations typically suggest: consumption of fruits, vegetables and whole grains; healthy protein sources such as fish and seafood, lean meat and poultry, legumes, nuts and seeds; reduced dairy fats; healthy fat choices; and herbs and spices to flavour foods, instead of adding salt.

An important scientific question that has emerged and requires clarification relates to the relationship between intake of unprocessed meats (beef, lamb, pork, and poultry) and cardiovascular health. Specifically with regards to meats, the Australian Dietary Guidelines suggest lean red meats and poultry are core foods that can be part of a healthy diet, with a quantitative recommendation for a maximum weekly intake of red meat (<455 g/week) informed by an evidence review[4], but does not recommend a maximum weekly level for poultry. From the 2011–12 National Nutrition and Physical Activity Survey, the median (25th to 75th percentile) consumption of red meat and poultry among Australians was 104 (54–169) grams per day and 100 (60–176.2) grams per day respectively.[5, 6] Assuming these median intakes are representative of daily intakes, the red meat intake per week can be estimated at 728 grams per week, which is higher than the recommended amount. The Heart Foundation of Australia commissioned this review of relevant literature on the relationship between intake of meat and CVD, to use the evidence to inform whether its current recommendations related to the intake of unprocessed meats should be revised.

Review questions

The review aimed to address the following questions:

Question 1:
Is unprocessed meat and poultry consumption in adult populations (similar to Australia) associated with risk of cardiovascular disease?

Question 2:
Is there a level of unprocessed meat and poultry consumption in adult populations (similar to Australia) at which risk of cardiovascular disease increases?

Question 3:
What is the effect on risk of cardiovascular disease when unprocessed meat and poultry is added to healthy eating patterns in adult populations (similar to Australia)?

1. Is unprocessed meat and poultry consumption in adult populations (similar to Australia) associated with risk of cardiovascular disease?

Methods

Data sources

Peer review literature was searched using electronic databases including Medline, Embase, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews for Questions 1 and 2. For Question 3, the databases searched included Medline, Embase, and Cochrane Central Register of Controlled Trials. Studies were restricted to those published from January 2010 to October 2018 and published in English. Key search terms are described in **Appendix 1**.

Eligibility criteria

For Questions 1 and 2, eligible studies included systematic reviews and meta-analyses of prospective cohort studies that assessed the association of unprocessed meat intake and relevant CVD outcomes, as well as randomised controlled trials (RCT) of unprocessed meat intake and relevant CVD outcomes, **(Table 1)**. Cross-sectional studies were excluded from this review for the following reasons; they provide a snapshot of the association between exposure and outcome at only one point in time, they are prone to confounding and reversing causation, and they are unable to establish temporal sequence and infer causal relationship. Outcomes of interest included CVD, coronary heart disease, atrial fibrillation, heart failure, stroke, incidence of hypertension, change in systolic blood pressure (SBP) and diastolic blood pressure (DBP), change in lipid profile, and weight gain. We also searched for and included recently published prospective cohort studies and RCTs not included in prior systematic review and meta-analyses.

For Question 3, RCTs were included **(Table 2)**. Specifically, we searched for RCTs that randomised participants to healthy dietary patterns, with at least one of the randomised groups consuming the standard 'healthy dietary pattern' (for example, the Mediterranean diet), and those in the intervention group consuming a modified version of the healthy dietary pattern that includes additional servings of unprocessed meat.

Previous systematic reviews and meta-analyses included all relevant studies, regardless of where the studies were conducted. To manage scope and maximize applicability to the Australian population, newly published individual prospective cohort studies and RCT were eligible if they were conducted among adult populations similar to Australia. These were defined to include USA, UK, Western and Northern Europe, Canada and New Zealand.

Table 1: Inclusion and exclusion criteria to determine study eligibility for Questions 1 and 2

Study characteristics	Included	Excluded
Exposures	Unprocessed beef, lamb, pork, chicken; studies that combined unprocessed and processed meat but analysed the data separately	Fish and seafood, processed meat products
Outcomes	Cardiovascular disease, coronary heart disease, atrial fibrillation, heart failure, stroke, incidence of hypertension, blood pressure, lipid profile, weight gain	Trials shorter than 3 months for weight gain
Populations	Adults (≥18 years) similar to Australia (US, UK, Western and Northern Europe, Canada and New Zealand)	Children, adolescents, adults with serious illness (e.g. cancer), and pregnant women
Study designs	Meta-analyses of prospective cohort studies and randomised controlled trials, prospective cohort studies and randomised controlled trials not included in recent meta-analyses	Commentary, narrative reviews, or non-empirical peer review literature , cross-sectional studies
Years published	2010-2018	Before 2010
Other criteria	English language, humans If duplicate publications from the same cohort, the publication with the largest sample size/number of cases was used If multiple publications from the same trial but on different outcomes, all publications with the relevant outcomes were included	Non-English studies, animal studies

Table 2: Inclusion and exclusion criteria to determine study eligibility for Question 3

Study characteristics	Included	Excluded
Exposures 1	Unprocessed beef, lamb, pork, chicken	Fish and seafood, processed meat products
Exposures 2	Healthy dietary pattern, prudent dietary pattern, Mediterranean dietary pattern, vegetarian dietary pattern, DASH dietary pattern, Nordic dietary pattern, Tibetan dietary pattern, portfolio dietary pattern	
Outcomes	Cardiovascular disease, coronary heart disease, atrial fibrillation, heart failure, stroke, incidence of hypertension, blood pressure, lipid profile, weight gain	Trials shorter than 3 months for weight gain
Populations	Adults (≥18 years) similar to Australia (US, UK, Western and Northern Europe, Canada and New Zealand)	Children, adolescents, adults with serious illness (e.g. cancer), and pregnant women
Study designs	Randomised controlled trials	Observational studies, commentary, narrative reviews, or non-empirical peer review literature, animal studies
Years published	2010-2018	Before 2010
Other criteria	English language, humans If duplicate publications from the same cohort, the publication with the largest sample size/number of cases was used If multiple publications from the same trial but on different outcomes, all publications with the relevant outcomes were included	Non-English studies, animal studies

Study selection

Following the search, duplicate articles were excluded. The titles and abstracts of the remaining records were screened for inclusion by one reviewer (RN). Full texts of publications that remained after title and abstract screening were then assessed for eligibility independently and in duplicate by three reviewers (RN, MZ and MM), with differences resolved by consensus.

A summary of the literature search, screening process, and number of articles included and excluded are shown in Figures 1 and 2. For Question 1 and 2, 992 studies were identified initially, and 709 were excluded based on title and abstract. A total of 26 articles were excluded after full text screening **(Figure 1)**. Articles were excluded if they were already included in identified meta-analyses, if they did not assess relevant outcomes, if they did not study unprocessed meat intake, or if they did not separate out flesh meat (unprocessed) from processed meat. After final exclusions, 19 studies were identified including four meta-analyses, one randomised controlled trial and 14 new prospective cohort studies (not already included in the previous meta-analyses or representing updated analyses of previously published results).

For Question 3, 172 studies were identified from the databases. After removal of duplicates, 142 articles were screened based on title and abstract **(Figure 2)**. 137 articles were excluded for reasons of relevance, such as animal studies, observational studies, studies of populations not similar to Australia, studies on children and adolescents, studies that did not assess relevant CVD outcome, studies during pregnancy, reviews, conference abstracts, and studies where the design was not as specified in the brief or where no dietary pattern was examined. The remaining five articles were all eligible to be included in data synthesis after full text screening.

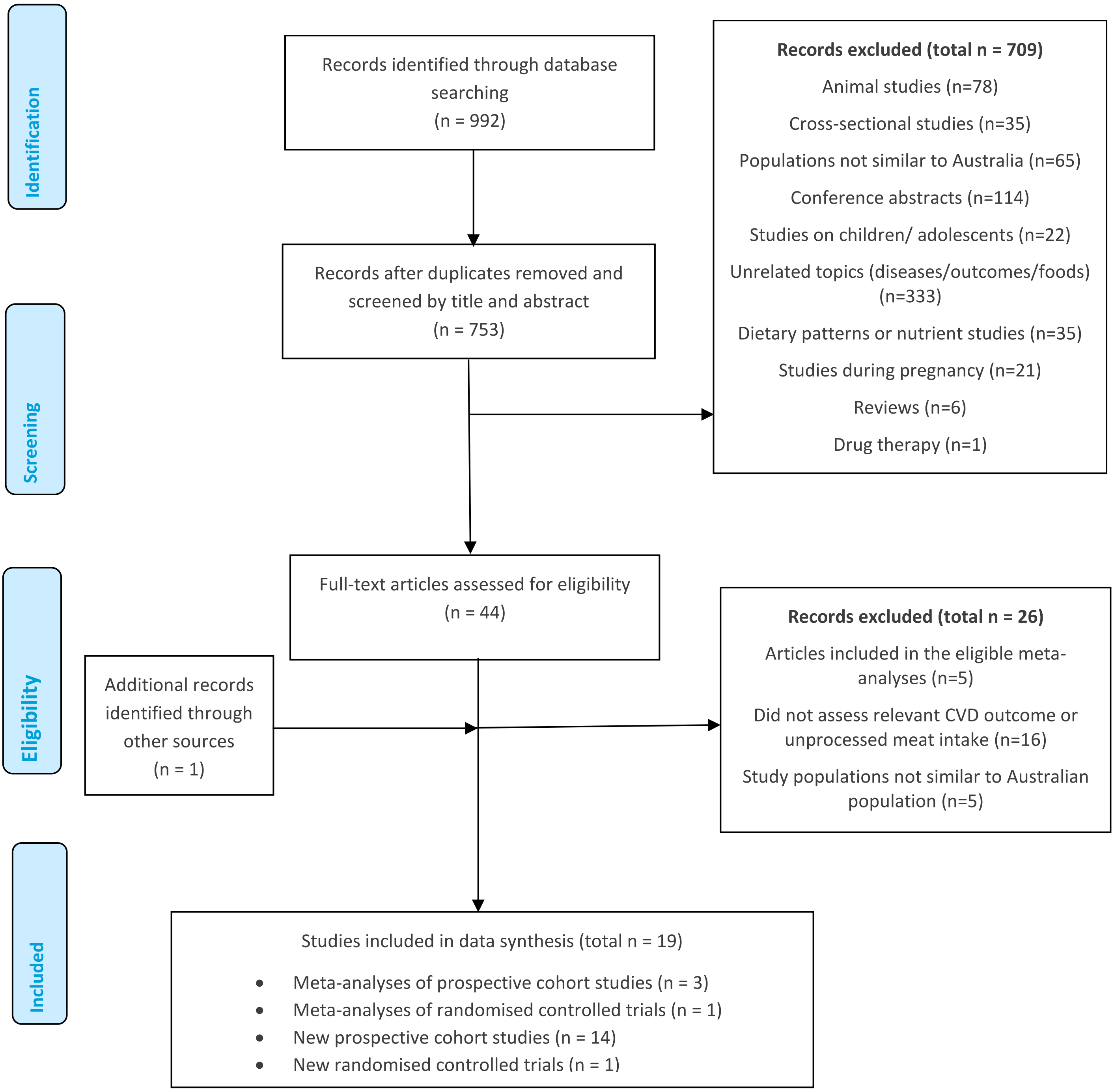


Figure 1: Flow diagram of screening and identification of eligible studies for Questions 1 and 2

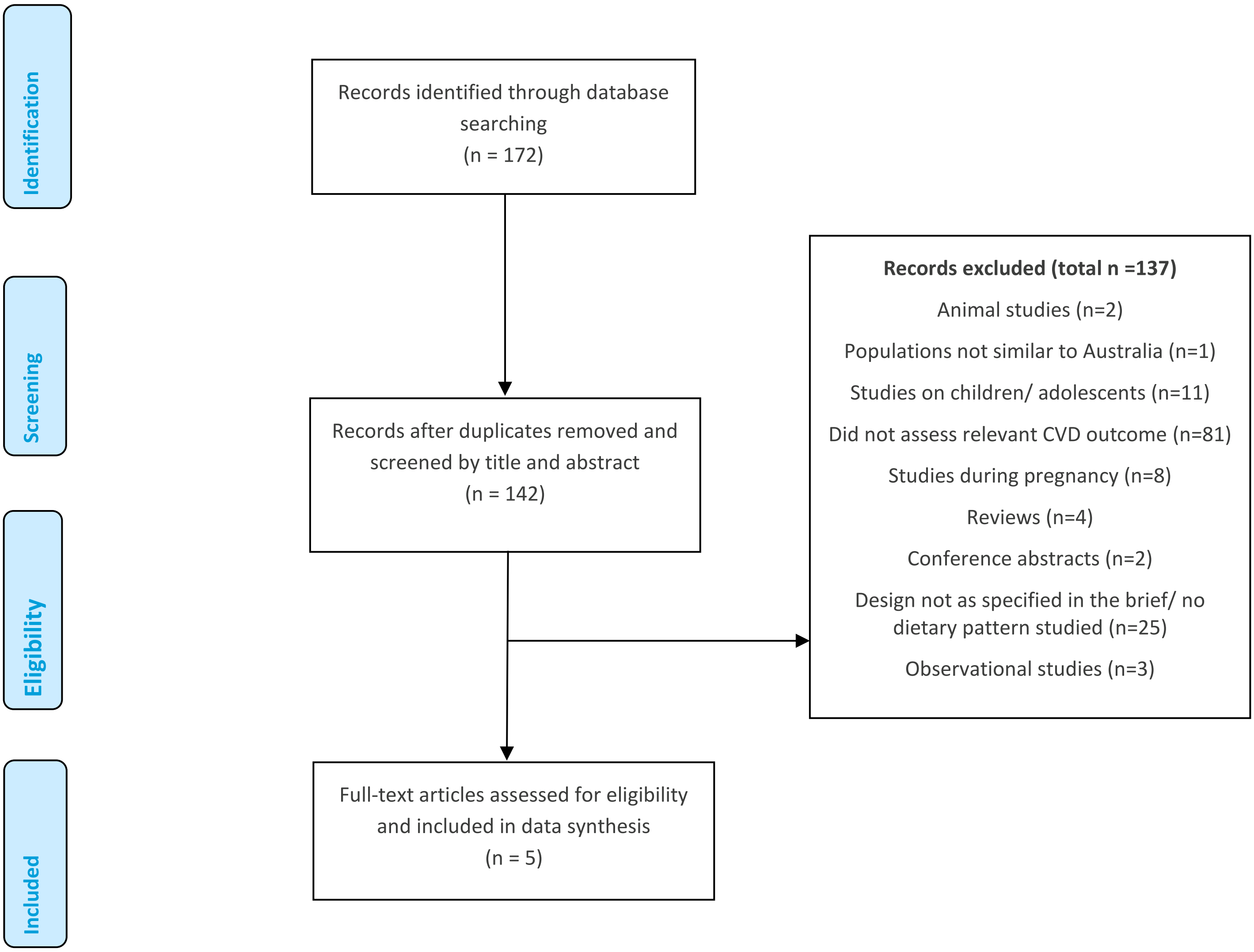


Figure 2: Flow diagram of screening and identification of eligible studies for Question 3

Data synthesis and evaluation of study quality

Data from eligible studies were extracted into summary tables **(Appendix 2 and 3)**, including the following key study variables: author and year the study was conducted, country in which the study was conducted, research questions, population characteristics, definition of the unprocessed meat studied, CVD outcome measured, results including effect sizes and uncertainty intervals, results related to whether the study assessed dose-response effect of unprocessed meat intake and whether threshold effect was detected (for instance, if CVD risk is elevated only above a certain intake level), quality of study (see further details below), and sources of funding.

The results summary statistics (effect sizes and confidence intervals) from included studies were summarised as forest plots. Quality of cohort studies were assessed using previously established methods [7, 8], whereby five design criteria are considered: appropriateness and reporting of inclusion and exclusion criteria, methods for assessment of exposure, methods for assessment of outcome, adjustment for confounding, and evidence of bias. For adjustment of confounding, we ascertained whether the authors adjusted for age, gender, education, income, smoking, prevalence of type 2 diabetes (for analysis of CVD outcomes), treatment of subjects with existing hypertension (for analysis of CVD outcomes), physical activity, and at least one or two dietary variables (total energy intake, and fruit and vegetable intake). In assessing the evidence of bias, we checked for bias due to attrition or including participants with existing CVD at baseline, which could cause reverse causation (existing CVD may lead to change in meat intake). Each criterion was allocated a score of 1 (if criteria were met) or 0 (if criteria were not met). The scores were summed and studies with scores from 0 to 3 and 4 to 5 were considered lower and higher quality, respectively. Quality assessment was conducted for both new prospective cohort studies, as well as each individual study included in prior meta-analyses.

The quality of RCTs was assessed using the Cochrane risk-of-bias assessment tool.[9] Risk of bias was assessed under pre-defined domains of bias including: random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessment; incomplete outcome data; selective reporting; and other biases. Quality assessment was completed for all new RCTs identified in this report. For the study by O'Connor et al.[10] a systematic review of RCTs, the authors had already conducted quality assessment using the Cochrane assessment tool and their summary of the study quality was used.

Studies were further separated into primary studies, which are those that reported results separately for unprocessed and processed meat and are thus of direct interest to our overall data synthesis, and secondary studies, which did not differentiate between processed and unprocessed meat (for instance, reporting 'total red meat') and were thus not directly relevant to this report, but are presented to provide a comprehensive overview of recent literature.

Findings

Findings relevant to research Questions 1 and 2

Study characteristics

There were three systematic reviews and meta-analyses of prospective cohort studies, all of which focused on clinical CVD outcomes (total CVD, CVD mortality, coronary heart disease, myocardial infarction, and stroke) **(Table 3)**. The systematic reviews and meta-analyses reported results separately for unprocessed red meat (three studies) and poultry (one study); none reported for total unprocessed meats, that is, red meats and poultry together. In addition, 14 new prospective cohort studies were identified that reported results for incident clinical CVD (six for unprocessed red meat, four for poultry), heart failure (four for unprocessed red meat, zero for poultry), incident hypertension (two for unprocessed red meat, one for poultry), and weight gain (two for unprocessed red meat, two for poultry).

There was one systematic review and meta-analysis of RCTs, which focused on the effect of unprocessed red meat intake on blood pressure and lipid profile. One new RCT was identified that investigated the effect of red meat on change in blood pressure and lipid levels.

For this review, we reported intake data in grams as provided in the studies. However, where meat intake was reported as a number of servings, in order to standardise we converted to grams using data provided in the paper and then converted to a standard number of serving, whereby one serving is equivalent to 100 grams of unprocessed red meat or poultry. The Australian Dietary Guidelines state that one serving of red meat and poultry is equivalent to 90–100 grams raw weight or 65 grams and 80 grams for cooked red meat and poultry respectively.[11] The definitions of unprocessed meats and outcomes assessed by each study are shown in **Appendix 4.**

Table 3: Characteristics of included studies for Research Questions 1 and 2 by CVD outcomes

Outcomes	Meta-analysis of cohort studies [1]	New cohort studies [1]	Meta-analysis of randomised controlled trials [1]	New randomised controlled trials [1]
Evidence based on prospective cohorts only				
Clinical CVD (CHD and MI incident and mortality)	2	6	0	0
Incident stroke	2	2	0	0
Incident heart failure	0	4	0	0
Weight gain	0	2	0	0
Evidence based on prospective cohorts and RCTs				
Incident hypertension	0	2	0	0
Change in blood pressure	0	0	1	1
Change in lipid profile	0	0	1	1

Note – CHD = coronary heart disease; CVD = cardiovascular disease; MI = myocardial infarction

[1] Some studies reported results on multiple outcomes, hence the number in each column may add up to more than the number of studies available.

Association of unprocessed meat intake and incident CVD

Studies presented below are further separated into *primary studies*, which are those that reported results separately for unprocessed and processed meat, and *secondary studies*, which did not differentiate between processed and unprocessed meat (for instance, reported 'total red meat').

Meta-analyses of prospective cohort studies – primary studies

Micha et al.[7]

Conducted a systematic review and meta-analysis of prospective cohorts and case-control studies to assess the association of red, processed, and total meat intake and risk of CHD, stroke, and type 2 diabetes. Authors also searched for but did not identify any relevant RCT that addressed the research question. Four studies met the eligibility criteria for red meat intake and risk of CHD (conducted in the US, UK, Australia, and Spain), and two studies met the eligibility criteria for the analysis of stroke (conducted in Japan and the US). In total, the analyses of CHD included 56,311 participants with 769 incident events, whereas for stroke there were 106,684 participants and 1700 incident events. Red meat was defined as unprocessed meat including from beef, hamburgers, lamb, pork or game, and excluded poultry, fish or eggs.

In pooled results, red meat intake was not associated with risk of incident CHD (per 100g/day, RR=1.00, 95% CI=0.81-1.23), with little evidence of between-study heterogeneity. Findings were similar when restricted to prospective cohort studies only. In contrast, processed meats were associated with significantly higher risk of CHD (per 50g/day, RR=1.42, 95% CI=1.07-1.89). Red meat consumption was also not significantly associated with risk of stroke (per 100g/day, RR=1.17, 95% CI=0.40-3.43). Importantly, the studies evaluated different types of red meats and stroke outcome types (ischemic stroke and stroke mortality), limiting the ability to pool the results.

There was little evidence to suggest publication bias. Across the cohort studies that assessed red meat intake (excluding the study in Japan), participants in the highest intake category typically had between 80 and 190 grams per day (0.8-1.9 serves/day) of red meat intake, compared with those in the lowest category (≤50 g/day, ≤0.5 serve/day). The authors did not assess the potential non-linear threshold effect between red meat intake and CHD and stroke outcomes. Quality assessment of the individual cohorts suggest that three (50%) were of good to high quality (score ≥4), with three (50%, each with a score of 3) of lower quality.

Chen et al.[12]

Conducted a meta-analysis of prospective cohort studies to assess the relationship of unprocessed red meat and processed meat intake and risk of stroke. Five cohorts meeting eligibility criteria were included in the data synthesis, with two from Sweden, two from the US, and one from Japan. In total, there were 239,251 participants and 9593 incident stroke events across the five cohorts. Red meat was defined as unprocessed meat from beef, veal, pork, mutton, and lamb, and excluding poultry, fish or eggs. The authors did not conduct analyses related to total unprocessed meat intake with stroke outcomes (i.e. did not include studies that assessed white meat). Pooling results across studies, unprocessed red meat intake was significantly associated with higher risk of all-cause stroke (top vs. bottom intake category, RR=1.09, 95% CI=1.01–1.18), ischemic stroke (RR=1.13, 95% CI=1.01–1.25), but not haemorrhagic stroke (RR=0.99, 95% CI=0.77–1.28). In linear dose-response analysis, 100 grams per day of unprocessed red meat consumption was associated with an increase of 13 percentage points for total strokes (RR=1.13, 95% CI=1.03-1.23). Results were very consistent across studies with little evidence of heterogeneity in findings.

Statistical tests did not suggest significant publication bias. In the studies conducted in the US and Sweden, participants in the highest intake category typically consumed between 50 and 100 grams per day (0.5-1 serve/day) of unprocessed red meat intake, compared with those in the lowest category (≤30 g/day, ≤0.3 serve per day). A strength of this study was the strict inclusion criteria, whereby individual studies that did not clearly describe the definition of red meat were excluded. The study also included more studies with substantially higher total numbers of stroke cases compared to the prior meta-analysis by Micha et al.[7] The authors did not assess potential non-linear threshold effects between red meat intake and stroke outcomes. Data was presented for only the top compared to the bottom categories of intake. Quality assessment of the individual cohorts suggest that all the studies were of good to high quality (score≥4).

Abete et al.[13]

Conducted a meta-analysis that included nine independent prospective cohort studies (population= 1,660,588) that assessed red and/or white meat intake with CVD (population =1,615,868) and CHD (population=230,693) mortality. The majority (six) of the studies were conducted in the US or European countries (including the UK), with the remainder (three) conducted in Asian countries. Red meat was defined as fresh meat including beef, veal, lamb, pork, hamburger, and meatballs, whereas white meat was defined as including poultry (chicken and turkey) and rabbit. The authors did not report analyses related to total unprocessed meat intake with mortality outcomes, that is, red and white meats were not assessed together as an exposure. In pooled analyses, red meat consumption was related to a higher risk of CVD mortality in both categorical analyses (top vs. lowest intake category, RR=1.16, 95% CI=1.03–1.32) and dose-response analyses (per 100g/day, RR=1.15, 95% CI=1.05-1.26). Substantial heterogeneity in the pooled results was noted (I^2>75%). In sensitivity analyses, the exclusion of Asian studies reduced heterogeneity in the remaining studies carried out in Europe and the US, and strengthened the associations with CVD mortality (RR=1.33, 95% CI, 1.26-1.40). Red meat intake was not significantly associated with CHD mortality (RR=1·02, 95% CI=0·72, 1·46; I^2=70·3, P=0·018). White meat consumption was also not associated with CVD or CHD mortality.

The authors reported that there was little evidence of publication bias. In the studies done in the UK, USA and European counties, red meat intake in the highest category were generally between 100 and 200 grams per day (one to two serves per day), compared to generally less than 100 grams per day (<1 serve/day) in the lowest category. By contrast, for white meat the highest intake ranged between ~50 to 100 grams per day (0.5–1 serves/day). The authors did not assess potential non-linear threshold effects between red and white meat intake and CVD outcomes. Quality assessment of the individual cohorts included in the meta-analyses identified that seven (78%) were of good to high quality (score ≥=4), with two (22%) of lower quality.

New prospective cohort studies – primary studies

Bernstein et al.[14]

Conducted an investigation in the Nurses' Health Study in the US to assess the association of major dietary protein sources (including unprocessed red meat and poultry) and risk of CHD in women. The study included ~84,000 female nurses with 3162 incident CHD events during follow up. Red meat without processed meat was not clearly defined, but likely included hamburger, and beef, pork and lamb as a mixed and main dish. The 'poultry' category included processed meats (hotdogs), and is hence not relevant for this review, but the authors analysed chicken with and without skin separately. Higher intake of unprocessed red meat was associated with higher risk of incident CHD (per 100g/day, RR=1.19, 95% CI=1.07-1.32). In this study, a serving size of beef, pork or lamb was equivalent to ~140 grams, while a serving of chicken was equivalent to ~85 grams. Participants in the top category of unprocessed red meat intake consumed on average 168 grams per day (one to two serves per day) compared to 42 grams per day (0.3 serves/day) for those in the lowest category. A higher intake of chicken (with and without skin) was not significantly associated with risk of CHD (top vs. lowest intake category averaged ~34 grams per day (0.4 serves/day) compared to 4.25 grams per day (0.05 serves/day).

Von Ruesten et al.[15]

In the German EPIC-Potsdam cohort, the association of unprocessed red meat and poultry with incident CVD was investigated among ~23,000 participants. Unprocessed red meat was defined to include beef, hamburger/meat loaf, Bolognese sauce, pork, smoked pork, veal, lamb, and rabbit; whereas poultry included turkey and chicken. During eight years of follow-up, 363 incident cases of CVD were identified, and red meat (per 100g/day, RR=1.40, 95% CI=0.87-2.25) and poultry intake (per 100g/day, RR=0.57, 95% CI=0.21-1.51) were not significantly associated with CVD risk. Participants in the top quintile of unprocessed red meat intake consumed on average about 98 grams per day and 63 grams per day in men and women respectively, compared to about 18 grams per day in men and 11 grams per day in women for those in the lowest quintile. For poultry, the average intake in the top compared to the lowest quintile were ~32 and 3 grams per day, respectively for men and about ~24 and 2 grams per day for women.

Haring et al.[16]

Assessed the association of major dietary protein sources with incident CHD in a community-based cohort in the US (Atherosclerosis Risk in Communities study, ARIC). The study included 12,066 adults with median follow-up of 22 years, during which time 1146 CHD events occurred. The study assessed both unprocessed red meat and poultry intake, although what specific product types were included in these categories was not defined. Consumption of red meat (top vs. lowest intake category, RR=1.13, 95% CI=0.89-1.44) and poultry (RR=0.79, 95% CI=0.64-0.98) were not associated with CHD. Average intakes of red meat in the highest and lowest categories were 110 compared to 10 grams per day (1.1 vs 0.1 serves/day), while for poultry it was 80 compared to 10 grams per day (0.8 vs 0.1 serves/day).

Haring et al.[17]

Assessed the association of major dietary protein sources with incident stroke in the ARIC cohort in the US. The study included 11,601 adults who were followed up for a median duration of 22.7 years, during which 699 incident stroke events occurred. Similarly to the paper by the same group of authors in 2014[16], in this report results were described separately for red meat and processed meat, but the types of meat products considered 'red meat' were not specified. This was also the case for poultry. Intake of red meat was associated with increased risk of all-cause stroke (top vs. bottom quintile, RR=1.41, 95% CI=1.04, 1.92), ischemic stroke (RR=1.47, 95% CI=1.06, 2.05), but not haemorrhagic stroke (RR=1.13, 95% CI=0.53, 2.45). Poultry intake was not associated with risk of all-cause nor sub-types of stroke outcomes. The average intakes of red meat in the top compared to the bottom quintile of study participants were ~110 and 10 grams per day, respectively. By contrast, poultry intakes were 80 and 10 grams per day for the top and bottom quintiles.

New prospective cohort studies – secondary studies

Bellavia et al.[18]

A Swedish study of 74,645 adults that investigated whether total red meat consumption was associated with the risk of CVD mortality. During 16 years of follow-up, 5495 cases of CVD deaths occurred. Compared with participants in the lowest quintile of total red meat consumption (average 31 grams per day), those in the highest quintile (average 140 g/day) had a 29% increased risk of CVD mortality (RR=1.29, 95% CI=1.14–1.46). The study further reported that a higher intake of fruits and vegetables did not appear to counterbalance the negative associations between high total red meat consumption and CVD mortality.

Quintana Pacheco et al.[19]

Examined the association in a German cohort study between total red meat consumption (including unprocessed and processed) and CVD risk, and whether such associations could be mediated by plasma ferritin concentration (a marker of iron load). The study's outcomes of interest included myocardial infarction, stroke and CVD mortality. Higher intake of 50 grams of total red meat per day was associated with an 18% increase in risk of myocardial infarction (RR=1.18, 95% CI=1.05-1.33); the relationship did not appear to be mediated by plasma ferritin. Total red meat intake was not significantly associated with stroke and CVD mortality. We did not assess the quality of these studies as the results are considered secondary and not directly relevant to our overall synthesis of the literature.

Association of unprocessed meat intake and incident heart failure

New prospective cohort studies – primary studies

Kaluza et al.[20]

In a population-based prospective cohort study of 37,035 Swedish men, the association of unprocessed red meat consumption (pork, beef/veal, and minced meat) with incident heart failure (HF) and deaths due to HF was assessed. During an average of 11.8 years of follow up 2891 incident heart failure events occurred, as well as 266 deaths from heart failure. Consumption of unprocessed red meat was not significantly related to the risk of incident HF (top vs bottom quartile of intake, RR=0.99, 95% CI=0.87-1.13) nor HF deaths (RR=0.77, 95% CI=0.47-1.27). Average consumption of unprocessed red meat was 83 grams per day amongst participants in the highest quartile of intake, compared to 17 grams per day in the lowest. In contrast to unprocessed red meat, processed red meat (sausages, ham, salami, blood pudding and liver pate), was associated with a higher risk of incident HF and HF deaths.

Kaluza et al.[21]

In a population-based prospective cohort of Swedish women (n=34,057), the association of unprocessed, processed, and total red meat intake with incidence of HF was examined. Unprocessed red meat included pork, beef/veal, and minced meat. During a mean of 13.2 years of follow-up, 2806 cases of first HF event occurred. Unprocessed red meat consumption was not associated with incidence of HF (top vs bottom tertiles, RR=1.00, 95% CI=0.89–1.13). Similar to findings in Swedish men[20], processed meat was related to a higher risk of HF (~30% higher risk in comparing the top to bottom tertiles of intake, which on average were 60 g vs 16 g/day). Average consumption of unprocessed red meat was 58 grams per day amongst participants in the highest tertile of intake, compared to 14 grams per day in the lowest category.

New prospective cohort studies – secondary studies

Ashaye et al.[22]

This study assessed the association of the total unprocessed and processed red meat intake (beef, pork, lamb as main dishes or mixed dishes, ham and hotdogs) with incident heart failure among 21,120 male health professionals in the US (the Physician's Health Study). During an average of 19.9 years of follow-up 1204 new cases of heart failure occurred. Participants in the highest category of total red meat intake (on average 140 grams per day) compared to the lowest category (20 grams per day), had a 24% higher risk of heart failure (RR=1.24, 95% CI=1.03–1.48).

Wirth et al.[23]

The relationship between meat intake and heart failure was also investigated in 24,008 participants of the EPIC-Potsdam study in Germany. After follow-up of 8.2 years with 209 new cases of heart failure, those with higher baseline meat intake were associated with a higher risk of heart failure (top vs bottom quintile of intake, RR=2.04, 95% CI=1.17–3.55). However, the definition of meat was not provided in this study, which likely included both unprocessed and processed meat.

Association of unprocessed meat intake and weight gain

New prospective cohort studies – primary studies

Vergnaud et al.[24]

Investigated the association of meat intake (total, unprocessed red meat, poultry, and processed meat) and weight gain over five years of follow-up, among 373,803 adults across 10 European countries (France, Spain, Italy, England, Greece, Germany, Sweden, Denmark, Norway and the Netherlands). Red meat included beef, veal, pork, and lamb, whereas poultry included mainly chicken, and in some cohorts also turkey and rabbit. In the overall analysis, unprocessed red meat intake was associated with weight gain (per 100 kcal/day higher level of meat consumption, weight change=15 grams/year, 95% CI=1-28 grams/year) (250 g/day of unprocessed red meat was equivalent to ~450 kcal). However, exclusion of participants with chronic diseases at baseline (who are more likely to be attempting weight loss through diet changes and hence bias the results) and those likely to misreport energy intake attenuated the association of unprocessed red meat and weight gain (per 100kcal/day higher level of meat consumption, weight change=8 grams/year, 95% CI=-9-25 grams/year). Poultry intake was associated weakly with weight gain after exclusion of participants with chronic disease at baseline and those likely to misreport energy intake (estimated per 100kcal/day higher level of poultry consumption, weight change=27 grams/year, 95% CI=-1–53 grams/year). The relation of unprocessed red meat and poultry intake with weight gain did not appear to be modified by the participants' background dietary pattern, which was assessed by assigning a 'prudent dietary score'. The study did not present the range of unprocessed red meat and poultry intake across the study sites.

Smith et al.[25]

Assessed the association of changes in intake in the subtypes of unprocessed red meat and poultry with long-term weight gain in 120,784 men and women who were followed up for between 16 to 24 years. This was possible because dietary intake was assessed regularly, thus allowing the examination of how change in meat intake related to weight change in the same four-year period; this approach has been shown to reduce bias and improve consistency in findings relative to analysis using only baseline dietary intake.[26]

Unprocessed red meat included hamburger (regular and lean), beef, lamb and pork (as main dish or mixed dish), whereas poultry included chicken with and without skin. Results were very consistent across the three cohorts and are subsequently reported as pooled across studies. Unprocessed red meats were significantly related to weight gain (per increased servings/day, 0.61 kg per 4 years, 95% CI=0.39 kg, 0.83 kg). Increase in specific types of unprocessed red meat intake were consistently associated with weight gain. However, the magnitude of associations differed substantially. For instance, whereas an increase in a serve per day (100 g/day) of regular hamburger was related to 1.03 kg of weight gain per four years, an increase in a serve/day (100 g/day) of beef, lamb, or pork as main dish was related to 0.35 kg of weight gain per four years. For poultry, opposite directions of associations were observed for chicken with skin (per increased servings per day, +0.48 kg per 4 years, 95% CI=0.06 kg, 0.90 kg), and chicken without skin (-0.48 kg per 4 years, 95% CI=-0.70 kg, -0.27 kg).

Effect of unprocessed meat intake on CVD risk factors (risk of developing hypertension, and change in lipid profile and blood pressure)

Meta-analyses of RCTs – primary studies

O'Connor et al.[10]

Conducted a systematic review and meta-analyses of randomised controlled trials to assess the effect of consuming a total of 35 grams or more of red meat per day on blood lipids, lipoproteins and blood pressure in adults. The study was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

Overall, 24 studies were included in the meta-analysis. The studies were conducted across diverse populations (54% of which are similar to the Australian population – conducted in Australia, US, Western and Northern Europe, Canada and New Zealand), with the majority of the studies lasting up to eight weeks per treatment (n=15, 62.5%). The total median red meat consumption in the control group was 0 g/day or 0 serves/day (range 0-30 g/day, 0-0.4 serves/day) and in the intervention groups was 140 grams per day or 2 serves per day (range 68-500 g/day, 1-7.1 serves/day). The included studies had diverse study designs and aims, including trials that tested for weight loss as part of the intervention, intervention delivery (provision vs. advice to consume red meat), types of red meat (15 studies used unprocessed red meat, one included processed red meat, and eight studies were unclear about the degree of processing), and the comparator in the control groups was either less red meat (1), fish (4), chicken (3), fish or chicken (8), soy (1), tofu (1), non-meat supplement (1), plant protein (4) or fish or plant protein (1).

Pooling results across studies, total red meat intakes of 50 grams or more per day in the intervention group compared to the control group did not significantly affect any of the CVD risk factors investigated including: total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), TC/HDL-C ratio, SBP and DBP. A number of relevant sensitivity analyses were conducted, none of which affected the findings – such as the exclusion of studies that assessed processed red meats, excluding studies that did not specify the degree of meat processing, excluding studies of weight-loss diets, as well as further stratification by the amount of total red meat consumed in the intervention groups (100–190g, 200–290, and ≥300 g/day of red meat).

Methodological qualities of the included RCTs were appraised using the modified Cochrane risk-of-bias assessment tool. A number of critical methodological limitations were identified by the authors of the meta-analysis. For instance, researchers disclosed allocation concealment methods in two studies, but the remaining studies were unclear about allocation methods. Also, except for three studies, it was unclear if the researchers were blinded with regards to which intervention a participant received.

New prospective cohort studies – primary studies

Borgi et al.[27]

Assessed the effect of consuming meat and poultry on the risk of developing hypertension in 188,518 adults enrolled in three cohorts of health professionals. Higher consumption of meat and poultry in the highest quintile (≥100 g/day, ≥1 serve/day) compared to the lowest quintile (<100 g/month, <1 serve/month) was associated with increased risk of developing hypertension (unprocessed red meat: RR=1.24, 95% CI=1.17–1.31, Poultry: RR=1.22, 95% CI=1.12–1.34). In this study, sodium intake was not adjusted for.

Lajous et al.[28]

Investigated the association between consumption of unprocessed red meat (beef, pork, veal, horse and sheep) with incident hypertension in ~44,000 French women with a mean age of 52 years. The highest quintile consumed 500 or more grams per week (5 serves/week) of unprocessed red meat compared to less than 100 grams per week (1 serve/week) in the lowest quintile. After 14 years of follow-up, there was no association between unprocessed red meat consumption and hypertension (RR for each 100 g/day=1.00, 95% CI=1.00, 1.01).

New randomised controlled trials – secondary studies

Murphy et al.[29]

Assessed the impact of regular consumption of fresh lean pork on risk factors for CVD. In this study, 164 Australian overweight/obese adults consumed one kilogram of pork per week (seven servings per week, the study defined a serving as 150 grams) by substituting for other foods in comparison to under 100 grams of pork per week in the control group. After six months, there were no significant between-group effects on

CVD risk factors. In this study, sausages were included in the intervention diet. Risk-of-bias assessment indicated that concealment of a participant's allocation to either the intervention or the control group was not reported. In addition, it was not clear whether there was blinding of participants and outcome assessors.

Summary of quality of included studies

The quality of prospective cohort studies based on our appraisal was mostly good with most studies having a score of more than 4 (n=12, 86%). Though most studies adjusted for confounders, residual confounding cannot be excluded. In some of the cohort studies, covariates that could be either confounders or mediators (for example, blood pressure, which could itself be influenced by unprocessed meat intake and lie on the causal pathway to CVD) were adjusted for, which raises potential concern about over-adjustment. Conversely, the large sample sizes (and event rates) of the available prospective cohort studies meant that there was strong statistical power to detect even relatively small associations and the meta-analyses generally did not detect evidence for publication bias. A strength of all of the meta-analyses is that they included only prospective cohorts, reducing likelihood of selection and recall bias.

For the RCTs, several potential sources of bias were reported. Of important concern was the lack of reporting for allocation concealment methods and whether the researchers were blinded with regards to which intervention a participant received, which could lead to significant selection and performance bias.

Findings relevant to research Question 3

Study characteristics

Following screening and applying the inclusion and exclusion criteria, five RCTs met eligibility and were retained for data synthesis. The studies investigated the effect of incorporating unprocessed red meat (beef or pork, four studies) or chicken (one study) as part of two healthy dietary patterns; dietary approaches to stop hypertension (DASH) diet (four studies) and the Mediterranean diet (one study). All the trials were conducted in the US, included both men and women with age ranges between 21 and 75 years, and the intervention periods ranged between 12 weeks and six months. Outcomes assessed included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Incorporation of unprocessed meat as part of the DASH dietary pattern and effect on intermediate CVD risk factors

The original DASH diet was designed to emphasise intake of fruit and vegetables, low-fat dairy, whole grains, nuts, legumes and seeds, and poultry and fish, with reduced intake of fats, red meat, sodium, and added sugars, although low intakes of unprocessed red meat was allowed – 33 grams of beef, pork or ham per day[30] or 104 grams per day for meat, fish and poultry combined.[31] The studies outlined below tested the effect of adding unprocessed meat to this background healthy dietary pattern.

Roussell et al.[32]

In a randomised crossover controlled feeding trial, Roussell investigated the effect of DASH diet (restricting saturated fat to 6% of daily energy, with 28g/day of lean beef), and two modified DASH diets that had higher levels of lean beef (113 grams per day and 153 grams per day) to a control diet (12% saturated fat, and 20g/day lean beef). The primary outcome was changes in LDL-C, and secondary outcomes that included other CVD lipid risk factors, and blood pressure (reported in Roussell et al. 2014, see below). The study recruited 36 hypercholesterolemic, normo/pre-hypertensive (blood pressure <140/90 mmHg) participants without CVD, aged between 30 and 65 years. Each intervention period lasted five weeks (with one week washout in between), with all meals provided and total energy held constant for each participant throughout, and with the participants weighed daily to ensure stable weight. The lean beef used in the study was prepared by braising, grilling or frying, and never over an open flame to prevent charring.

In comparison to the DASH diet **(Appendix 5)**, one of the modified DASH diets (called the BOLD diet in the study), contained similar servings per day of most of the key dietary groups including fruits and vegetables, grains and dairy products, but had moderately reduced serves of legumes and other sources of vegetable protein (DASH: 59g, BOLD: 36g), and substantially reduced poultry, pork, and fish (DASH: 103g, BOLD: 28g). In effect, the higher intake of lean beef 'replaced' these other sources of protein. For the second modified DASH diet (called BOLD+), in order to achieve the targeted protein intake (27% of energy), intakes of other protein sources including low-fat dairy (DASH: 2.3 servings per day, BOLD+:4.7 servings per day), legumes and other vegetable proteins (DASH: 59g, BOLD+: 118g) increased along with lean beef, but with the intake of poultry, pork, and fish decreased (DASH: 103g, BOLD+: 28g). The BOLD+ diet therefore appears to depart substantially from the DASH diet with regards to the amount of key food groups served. In this study, adherence to the prescribed diets was 93% according to daily self-reporting forms.

Compared to the control diet, each of the intervention diets reduced total cholesterol by between 3.8% and 4.6%, and LDL cholesterol by between 4.4% and 5.5%. There were no significant differences in the Apolipoprotein A-I to Apolipoprotein B (Apo AI/Apo-B) ratio at the end of each intervention diet compared to the control diet. There were also no significant differences in any of the lipid and lipoprotein parameters between the intervention groups, that is, between BOLD and BOLD+ (P>0.1).

Roussell et al.[33]

Based on the same RCT conducted by Roussell et al. in 2012[32], this publication reported the effects of the DASH, BOLD, and BOLD+ diet on the secondary endpoints of SBP, DBP and additional measures of vascular health. Compared to both the control diet and the DASH diet, the BOLD diet did not affect SBP, whereas the BOLD+ diet marginally lowered SBP (end of trial mean SBP in DASH group and BOLD+ group: 112.9 vs. 111.4 mm Hg). There were no differences between any of the groups for DBP. The BOLD diet significantly reduced the Augmentation Index (a marker of arterial stiffness) compared to the control, DASH, and BOLD+ diets.

The studies conducted and reported by Roussell et al. had various sources of biases **(Appendix 6)**. Key concerns related to selection bias due to not reporting the method of concealment of allocations. In addition, the studies did not report blinding of outcome assessors, if there were differential numbers and characteristics of subjects who dropped out of the treatment groups, and the reasons for dropout. The studies received funding from meat industry organisations, which could also be a source of bias.

Sayer et al.[34]

Tested the effect of incorporation of lean pork as opposed to chicken and fish as the predominant protein source in the DASH dietary pattern on blood pressure, in a randomised crossover study. The study involved 19 adults with a mean age of 61 years. The intervention included two six-week diet periods separated by four weeks of wash-out on habitual diet. The primary outcome was changes in SBP, and secondary outcomes included CVD lipid risk factors.

The experimental diets were: DASH diet with lean pork (DASH-P) (provided fresh pork tenderloin and uncured ham trimmed of visible fat), compared to the 'default DASH diet', with lean chicken or fish (DASH-CF) (provided boneless, skinless chicken breast and tilapia fillets). In this study, amounts of meat intake in grams or servings were not reported, although the same authors reported the lean pork intake was ~120 grams per day in a separate publication.[35] Fifty-five percent of total protein intake was from either lean pork or chicken and fish and the remaining 45% was from dairy, vegetable and other animal (for instance, beef) sources. Two servings of beef tenderloin trimmed of visible fat were also provided each week during both interventions. Apart from provision of the meats, dietary control during the study was achieved by using dietary counselling following a prescribed menu. Compliance was checked using daily menu checklists and reported as 95% or greater for both DASH-P and DASH-CF, with only minor differences in macronutrient intake noted between groups.

There were no significant differences in SBP or DBP (measured manually or by 24-hour BP monitoring) between DASH-CF and DASH-P — for instance, post-intervention manually measured SBP (mean ± SEM) for DASH-CF and DASH-P were 122 ± 2 and 123 ± 3, respectively. CVD lipid risk factors (TC, LDL-C, HDL-C, and TG) were also largely similar post-intervention comparing DASH-P to DASH-CF.

This study scored a medium–high risk of bias since the method of concealment of allocations was not reported; nor did the study report blinding of outcome assessors. Attrition bias was unclear since the number of subjects who dropped out of each intervention group was not reported. There may be other biases, with the comparison of the two treatment diets showing differences in macronutrient distribution, and due to the funding of the study by a meat industry organisation.

New randomised controlled trials – secondary studies

Hill et al.[36]

Assessed the effect of three diets controlled for saturated fatty acid with varying amounts of protein from plant and animal (predominantly lean beef) sources on metabolic syndrome including lipids and blood pressure changes in 62 overweight and obese adults, aged between 30 and 60 years. The experimental diets were:

1. Healthy American diet (baseline and control)
2. Modified DASH diet rich in plant protein (18% protein, two-thirds plant sources) with 11.7 grams per day of lean beef (M-DASH)
3. Modified DASH diet rich in animal protein (Beef in an Optimal Lean Diet (BOLD): 18.4% protein, two-thirds animal sources) with 139 grams per day of lean beef (BOLD)
4. Moderate-protein diet (Beef in an Optimal Lean Diet Plus Protein: 27% protein, two-thirds animal sources) with 196.2 grams per day of lean beef (BOLD+).

All the diets were compared at three energy balance levels; five weeks energy equilibrium (weight maintenance (WM), a six-week weight loss phase (500 kcal/d deficit) including exercise (WL) (food provided), and 12 weeks free living weight loss phase (FL) (no food provided). All metabolic syndrome criteria decreased independently of diet composition (main effect of phase, P<0.01; between diets, P>0.05). There was no significant reduction in SBP in the WM phase, but there were significant reductions during the WL phase (baseline and WM compared with WL, P<0.05) (-6.9 mmHg in M-DASH, -2.4 mmHg in BOLD, and -7.4 mmHg in BOLD+). In the FL phase, SBP increased slightly (although not significantly) from WL but remained significantly lower than baseline (baseline compared with FL, P< 0.01). DBP decreased only after the WL phase, and the effect was sustained through the FL phase (baseline compared with WL, FL, P<0.001). Total cholesterol and LDL cholesterol reduced after the WM and WL phases (baseline compared with WM, WL, P<0.05) but returned to baseline levels after FL. In this study, the authors noted that weight loss was the primary mediator of metabolic syndrome resolution in their study population regardless of protein source or amount. They also noted that the study was not originally powered to detect differences between groups but rather differences between the baseline and the experimental diets. Therefore we consider this study as secondary as it was not powered to answer the main question of interest to the review.

Risk-of-bias assessment was low–medium due to a lack of reporting on the method of concealment of allocations, and funding received from a meat industry organisation.

Incorporation of unprocessed meat as part of the Mediterranean dietary pattern and effect on intermediate CVD risk factors

The Mediterranean diet is generally high in plant foods such as whole grain cereals, fresh fruits, vegetables, beans, nuts and seeds, and olive oil is generally the major source of fat and wine is consumed moderately with meals.[37] It can have moderate amounts of dairy foods, fish and poultry and low amounts of red meat (total meat intake less than one serving per day) but there may be some variation in food composition between regions.

O'Connor et al.[38]

Conducted a randomised crossover trial involving 41 overweight or obese adults with a mean age of 46 years, to test the effect of a 'currently recommended' Mediterranean style eating pattern (avoided red meat in favour of poultry, MED-Control) and a modified Mediterranean diet (replaced poultry with lean red meat, MED-Red). The study consisted of two five-week interventions separated by four weeks of self-selected eating (washout phase). Primary outcomes were fasting serum TC and SBP, and secondary outcomes included LDL-C, HDL-C, TG, and the Framingham Heart Study 10-year CVD risk score.

All meals were prepared and provided to participants at a clinical research centre. Red meats and poultry provided were lean beef or pork tenderloins and chicken or turkey breasts (with skin removed prior to cooking). In the prescribed dietary patterns, unprocessed red meat largely replaced the intake of poultry **(Appendix 7)**, with other minor differences noted including intakes of refined grains, dairy, and vegetables. Mean self-reported compliance to the provided diets was ≥ 95% for both MED-control and MED-Red.

Both MED-control and MED-Red reduced TC compared to baseline diets, with effects marginally higher for MED-Red (mean ± SEM, -0.4 ± 0.1 mM) than Med-Control (-0.2 ± 0.1 mM). LDL-C also reduced slightly more following the MED-Red diet, but effects were comparable between the two diets for HDL-C, TG, and SBP. Both diets also decreased the Framingham Heart Study 10-year CVD risk, with no significant differences between the diets. The study was assessed to be at low–medium risk of biases, since the study did not report on the method of concealment of allocations. Attrition bias was unclear since the study did not report the experimental groups of the participants who dropped out post-randomisation, comparison of dropouts and participants was not provided, and funding was from a meat industry organisation.

Discussion/synthesis of findings

Unprocessed red meat and poultry intake and risk of clinical CVD

Overall results related to unprocessed red meat and poultry intake and clinical CVD from primary studies are summarised in **Figures 4 and 5**. These are presented as visual aids to allow readers to see results of existing meta-analyses and new observational studies. These were generally consistent for each of the outcome types.

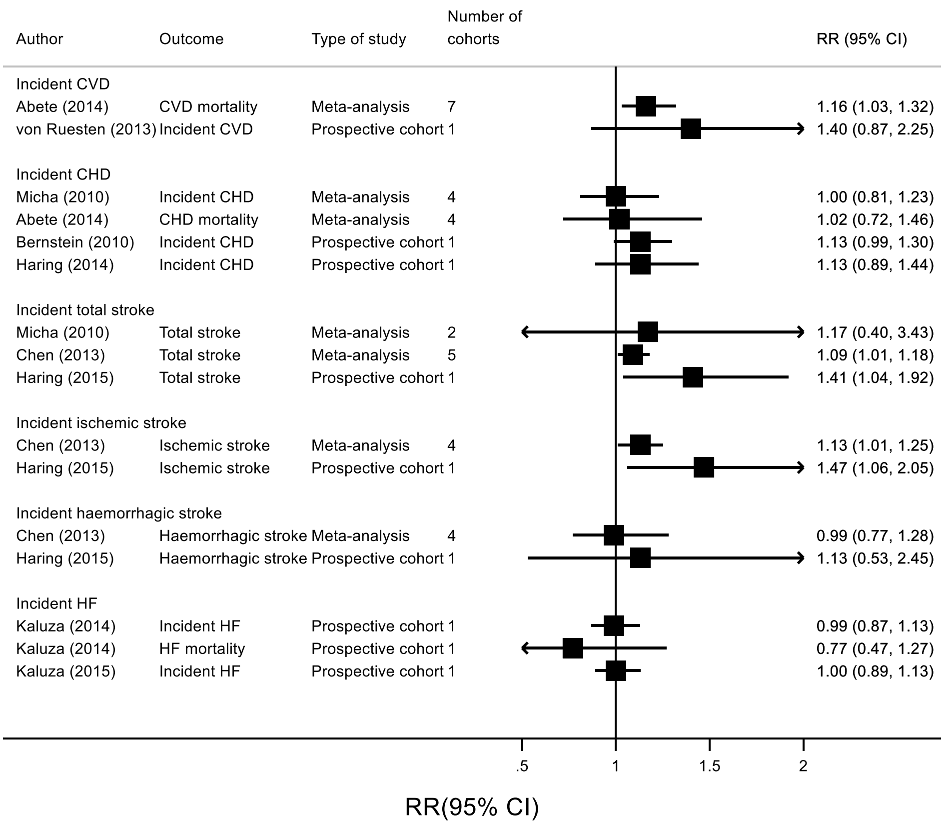


Figure 4: Summary of unprocessed red meat intake and risk of clinical CVD.
The square black boxes indicate effect estimates; 95% confidence intervals are shown. On the x-axis, red meat is associated with greater risk on the right side of 1, and red meat is associated with lower risk on the left side of 1.

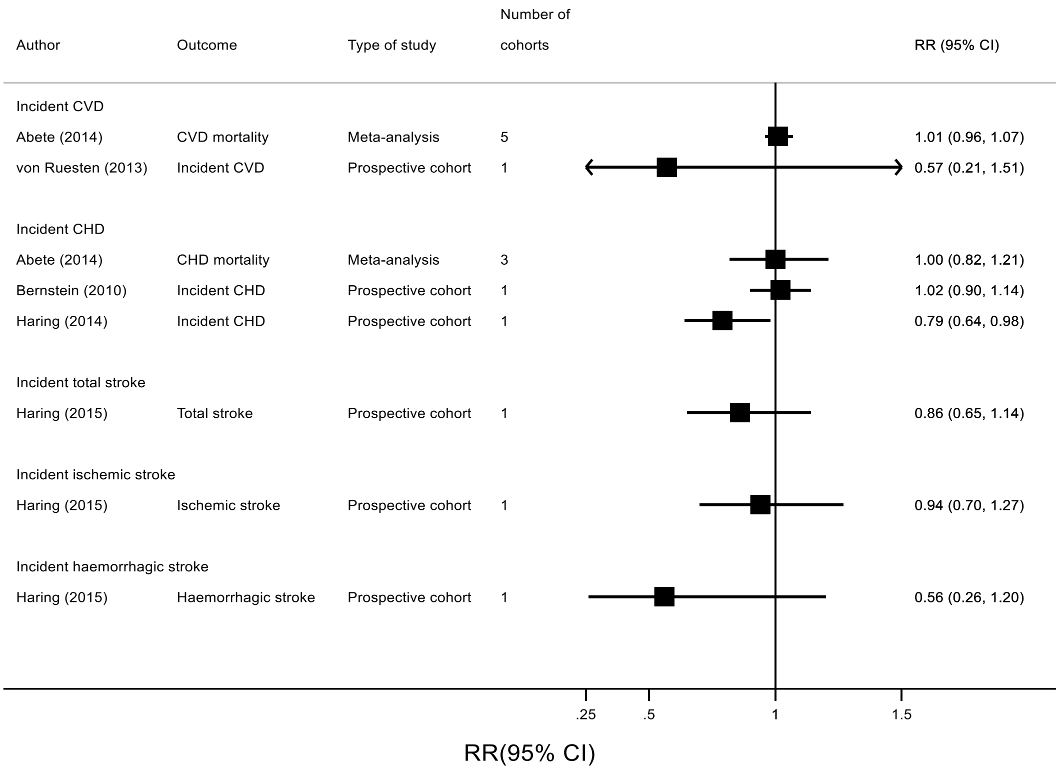


Figure 5: Summary of white meat intake and risk of clinical CVD.
The square black boxes indicate effect estimates; 95% confidence intervals are shown. On the x-axis, white meat is associated with greater risk on the right side of 1, and white meat is associated with lower risk on the left side of 1.

Evidence identified in this report indicates that red meat intake does not appear to be related to the risk of CHD. Results appear consistent among the two meta-analyses by Micha et al.[7] and Abete et al.[13], with mixed findings based on the two new cohort studies by Bernstein et al.[14] and Haring et al.[17] However, higher intake is associated with risk of incident stroke and CVD mortality. For stroke, the earlier meta-analysis by Micha et al.[7] did not find a significant association. However, it only included two studies with limited sample size. The subsequent meta-analysis by Chen et al.[12] (incorporating nearly four times the number of cases) suggested a slightly elevated risk associated with red meat intake. This is further supported by a recent study by Haring et al.[17] Red meat intake appears to be associated specifically with ischemic stroke, rather than with haemorrhagic stroke. Increased risk of stroke could contribute to a moderately elevated risk of incident CVD. The increased risk of stroke could potentially be explained by heme iron present in red meat due to its pro-oxidative properties[39] and also to hypertension as a mediator. For poultry intake, the evidence reviewed suggests a largely neutral association with CVD risk. There was less evidence available than for red meat intake, but findings were consistent across studies.

Several 'secondary papers' were also identified that suggested that higher total red meat consumption is related to elevated risk of CVD and CHD. Such relations could be driven by processed meats, which prior studies suggest may be more harmful than red meat due to higher levels of sodium and nitrite.[7] Regarding dose-response, none of the studies considered non-linear relationships, assuming relationships to be linear. So it is not feasible to evaluate whether risk starts to increase only above a certain threshold amount. Most frequently those in the top category consumed 100 to 200 grams per day, compared to less than 50 grams per day for those in the lowest intake category.

Unprocessed red meat intake and risk of heart failure

Overall results related to unprocessed red meat and incident heart failure are summarized in **Figure 6**.

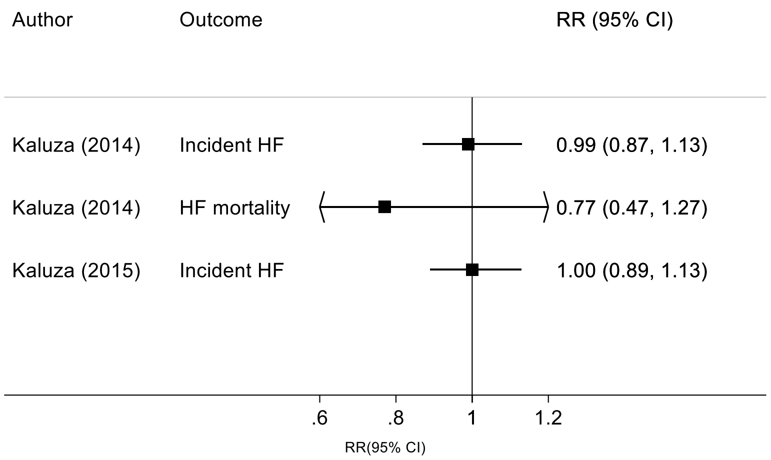


Figure 6: Summary of red meat intake and risk of incident heart failure.
The square black boxes indicate effect estimates; 95% confidence intervals are shown. On the x-axis, red meat is associated with greater risk on the right side of 1, and red meat is associated with lower risk on the left side of 1.

There is very little evidence that higher intake of unprocessed meat intake is related to risk of HF, at least within the exposure ranges studied in the Swedish cohort (up to 80 g/day). Interestingly, similar exposure ranges of processed meat are associated with substantially higher risk of HF, suggesting the possibility that components in processed meats other than saturated fat (which is similar to unprocessed meat) are potentially responsible. Such components include sodium (400% higher in processed meat), nitrites (50% higher)[40], and other substances like polycyclic aromatic hydrocarbon (PAH) generated during smoking.[41] Overall, the evidence is limited relating to HF, but studies are assessed to be of high quality with large sample sizes and reasonable statistical power.

Unprocessed red meat and white meat intake and weight gain

Recent prospective cohort data from the US and European countries appear to generally indicate that higher unprocessed red meat and poultry consumption are associated with moderate weight gain. The magnitude of effects (and even direction of association) appear to depend on specific types of unprocessed meats; for example, effects are largest for hamburgers and substantially smaller for unprocessed red meat eaten as a main dish; with opposing directions of association for chicken with or without skin.[25] The magnitudes of weight gain are relatively small for most types of unprocessed red meat and poultry (~+0.5kg per 4 years) but could be significant at the population level and over the long term. Interaction with glycaemic load (GL) suggests we may also need to emphasize improving quality of foods rich in carbohydrate. Overall, these findings are consistent with current guidelines that recommend limiting intake of unprocessed red meat (especially hamburgers). The effects of poultry on weight change requires further investigation.

Unprocessed red meat intake and effect on lipid profile and blood pressure

The meta-analysis by O'Connor et al.[10] suggests that there is no appreciable impact of red meat consumption on traditional CVD risk factors including blood pressure and lipid profile. A number of important limitations should be taken into account when interpreting this study. For instance, a number of potential sources of bias were apparent for the RCTs included in their systematic review, such as the lack of blinding of the study investigators, which raises substantial concern about performance bias. The findings should also not be interpreted as supporting increased intake of unprocessed red meat, as evidence from RCTs clearly does not suggest that increased red meat intake led to improvements in CVD risk factors.

Cardiovascular effect of including unprocessed red meat and poultry as part of healthy dietary patterns

Our review identified limited evidence that suggests DASH or Mediterranean dietary patterns that replace poultry or fish with moderate amounts of lean pork and beef can lead to improved cardiovascular risk factors including TC, LDL-C and SBP in the short-term. A question that should be considered when interpreting these studies is which food groups were used to replace the lean unprocessed red meats or vice versa, with only one study[38] specifying that red meat replace chicken, whereas in other studies[32-34] it was not clear about the relative quantity of fish and poultry that were replaced. Given the robust evidence supporting the cardiometabolic benefits of fish consumption[42], and the lack of independent benefits of unprocessed red meat intake[10], the totality of evidence would not support replacement of fish with unprocessed red meat. Based on the studies reviewed, the quantity of unprocessed red meat that could be considered as a replacement for poultry is between 0.7 servings (~70g/day) and 1.2 servings per day (~120g/day).

The review prior to this one[3] provided strong evidence for DASH and moderate evidence for Mediterranean diet to reduce risks of CVD. The findings of the current review support the findings of the earlier review (in the included papers DASH and Mediterranean diet improved CVD risk factors), and further suggest lean red meat could be included to up to ~one serve per day as a replacement for poultry, possibly as a way to enhance adherence to such dietary patterns. These findings should be interpreted within the context of some of the methodological limitations of the RCTs. Studies were generally well conducted, however, potential for selection bias and performance bias was apparent. The duration of studies tended to be short, and the findings may not reflect long term effects. It is also noted that all the RCTs identified for this report were funded by the meat industry, which raises the potential concern of biased and selective reporting.[43]

Conclusion

While the evidence from prospective cohort studies suggests unprocessed red meat intake is related to higher risk of weight gain and elevated stroke risk, evidence based on RCTs did not reflect higher adverse outcomes related to increased red meat intake and CVD risk factors. This could be explained by various reasons. For instance:

- There may be other CVD risk factors not assessed by the RCTs
- RCTs were mostly of limited duration (less than 12 weeks) and short-term effects may not be relevant or comparable to long term population-based studies
- The possibility of publication bias cannot be excluded, which could affect both prospective cohort studies and RCTs (although the likelihood is larger for the latter due to industry funding)
- Most RCTs assessed substitution of unprocessed meat intake with other protein sources such as plant-based protein
- Another confounder could be the overall dietary pattern as higher-intake meat eaters may also consume more vegetables.[44]

The totality of evidence reviewed in this report suggests that white meat (poultry, turkey and rabbit) have relatively neutral, whereas unprocessed red meat (beef, pork, veal, and lamb) likely have moderately adverse outcomes on cardiovascular effects, particularly related to weight gain and stroke risk. A limited body of evidence also suggests, however, within specific healthy dietary patterns[34], that replacement of poultry with moderate amounts of unprocessed red meat (beef or pork) is unlikely to mitigate the overall cardiovascular benefits of these diets. It should be noted that these effects of unprocessed red meat are nested within healthy dietary patterns and are likely to be not comparable to prospective cohorts' findings that were reviewed. Most prospective cohort studies included in this review were carried out with populations that have an overall poor dietary quality.[45, 46] The definition of red meat was generally consistent, but there were some minor differences observed. The most commonly used definitions for unprocessed red meat were beef, veal, lamb, pork and hamburger, while the most common for white meat were chicken and turkey. Rabbits were sometimes classified as red meat.

With regard to dietary recommendations, the findings of this review suggest considering specific dietary recommendations for different populations:

1. For the general population, emphasis should be on healthy dietary patterns, with preference for plant protein sources and fish rather than unprocessed poultry and red meat. Based on evidence from prospective cohort studies, up to 50 grams per day of unprocessed red meat is reasonable; this was the highest amount reported for the lowest intake category across studies. For poultry, there is no strong evidence for recommending a limit on intake level.

2. In clinical populations assisted by dietitians or in other instances where individuals are already achieving dietary patterns highly consistent with the DASH or Mediterranean diet, up to one serve (100 g/day) of unprocessed red meat or poultry is reasonable if it enables an individual to achieve adherence to the healthy dietary pattern. Consumption of this amount was shown to reduce total cholesterol, LDL and HDL cholesterol, DBP and SBP in this review.

Several gaps in research are apparent — though meat intake may be part of various dietary patterns[3], evidence in this review pertains to DASH and Mediterranean dietary patterns only, and the effect of incorporating unprocessed meat for other healthy dietary patterns is unclear for addressing Question 3 in this review. RCTs have assessed only a limited set of CVD risk factors. Given the emerging link between unprocessed red meat intake and the risk of type 2 diabetes in prospective cohort studies[47], RCTs powered to study markers of glucose-insulin homeostasis are needed. In relation to cancer, the World Cancer Research Fund Continuous Update Project provides up to date information from research on meat and cancer.[48] Future studies funded by independent government and NGO organization with improved study design (for example, the incorporation of blinding of assessors/investigators) are needed to strengthen the evidence base and minimize concerns over selective and biased reporting. In addition, cooking methods may modify the effect of unprocessed meat[49] and this warrants further investigations.

Applicability

Findings from this review are likely relevant to the Australian population. Our selection strategy limited to studies with demographic and dietary characteristics relatively similar to Australians. In the meta-analysis by Abete et al.[13], the association was strengthened when it focused on Western studies, which could be due to higher intake of red meat in these populations compared to Asian populations, or different cooking methods. Cohort studies were recruited from diverse populations (for instance, including community-based cohorts as well as more 'focused' cohorts like health professionals). Currently, Australians consume a median (25^{th} to 75^{th} percentile) amount of 104 (54-169) grams of unprocessed red meat per day, and 100 (60-176.2) grams per day of poultry.[5] These intakes are comparable to the ones identified in this review.

Appendices

Appendix 1

Question 1 and 2 search strategy (including MESH terms)

Population: Adults

Exposure: (MESH descriptor: meat OR "red meat" OR poultry) OR (beef OR lamb OR pork OR chicken OR "unprocessed meat")

AND

Outcome: (MESH descriptor: "cardiovascular disease") OR (MESH descriptor: "coronary disease") OR (MESH descriptor: arteriosclerosis) OR (MESH descriptor: "atrial fibrillation") OR (MESH descriptor: "heart failure") OR (MESH descriptor: "hypertension") OR (MESH descriptor: "blood pressure") OR (MESH descriptor: "stroke") OR (MESH descriptor: "HDL cholesterol" OR "LDL cholesterol" OR "VLDL cholesterol") OR (MESH descriptor: triglycerides) OR (MESH descriptor: "weight gain")

AND

Study design: (MESH descriptor: meta-analysis) OR (MESH descriptor: observational) OR (MESH descriptor: epidemiologic) OR (MESH descriptor: prospective) OR (MESH descriptor: cohort) OR (MESH descriptor: follow-up) OR (MESH descriptor: longitudinal) OR (MESH descriptor: clinical trial) OR randomized OR randomised OR RCT

Databases searched: Medline, Embase, Cochrane Central Register of Controlled Trials,

Cochrane Database of Systematic Reviews

Published from January 2010 to 15th October 2018

Number of records identified

Database	Number of records
Medline	169
Embase	527
Cochrane Central Register of Controlled Trials	208
Cochrane Database of Systematic Reviews	88
Total	**992**
Number after duplicates were removed	753

Question 3 Search strategy (including MESH terms)

Population: adults

Exposure 1: (MESH descriptor: meat OR "red meat" OR poultry) OR (beef OR lamb OR pork OR chicken OR "unprocessed meat")

AND

Exposure 2: (MESH descriptor: diet OR "healthy diet*" OR "Mediterranean region" OR "vegetarian diet") OR ("DASH*" OR "Nordic*" OR "Tibetan*" OR "portfolio*" OR "eating pattern" OR prudent*" OR "Mediterranean*")

Outcome: (MESH descriptor: "cardiovascular disease") OR (MESH descriptor: "stroke") OR (MESH descriptor: "blood pressure") OR (MESH descriptor: arteriosclerosis) OR (MESH descriptor: "atrial fibrillation") OR (MESH descriptor: "heart failure") OR (MESH descriptor: "hypertension" OR (MESH descriptor: "HDL cholesterol" OR "LDL cholesterol" OR "VLDL cholesterol") OR (MESH descriptor: triglycerides) OR (MESH descriptor: "weight gain")

AND

Study design: (MESH descriptor: meta-analysis) OR (MESH descriptor: clinical trial) OR (randomized OR randomised OR RCT)

Published from January 2010 to 15th October 2018

Databases searched: Medline, Embase, Cochrane Central Register of Controlled Trials,

Cochrane Database of Systematic Reviews

Number of records identified

Database	Number of records identified
Medline	33
Embase	20
Cochrane Central Register of Controlled Trials	40
Cochrane Database of Systematic Reviews	79
Total	**172**
Number after duplicates were removed	141

Appendix 2

Summary tables for Questions 1 and 2

Meta-analyses (n=4)

Author, year, Study type, country	Research questions	Population characteristics	Details of the meat studied (i.e. type, serving size)	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment
Abete et al. 2014 Meta-analysis of cohort studies 9 studies: Europe (1 study), US (4 studies), Asia (3 studies- cohorts from Japan, China, Korea, Bangladesh,	What is the association between consumption of red and white meat and the risk of death from CVD and IHD?	7 cohorts, 1,615,868 individuals (for CVD mortality) 4 cohorts, 230,693 individuals (for IHD mortality)	Red and white meat Serving sizes were different in each study	CVD mortality IHD mortality	Risk estimates for the comparison of the highest v. the lowest consumption category of red meat and CVD mortality (RR 1·16; 95% CI 1·03, 1·32; I^2=82·5, P<0·001) In the sensitivity analysis of red meat intake, the heterogeneity decreased substantially (I^2 =14·7 %, P=0·319) when Asian studies were excluded and the association was strengthened (RR 1·33; 95% CI 1·26, 1·40) White meat (RR 1·01; 95% CI 0·96, 1·07; I^2= 10·6, P=0·348) consumption was not associated with CVD mortality in the analysis of the highest v. the lowest consumption category	Not reported	In the association between red meat and IHD mortality and (RR 1·02; 95% CI 0·72, 1·46; I^2=70·3, P=0·018) the article reported this as significant, while the RR shows it's not significant. Reported no funding received	Score ≥4 (n=7) Score <4 (n=2)

Author, year, Study type, country	Research questions	Population characteristics	Details of the meat studied (i.e. type, serving size)	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment
Taiwan), UK (1 study)					RR per 100 g/d increase in red meat intake (RR 1·15; 95% CI 1·05, 1·26; I^2= 76·6 %, P<0·001) were positively associated with CVD mortality: No associations observed between white meat consumption and CVD mortality in the dose–response meta-analysis Red meat consumption was not associated with IHD mortality (RR 1·02; 95% CI 0·72, 1·46; I^2=70·3, P=0·018) White meat (RR 1·00; 95% CI 0·82, 1·21; I^2=0, P=0·780) consumption was not associated with IHD mortality			
Chen et al. 2013	What is the association between consumptio n of red meat and	239,251 subjects and 9593 stroke events	Red meat included beef, veal, pork, mutton and lamb	Stroke	Comparing the highest category of consumption with lowest category, the pooled relative risks (RRs) of total stroke for red meat were 1.09; 95% CI, 1.01–1.18) and	Not reported	Low heterogeneity (0.0%, p=0.923) accounted for by strict inclusion	Score of 4 (n=3) Score of 5 (n=2)

Author, year, Study type, country	Research questions	Population characteristics	Details of the meat studied (i.e. type, serving size)	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment
Meta-analysis of prospective cohort studies 5 studies: Japan (1 study), Sweden (2 studies), US (2 studies)	risk of stroke?	Mean follow-up: 10.1 to 26 years	Lowest vs highest categories in different studies: Never vs almost daily <16.5 vs ≥48.8g/day <33.5 vs ≥83.1g/day 0.28 vs 1.08 servings/day 0.14 vs 1.11 servings/day		1.13 (95% CI, 1.01–1.25) for ischemic stroke No association between red meat and haemorrhagic stroke (0.99; 95% CI, 0.77–1.28) The risk of stroke increased significantly by 13% for each 100 g per day increment in red meat consumption (RR=1.13; 95% CI, 1.03–1.23)		criteria (excluded studies in which the types of meat has not been clearly described) Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions	
Micha et al. 2010 Meta-analysis CHD:	What is the relationship between red meat consumptio n with risk of coronary heart disease	CHD: 56,311 participants Stroke: 106,684 participants	Unprocessed red meat Dietary collection tool: studies used validated	CHD events Stroke incidence	CHD: 769 CHD events Unprocessed red meat intake was not associated with CHD RR per 100-g serving per day=1.00; 95% CI, 0.81 to 1.23; P for heterogeneity=0.36 Stroke:	Not reported	Funded by the Bill & Melinda Gates Foundation/ World Health Organization Global Burden	Score of >4 (n=3) Score of 3 (n=3)

Author, year, Study type, country	Research questions	Population characteristics	Details of the meat studied (i.e. type, serving size)	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment
3 cohort studies (UK, US, Australia) 1 case control study (Spain) Stroke: 2 studies (US, Japan)	(CHD) and stroke?		multi-item FFQ or interview-based or fewer-item FFQ		Consumption of red meat was not associated with stroke RR=1.17; 95% CI, 0.40 to 3.43 Averaged across studies, consumption (mean±SD) levels in the lowest versus highest category of intake were 1.1±1.1 versus 8.3±2.7 servings per week for unprocessed red meat		of Diseases, Risk Factors, and Injuries Study; the National Heart, Lung, and Blood Foundation, National Institutes of Health and the Searle Scholars Program	
O'Connor, 2017 Meta-analysis of randomised controlled trials	What is the effect of consuming ≥0.5 servings of total red meat/day (3.5 servings/ week) on blood lipids, lipoproteins,	Subjects aged ≥19 years Intervention lengths varied from 2 to 32 weeks	Intervention: consumption of ≥0.5 servings/day (35g) red meat Comparator: consumption of <0.5 servings/day	Total cholesterol (TC), LDL cholesterol, HDL cholesterol, triglycerides, ratio of TC to	Red meat intake did not affect lipid-lipoprotein profiles or BP values post intervention (P>0.05) or changes over time. Weighted mean differences: TC (-0.01 mmol/L ; 95% CI, -0.08, 0.06 mmol/L) LDL cholesterol (0.02 mmol/L; (95% CI, -0.05, 0.08 mmol/L)	Not reported	Minimally processed meats consumed in 15 studies, highly processed meats in 1 study, and extent of meat processing was	Risk of bias assessed using the Cochrane risk-of-bias assessment tool

Author, year, Study type, country	Research questions	Population characteristics	Details of the meat studied (i.e. type, serving size)	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment
24 RCTs (studies with more than 1 control or intervention groups reported as one study) Various countries	and blood pressure (BP) in adults?		(35g) red meat or other protein source (fish, soy, chicken)	HDL cholesterol (TC:HDL), systolic blood pressure (SBP), diastolic blood pressure (DBP)	HDL cholesterol (0.03 mmol/L; 95% CI, -0.01, 0.07 mmol/L) Triglycerides (0.04 mmol/L; 95% CI, -0.02, 0.10 mmol/L) TC:HDL (-0.08 mmol/L; 95% CI, -0.26, 0.11 mmol/L) SBP (-1.0 mm Hg; 95%CI, -2.4, 0.78 mm Hg) DBP (0.1 mm Hg; 95%CI, -1.2, 1.5 mm Hg) Heterogeneity ranged from 46 to 90%.		unclear in 8 studies. Funded by the Purdue University's Ingestive Behavior Research Center, National Institutes of Health T32 training grant and postdoctoral fellowship	

Prospective Cohort Studies (n=14)

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
Ashaye et al. 2011 Physicians' Health Study (1982-2008) US	What is the association between red meat consumption and incident heart failure (HF)?	21,120 apparently healthy men (mean age 54.6 years) Mean follow-up: 19.9 years	Red beef, pork, or lamb as main dish (steak, roast, ham, etc); beef, pork, or lamb as a sandwich or mixed dish; and hotdogs Dietary intake assessed through self-reported 19-items FFQ Lowest to highest category of intake	Heart failure	Age, aspirin assignment, smoking alcohol consumption, cereal consumption, parental history of MI prior to age 60 y, exercise, body mass index, prevalent diabetes, coronary heart disease, atrial fibrillation, and hypertension at 12 months	1204 (5.7%) new cases of HF There was a positive and graded relationship between red meat consumption and HF [hazard ratio (95% CI) from the lowest to the highest quintile of red meat (model 3, P for trend 0.007): Q1 = 1.0 (reference) Q2 = 1.02 (0.85-1.22) Q3 = 1.08 (0.90-1.30) Q4 = 1.17 (0.97-1.41) Q5 = 1.24 (1.03-1.48)	Not reported	Higher intake of red meat was associated with an increased risk of HF Red meat included processed meat such as ham and hotdogs Funded by grants CA-34944, CA-40360, CA-097193, HL-26490, HL092946, and HL- 34595, from the National Institute of	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
			servings/ week: Q1=1.5 vs Q5=9.5		post randomization			Health, Bethesda, MD.	
Bellavia et al. 2016 Sweden	Does the association between red meat consumption and the risk of CVD mortality differ across amounts of fruit and vegetable (FV) intake?	74,645 adults (40,089 men and 3+4,556 women) 16 years follow-up	Non-processed red meat (fresh and minced pork, beef, and veal) Processed red meat (sausages, hotdogs, salami, ham, processed meat cuts, liver pate, and blood sausage)	CVD mortality	Adjusted for sex, pack-years of smoking, physical activity, educational status, BMI, alcohol consumption, diabetes, fish consumption, and total energy	Mortality from CVD-related causes = 5495 cases Compared with participants in the lowest quintile of total red meat consumption, those in the highest quintile had a 29% increased risk of CVD mortality (HR: 1.29; 95% CI: 1.14, 1.46) Results were similar across amounts of FV consumption	Not reported	Processed and unprocessed meat analysed together Lamb and game consumption not collected in the questionnaire. Could potentially increase the precision of main exposures	3

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
			Dietary intake assessed through a 96-item FFQ Total red meat consumption, g/d (median): Q1=<46 (31) vs Q5=117.1-300 (140)			which was categorized into 3 predefined levels (low FV intake: <2 servings/d; medium FV intake: 2–4 servings/d; and high FV intake: >4 servings/d) No interaction between red meat and FV consumption was detected for CVD mortality (P=0.93) High intakes of red meat were associated with a higher risk of CVD mortality		Source of funding not reported	
Bernstein et al. 2010	What is the relationship between	84,136 women aged 30 to 55 years	Red meat:	Nonfatal myocardial	Adjusted for age, time period, total	2210 nonfatal infarctions and	Not reported	Poultry included	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
Nurses' Health Study US	major sources of dietary protein and the development of coronary heart disease (CHD)?	26 years follow-up (1980-2006)	Beef, pork and lamb Poultry included chicken with and without skin, chicken sandwich, and chicken/turkey hot dog Dietary intake assessed through a 116-item FFQ Unprocessed red meat consumption, servings/d: Q1=0.28 vs Q5=1.17	infarction Fatal CHD	energy, cereal fibre intake, alcohol, trans fat, body mass index, cigarette smoking, menopausal status, parental history of early myocardial infarction (before age 65 years for mother or age 55 years for father), multivitamin use, aspirin	952 deaths from CHD Higher intakes of red meat excluding processed meat were significantly associated with increased risk of CHD (RR: 1.13; 95% CI: 0.99, 1.30), P for trend 0.02. RR for 1 serving per day: 1.19 (1.07, 1.32) Higher intakes of poultry were significantly associated with lower risk of CHD (RR: 0.92; 95% CI: 0.80, 1.06), P for trend 0.02		chicken and turkey hot dog	

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
			Poultry consumption servings/d: Q1=0.07 vs Q5=0.56		use, physical exercise	RR for 1 serving per day: 0.90 (0.75, 1.08)			
Borgi et al. 2015 Nurses' Health Study (NHS), Nurses' Health Study II (NHSII) and Health Professionals Follow-Up Study (HPFS)	What is the association of different types of animal flesh with the risk of developing hypertension?	188,518 adults NHS, n=62,273 women, 30-55 years NHS II, n=88,831 women, 25-42 years HPFS, n=37,414	Unprocessed meat (beef, pork, lamb) Poultry (chicken and turkey, with or without skin) Dietary intake assessed through a validated more than 130 items FFQ	Incidence of hypertension	Adjusted for age, race/ ethnicity, BMI, current smoking status, physical activity, weight change per FFQ cycle, postmenopausal, alcohol intake, current oral contraceptive use, for Nurses'	78 208 participants reported a new diagnosis of hypertension Multivariable pooled HRs for intake of at least 1 serving/day compared with less than 1 serving/ month; Unprocessed red meat: 1.24 (1.17–1.31; P trend <0.001)	Not reported	Higher meat intake was associated with increased risk of hypertension Funded by the following grants: Nurses' Health Study (NHS; P01 CA87969), the Nurses' Health Study II (NHS II; UM1 CA176726), and the	5

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
US		men, 40-75 years >20 years follow-up			Health Study II), family history of hypertension, total energy intake, total fruits, vegetables, whole grains, sugar-sweetened beverage intake, artificially sweetened diet beverage intake, analgesic use	Poultry: 1.22 (1.12–1.34; P trend <0.001) Categories of consumption (servings): Q1=<1/month Q2=1-3/month Q3=1-3/week Q4=4-6/week Q5=≥1/day		Health Professionals Follow-Up Study (HPFS; UM1 CA167552). One author was funded by the American Heart Association (AHA) grant (14POST20380070)	
Haring et al. 2014 Atherosclerosis Risk in	What is the association between protein-rich food groups and the risk	12,066 Adults, aged 45–64 years	Red meat Poultry	Coronary heart disease events or deaths	Adjusted for age, sex, race, study, center, and total energy intake, smoking,	1147 CHD events Intake of unprocessed red meat and poultry	Not reported	Absence of an association between major dietary protein sources and risk for CHD may be	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
Communities (ARIC) Study US	for coronary heart disease (CHD)?	Median follow-up of 22 years	Dietary intake assessed through interviewer-administered 66-item FFQ Consumption servings/day: Red meat Q1=0.1 vs Q5=1.1 Poultry Q1=0.1 vs Q5=0.8		education, SBP, use of antihypertensive medication, HDLc, 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	were not associated with CHD Red meat HR; 95% CI; 1.13(0.89-1.44); P for trend 0.13) Poultry HR; 95% CI; 0.79(0.64-0.98); P for trend 0.16		explained in part by limited variation in consumptions of these food groups. Participants reported low meat intake in comparison to other similar studies. Funded by the National Heart, Lung, and Blood Institute	

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
Haring et al. 2015 Atherosclerosis Risk in Communities (ARIC) Study US	What is the relationship between protein-based food groups and the risk of stroke (haemorrhagic and ischemic) and silent cerebral infarcts?	11,601 adults, aged 45–64 years Median follow-up of 22.7 years	Red meat Poultry Dietary intake assessed through interviewer-administered 66-item FFQ Consumption servings/day: Red meat Q1=0.14 vs Q5=1.08 Poultry Q1=0.07 vs Q5=0.80	Stroke (definite or probable ischemic or haemorrhagic)	Adjusted for age, sex, race, study center, and total energy intake, smoking, cigarette years, education, SBP, use of antihypertensive medication, HDLc, total cholesterol, use of lipid lowering medication, body mass index, waist-to-hip ratio, alcohol intake, physical	699 stroke events Higher red meat consumption was associated with increased risk of total stroke and ischemic events Total stroke: HR; 95% CI; 1.41 (1.04–1.92); P for trend=0.01 Ischemic events: HR;95% CI, 1.47 (1.06–2.05); P for trend=0.01	Not reported	Funded by the National Heart, Lung, and Blood Institute	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
					activity, carbohydrate, fibre, fat, magnesium	No association between poultry intake and stroke HR;95% CI, 0.86(0.65-1.14); P for trend=0.55			
Kaluza et al. 2014 Sweden	What is the association between unprocessed red meat consumption with heart failure (HF) incidence?	37,035 men, aged 45 to 79 years Mean follow-up of 11.8 years	Unprocessed meat included pork, beef/veal, and minced meat Dietary intake assessed through a validated 96-item FFQ Unprocessed	Incidence and mortality of heart failure	Adjusted for age, education, smoking status, and pack-years of smoking, body mass index, total physical activity, aspirin use, supplement use, family history of myocardial infarction at	2891 incidences and 266 deaths from HF Consumption of unprocessed red meat was not associated with increased risk of incidence of HF or mortality from HF Incidence of HF: HR; 95% CI, 0.99(0.87-1.13), P for trend 0.75	Not reported	Possible explanations for the lack of association observed between unprocessed red meat and HF are that the consumption was not high enough or that the range was too narrow to provide a sufficient	5

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
			red meat consumption (g/day) Q1:<25 vs Q4:≥75		<60 y, intake of energy and consumption of alcohol, whole grain products, fruit, vegetable, and fish	Mortality from HF: HR; 95% CI, 0.77(0.47-1.27), P for trend 0.40		exposure gradient. Funded by the Swedish Research Council/Medicine and the Swedish Research Council/ Infrastructure	
Kaluza et al. 2015 Sweden	What is the association between unprocessed red meat consumption with heart failure (HF) incidence?	34,057 women, aged 48–83 years Mean follow-up of 13.2 years	Unprocessed meat included pork, beef/veal and minced meat Dietary intake was assessed through a validated self-administered	Incidence of HF	Adjusted for age, education, smoking status and pack-years of smoking, BMI, physical activity, aspirin use, family history of myocardial	2806 women diagnosed with HF Mean of unprocessed red meat consumption was 34±24 g/day Consumption of unprocessed meat was not associated with increased risk of HF incidence	Not reported	Source of funding not reported	5

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
			96-item FFQ Unprocessed red meat consumption (g/day) Q1:<25 vs Q4:≥75		infarction at <60 years, intake of energy, and consumption of alcohol, whole grain products, fruit, vegetables and fish	HR; 95% CI, 1.05(0.92-1.21), P for trend 0.75			
Lajous et al. 2014 France	What is the association between consumption of unprocessed red meat with incident hypertension?	N=44,616 disease-free French women (mean age 51.9 ± 6.3 y) answering a questionnaire 1993-1995 and followed up till 2008.	Servings/week (1 serving unprocessed red meat= 100g) Unprocessed red meat was defined as beef, pork, veal, horse, and sheep.	Incident hypertension or antihypertensive treatment	Adjusted for age, education, Smoking, physical activity, menopause or menopausal hormone therapy,	No association was observed between unprocessed red meat consumption and hypertension between the lowest and highest category of intake. HR= 0.99 (0.91, 1.08), P=0.63	None based on HR for categories	Funded by Non-restricted investigator-initiated grant from AstraZeneca and receives minor research support from Swiss Re.	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
		Average 13.8 y of follow-up (1993-2008) and 536,997 person years	Dietary intake assessed through a validated 208-item self-administered diet-history questionnaire. Consumption serve/week: Q1: <1 vs Q5: ≥5		and quartiles of energy intake, intakes of fruit and vegetables, alcohol, bread, and coffee, processed meat, BMI	HR for each 100-g serving/d was 1.00 (95% CI: 1.00, 1.01)			
Quintana et al. 2018 EPIC-Heidelberg Germany	Is the association between red meat consumption and CVD risk mediated by iron load in a	Case-cohort study with a random subcohort (n = 2738) and incident cases of MI (n = 555), stroke (n = 513), and CVD mortality (n = 381)	Per 50 g of daily red meat consumption Dietary intake assessed through a validated FFQ	Myocardial infarction Stroke	Adjusted for age and sex, waist circumference, height, alcohol consumption, fibre intake, energy, CRP,	Myocardial infarction: HR: 1.18 (1.05, 1.33), P<0.01 Stroke: HR: 1.11 (0.98, 1.26), P=0.09 CVD Mortality:	Not reported	Evaluated unprocessed and processed red meat Funded by the German Federal Ministry of Education and	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
	population-based human study?	from EPIC-Heidelberg, a German cohort of 13,611 female and 11,929 male participants aged 35–65 y recruited Follow-up 1994-2009		CVD mortality	LDL, smoking, Hypertension, education level and menopausal status, ferritin concentrations	HR: 1.15 (0.99, 1.34), P=0.06		Research, the German Cancer Research Center, Helmholtz Association of German Research Centres	
Smith et al. 2015 Nurses' Health Study, Nurses' Health Study II and Health Professionals Follow-Up Study	How do changes in intake of protein foods, GL, and their interrelationship influence long-term	N= 120,784 generally healthy participants from three US cohorts (NHS, NHS II, and HPFS; n=46,994 women in the NHS,	One-serving per day increase (over 4 years) in foods including unprocessed red meat; Hamburger; Regular hamburger;	4-year weight change (kilograms, kg) from self-reported data	Adjusted for age, baseline (of each 4-year period) body-mass index, sleep duration, and change in smoking status, physical	Unprocessed red meat HR: 0.66 (0.40, 0.92), P<0.0001 Hamburger HR: 1.27 (0.55, 1.98), P<0.001 Regular hamburger	Not reported	Supported by the Canadian Institutes of Health Research (fellowship award to JDS) and the National Heart, Lung and Blood Institute (grant	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
US	weight gain?	n=47,928 women in the NHS II, and n=25,862 men in the HPFS). At baseline, women in the NHS were age (mean ± SD) 48.9 ± 2.7 y; women in the NHS II, 37.7 ± 3.2 y; and men in the HPFS, 47.3 ± 2.7 y. Follow-up for 16–24 y	Lean hamburger; Beef, lamb or pork as main dish; Beef or lamb as a main dish; Pork as a main dish; Beef, lamb or pork as a mixed dish. Dietary intake assessed every 4 years by using a validated FFQ		activity, television watching, alcohol consumption, and the shown dietary factors, plus change in intake of fruit, vegetable, fried foods consumed at home, fried foods consumed away from home and trans fats, 4-year change in glycaemic index (GI)	HR: 1.13 (0.48, 1.78), P<0.001 Lean hamburger HR: 0.76 (0.49, 1.03), P<0.001 Beef, lamb or pork as main dish HR: 0.39 (0.27, 0.50), P<0.001 Beef or lamb as a main dish HR: 0.33 (0.13, 0.52), P=0.001 Pork as a main dish HR: 0.64 (0.43, 0.84), P<0.001 Beef, lamb or pork as a mixed dish HR: 0.55 (0.24, 0.87), P<0.001		R01 HL115189 to DM). The cohorts were supported by the NIH (grant P01 CA87969 for the Nurses' Health Study, grant UM1 CA176726 for the Nurses' Health Study II, and grant UM1 CA167552 for the Health Professionals Follow-Up Study	

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
						Poultry: Chicken with skin HR: 0.51 (0.08, 0.94 (p=0.02), P=0.02 Chicken without skin HR: -0.46 (-0.68, -0.24), P<0.001			
Vergnaud et al. 2010 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain,	What is the association between red meat, poultry and weight gain?	103,455 men and 270,348 women aged 25–70 y from 10 European countries from European Prospective Investigation into Cancer and Nutrition–	Energy from meat (100kcal/d) Red meat (beef, veal, pork, and lamb), poultry (mainly chicken and in some cohorts, turkey and rabbit)	Annual weight change (g/year) Weight and height measured at baseline and self-reported at	Adjusted for sex, age, and an indicator of meat consumption, educational level, physical activity level, smoking status, initial BMI, follow-up time, total energy intake,	Annual weight change (g/year) 95% CI per 100kcal increase in intake Red meat: 15 (1,28) Poultry: 45 (29,62) Exclusion of individuals with chronic diseases and those likely to misreport meat	Not examined	Among total meat and meat subtypes, poultry showed the strongest association with weight gain, authors suggest this is likely driven by subjects with previous illness or weight-loss attempts that lead to diet	3

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
Sweden, and the United Kingdom)		Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity (EPIC-PANACEA) project 1992 -2000 at baseline Follow-up for 5 years	Dietary intake assessed through a validated country specific questionnaire	follow-up	energy from alcohol, and plausible total energy intake reporting, dietary patterns	intake, the association between red meat and weight gain no longer significant: 8 (-9, 25) Association between red meat and weight gain was stronger in normal-weight, physically active, aged <25y or >65y subjects, smokers. Association between poultry and weight gain was stronger among age>45y and never/former smoker.		intervention, as well as those who misreported their dietary intakes. Funding declared from research organisations.	
Von Ruesten et al. 2013	What is the association between intakes of	23,531 German participants aged 35-65	100g/day Poultry: Broiler, turkey	CVD defined as	Adjusted for sex, smoking status, years	Red meat (100g/day) was not significantly associated with CVD	Not examined	This study examined the relationship between 45	4

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
Germany	poultry, red meat and CVD incidence?	years free of type 2 diabetes, CVD and cancer from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study between 1994-1998 at baseline Follow-up for 8 years	strips/turkey escalope/chicken fricassee Red meat: Steak/fillet/loin of beef, roast beef, beef roulade, beef goulash/meat cut into small pieces, hamburger/meat loaf, Bolognese sauce, pork cutlet/chop/steak/filet/loin, roast pork, smoked pork chop/spare	myocardial infarction and stroke (363 cases) collected by self-administered question and medically verified based on inquiry to treating physicians, cancer registries or	of smoking, alcohol consumption, waist-to-hip ratio, body mass index, leisure-time physical activity, education, supplements use, total energy intake, prevalent hypertension and history of high blood lipid levels, other food group intakes.	incidence: HR 1.40 95% CI (0.87-2.25). Poultry (100g/day) was not significantly associated with CVD incidence: HR 0.57 95% CI (0.21-1.51)		food groups and chronic disease including CVD, type 2 diabetes, cancer Included processed meat intake Funding declared for EPIC-Potsdam study, no funding declared for the paper	

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
			ribs, cooked meat from pork/knuckle of pork, pork belly, liver, veal/lamb/ rabbit, pork goulash/meat cut into small pieces Dietary intake assessed through a validated FFQ	through death certificates					
Wirth et al. 2016 Germany	What is the association between meat intake and heart failure?	24,008 German participants aged 35-65 years free of heart failure and coronary heart disease	Meat intake was analysed as quintiles Dietary intake assessed	Incident heart failure (209 cases)	Adjusted for age, sex, total energy intake, educational degree,	Hazard ratio (HR) 95% CI Q1: ref Q2: 1.73 (1.0-2.8) Q3: 1.40 (0.7-2.4)	Even though it seems the quintile 5 was significantly associated	Definition of meat not provided This study examined the association	5

Author, year, study name, country	Research questions	Population characteristics, years of follow-up	Details of the meat studied, dietary assessment method	Outcome measures (CVD)	Adjustment for confounders	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment score
		from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study between 1994-1998 at baseline Follow-up for 8.2 years	through a validated FFQ		physical activity and smoking status, BMI and waist circumference, prevalent diseases (diabetes, hypertension and hyperlipidemia and other Mediterranean components (fish, fruit/nuts, vegetables, legumes, MUFA/SFA ratio, cereals, milk products	Q4:1.57 (0.6-2.5) Q5: 2.04 (1.2-3.5) Ptrend=0.01 Note: 95% CI values estimated from the error bars from the graph	with higher risk of HF from the graph, but as per results there is a dose response trend as indicated by significant P-trend value HRs and 95% CIs are stratified by age	between a Mediterranean dietary score, component of Mediterranean diet and HF risk. Funding declared for EPIC-Potsdam study, no funding declared for the paper	

Randomised Controlled Trials (n=1)

Author, year, country	Research questions	Population characteristics	Details of the meat studied (i.e. type, serving size), dietary assessment method	Intervention vs control diet	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding	Quality assessment
Murphy et al. 2012 Australia 6-month, randomized, controlled, parallel intervention trial	What is the impact of regular consumption of fresh lean pork on risk factors for CVD?	164 overweight/ obese adults, mean BMI 32 kg/m^2, 18-65 years Exclusion criteria: diagnosed diabetes or CVD; history of myocardial infarction or stroke; peripheral vascular disease; BP > 160/100 mmHg; liver or renal disease;	Pork (participants provided with lean steak, stir fry, diced, mince and sausages) Dietary intake assessed through a validated 74-item FFQ	Intervention kg pork/week by substituting for other foods Control: habitual diet, <100 g fresh pork per week	Not reported	Plasma levels of lipids, blood pressure, heart rate and arterial compliance	No difference in energy intake between groups over time Pork group consumed: Men: 946g/week (135g/day) Women: 682g/week (97g/day)	Not reported	Sausages included in the intervention diet Funded by Australian Pork Ltd. and the Pork Co-operative Research Centre (Roseworthy, SA, Australia) Authors declared no conflict of interest	Risk of bias assessment tool used

		anti-inflammatory, antihypertensive or hypocholesterolemic drug therapy that was not stable in the previous 3 months; already eating >100 g fresh pork per week; inability to consume pork as required					No significant effects on CVD risk factors after 6 months			

Appendix 3

Summary table: Question 3

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
Hill et al. 2015 US 6 months randomised, parallel arm, open-label, controlled feeding trial	Comparison of 3 diets controlled for saturated fatty acid with varying amounts of protein from plant and animal (predominantly lean beef) sources on metabolic syndrome (MetS) criteria	62 overweight and obese adults, 30-60 years Inclusion criteria: Metabolic syndrome, on BP medication and BP <160/100 mmHg, nonsmokers, free of established CVD, stroke, diabetes, liver, kidney or autoimmune disease Exclusion criteria: continued use of glucose and cholesterol/	Baseline diet: Healthy American diet Experimental diets: Modified DASH diet rich in plant protein (18% protein, two-thirds plant sources), lean beef 11.7g/day (M-DASH) vs Modified DASH diet rich in animal protein (Beef in an Optimal Lean Diet: 18.4% protein, two-thirds animal	age and sex diets matched for SFA and soy to isolate the effect of plant vs animal protein	Change in MetS criteria Total cholesterol (TC) HDL cholesterol LDL cholesterol SPB DBP	All MetS criteria decreased independent of diet composition (main effect of phase, P<0.01; between diets, P>0.05). Prevalence of MetS by the end of the WM phase: M-DASH 90% BOLD 70% BOLD+ 81% though no difference between groups Prevalence of MetS decreased to 50–60% after WL phase and was maintained through FL (HAD, WM vs WL, FL, P <0.01).	Not reported	Authors noted that weight loss was the primary mediator of MetS resolution in their study population regardless of protein source or amount Adherence ranged between 70%+ and 90% in the different diets and phases. Low compliance during WM phase in BOLD group Participants were required to consume all foods provided;

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
		lipid-lowering medication or supplements, pregnancy or lactation, weight loss of ≥10% of body weight within the 6 months before enrolling in the study, high alcohol consumption (≥14 drinks/week), participation in regular physical activity (>1 formal session/wk) with the intention of losing weight or increasing fitness, inability to complete the	sources), lean beef 139 g/day (BOLD) vs Moderate-protein diet (Beef in an Optimal Lean Diet Plus Protein: 27% protein, two-thirds animal sources), lean beef 196.2 g/day (BOLD+) All diets compared at 3 energy balance levels: 5 wks- energy equilibrium (weight			Triglycerides and HDL decreased only after WL phase (P<0.05) SBP decreased during the WM phase (baseline compared with WM, P = 0.07) (-3.05mmHg for M-DASH, -3.19mmHg for BOLD+, and -1.65 mmHg for BOLD) and decreased significantly during the WL phase (baseline, WM compared with WL, P<0.05) (-6.9 mmHg in M-DASH, -7.4 mmHg in BOLD+, and -2.4 mmHg in BOLD) FL phase, SBP increased slightly (although not significantly) from WL but remained significantly lower than baseline		therefore, a mechanism by which protein enhances weight loss (i.e., the reduced intake of food as a result of enhanced satiation) could not affect outcomes Originally not powered to detect differences between groups but rather differences between the baseline and the experimental diets Funding: supported by

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
		exercise testing protocol, vegetarianism, and lactose intolerance	maintenance (WM)) 6 wks – weight loss phase (minimum 500-kcal/d deficit) Plus exercise (WL) (food provided) 12 wks – free living weight loss phase (FL) (no food provided)			(baseline compared with FL, P< 0.01) DBP decreased only after the WL phase, and the effect was sustained through the FL phase (baseline compared with WL, FL, P<0.001) TC and LDL cholesterol reduced after the WM and WL phases (baseline compared with WM, WL, P<0.05) but returned to baseline levels after FL		The Beef Checkoff and the General Clinical Research Center, The Pennsylvania State University (NIH grant M01RR10732)
O'Connor et al. 2018 US 16 weeks randomi	Assessed the effects of consuming different amounts of lean, unprocessed red	41 subjects (28 women, 13 men) overweight or obese, 30-69 years (mean age: 46±2 y; mean body mass index (kg/m2): 30.5±0.6 Inclusion criteria:	Mediterranean (Med) Pattern for two 5-weeks interventions separated by 4 weeks of self-selected eating (washout phase)	Age, sex, and body weight at each time point	Total cholesterol LDL cholesterol	Cardiometabolic disease risk factors were measured for all subjects during both baseline periods and during the last week of each intervention. Total cholesterol decreased, but greater reductions occurred with Med-Red		Higher significant values in Med-Red vs Med-Control for energy, MUFA and potassium. Lower significant values for protein and PUFA. Also meat diet contains no refined

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
sed, crossover, investigator blinded, controlled feeding trial	meat in a Mediterranean Pattern on cardiometabolic disease (CMD) risk factors.	Not following a Mediterranean Pattern (as indicated by a score of <5 on the 14-item Mediterranean Diet Assessment Tool), total-C <6.70 mmol/L, LDL cholesterol <4.10 mmol/L, triglycerides <4.5 mmol/L, fasting glucose <6.1 mmol/L, systolic blood pressure <160 mm Hg, DBP <100 mm Hg, body mass <140 kg, no acute illness, nonsmokers, normal liver and kidney functions, and nondiabetic,	Med red: Med-style eating pattern with ~500 g lean (beef or pork) red meat/wk Med control: Med-style eating pattern with ~200 g lean (beef or pork) red meat/wk		HDL cholesterol Total- C:HDL cholesterol Triglycerides Blood pressure, Framingham Heart Study 10-y cardiovascular disease risk and vascular age	than with Med-Control (−0.4 ± 0.1 and −0.2 ± 0.1mmol/L, respectively, intervention × time=0.045). Low-density lipoprotein (LDL) decreased with Med-Red but was unchanged with Med-Control (−0.3 ± 0.1 and −0.1 ± 0.1 mmol/L, respectively, intervention× time = 0.038) High-density lipoprotein (HDL) decreased nondifferentially (−0.1 ± 0.0 mmol/L] Triglycerides and total cholesterol: HDL did not change with either Med-Red or Med-Control. All blood pressure parameters improved, except during sleep,		grains and 50% more dairy than control diet. Participants lost 0.6 kg more during Med-Red than during Med-Control, which was a statistically significant difference. However controlled for body weight at each time point. Dietary intake and compliance were measured from the menu check-off lists of 3 d during the last week of each intervention. The self -reported >95% menu compliance

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
		weight stable (±4.5 kg), have consistent physical activity levels for 3 mo prior to starting the study, and have stable medication use for 6 mo prior to and throughout the study				independent of the red meat intake amount Framingham Heart Study 10-y CVD risk decreased by 1% and vascular age increased by 2–3 y with a Mediterranean Pattern, independent of red meat intake amount		was not objectively confirmed. Funded by Beef Checkoff, the Pork Checkoff, the National Institute of Health's Ingestive Behavior Research Center at Purdue University and the National Institute of Health's Indiana Clinical and Translational Sciences Institute
Roussell et al. 2012 US 4-period (20	Effect on LDL cholesterol of cholesterol lowering diets with varying amounts	36 participants (21 women, 15 men), 30-65 years Inclusion criteria: LDL cholesterol concentrations >2.8 mmol/L, BMI	Intervention diets: Dietary Approaches to Stop Hypertension (DASH): 28 g beef/d	Age, weight, and baseline lipid concentrations	Change in total cholesterol (TC) and LDL cholesterol	Change in total cholesterol: Compared with consumption of HAD there was decrease in total cholesterol (TC) after consumption of: DASH		Adherence to the prescribed diets was 93% according to daily self-reporting forms. Body weight was maintained during the diet periods within 2.2 kg

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
weeks total) randomised, crossover, controlled feeding trial	of lean beef.	(in kg/m^2) of 18.5–37, triglycerides concentration <3.95 mmol/L, blood pressure <140/90 mm Hg, non-smokers, free of established CVD, stroke, diabetes, liver, kidney, or autoimmune disease Exclusion Criteria: Use of cholesterol and lipid-lowering medications or supplements, pregnancy or lactation, weight loss >10% of body weight within the 6	Beef in an Optimal Lean Diet (BOLD): 113 g beef/d Beef in an Optimal Lean Diet plus additional protein (BOLD+): 153 g beef/d Control diet: Healthy American diet (HAD), 20 g beef/d Consumed 4 diets (HAD, DASH, BOLD, and BOLD+ diets) for 5 wks each. Washout			(-0.49±0.11 mmol/L, P<0.05) BOLD (-0.48±0.10 mmol/L, P<0.05) BOLD+ (-0.50±0.10 mmol/L, P<0.05) Change in LDL cholesterol: Compared to HAD there was decrease in LDL cholesterol after consumption: DASH (-0.37±0.09 mmol/L, P<0.05) BOLD (-0.35±0.9 mmol/L, P<0.05) BOLD+		Total energy held constant for each participant throughout the 4-diet periods, and participants remained weight stable. Funded by the Beef Checkoff Program and the General Clinical Research Center, Pennsylvania State University (NIH grant M01RR10732).

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
		mo before enrolment in the study, vegetarianism	period 1 week between diets			(-0.345±0.09 mmol/L, P<0.05)		
Roussell et al. 2014 US 4-period (20 weeks total) randomised, crossover, controlled feeding trial	Effect of DASH-like diets that provided different amounts of protein from lean beef on vascular health.	36 normotensive participants (systolic blood pressure (SBP), 116±3.6mmHg) Same study as above (Roussell 2012)	Intervention diets: Dietary Approaches to Stop Hypertension (DASH): 28 g beef/d Beef in an Optimal Lean Diet (BOLD): 113 g beef/d Beef in an Optimal Lean Diet plus additional protein (BOLD+): 153 g beef/d	Age, weight and baseline blood pressure	Blood pressure	SBP decreased (P<0.05) in subjects on the BOLD+ diet (111.4±1.9mmHg) versus HAD (115.7±1.9). There were no significant effects of the DASH and BOLD diets on SBP. No significant effects of the dietary treatments on DBP		Funded by the Beef Checkoff Program and the General Clinical Research Center, Pennsylvania State University (NIH grant M01RR10732). Reported reasons for no effect on BP compared to the original DASH study: Participants were normotensive, fewer in number (36 vs 459), differences in total and saturated fat in control diets (DASH – 37% and 16%, HAD – 33% and 12%).

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
			Control diet: Healthy American diet (HAD), 20 g beef/d					
Sayer et al. 2015 US Randomised cross-over study	Evaluate whether the consumption of lean pork compared with the consumption of chicken and fish as the predominant protein source in a DASH-style diet affects	19 adults (13 women and 6 men), age 21–75 y (mean age 61y) Inclusion criteria: Systolic blood pressure (SBP) ≥120 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg, no acute illness, not diabetic, not currently (or within the past 3 mo)	Two 6-wk diet periods separated by 4 week wash-out on habitual diet Intervention: DASH + lean pork (DASH-P) (provided fresh pork tenderloin and uncured ham trimmed of visible fat) DASH + lean chicken or fish	Not reported	SBP and DBP Blood lipids	Ambulatory SBP change (Pre to post intervention, P<0.05): DASH-P: -7±2 mmHg DASH-CF: -8±2 mmHg Ambulatory DBP change (Pre to post intervention, P<0.05): DASH-P: -3±1 mmHg DASH-CF: -5±1 mmHg Consumption of these DASH-style diets for 6 wks reduced all measures of BP		Note differences in reported daily intakes of carbohydrates (58.1 vs 54.7%E), fat (25.4 vs 27.3%E), and protein (16.5 vs 17.9%E) between DASH-P and DASH-CF diets respectively. Similar results in prescribed diets. Dietary controls were accomplished by using dietary counselling to follow a prescribed menu (7-d cycle) of specific foods and

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
	blood pressure (BP).	participating in a vigorous exercise regimen or weight-loss program, willingness to eat study foods, ability to travel to the testing facility, and urinary continence. Individuals who were taking prescription medication for hypertension were included if there were no changes in the medication type or dosage for ≥90 d before and during the study period	(DASH-CF) (provided boneless, skinless chicken breast and tilapia fillets) Amounts of meat intake in grams/ servings not reported. 55% of total protein intake was from either lean pork or chicken and fish. The remaining 45% was from dairy, vegetable, and other animal (beef) sources. Note: Two servings of beef			(P<0.05) with no differences in responses between the DASH-CF and DASH-P Total cholesterol: Decreased after DASH-P (preintervention: 202±9 mg/dL; postintervention: 176±7 mg/dL; P-within-diet change , 0.05) but not the DASH-CF (preintervention: 196±8 mg/dL; postintervention: 183±8 mg/dL; P-within-diet change = 0.16) HDL cholesterol: Decreased after the DASH-P (preintervention: 58±4 mg/dL; postintervention: 52±3 mg/dL; P-within-diet change , 0.05) but not the DASH-CF (preintervention: 55±3 mg/dL;		beverages. Compliance checked by daily menu checklist (≥95% for both diets) Study was statistically powered to detect changes in BP Funded by National Pork Board, the NIH Indiana Clinical and Translational Sciences Institute, Clinical Research Center (grant UL1TR001108), and the USDA (2011-38420-20038)

Author, year, country, design	Research questions	Population characteristics/ Inclusion/ exclusion criteria	Intervention vs comparator diet/ dietary assessment method	Confounders adjusted for	Outcome measures (CVD)	Results	Threshold of effect	Comments/ bias/ funding
			tenderloin trimmed of visible fat were provided per week during both interventions			postintervention: 52±3 mg/dL; P-within-diet change = 0.17). Direct comparison of postintervention values indicated no differences in total cholesterol (P = 0.11) or HDL cholesterol (P = 0.60) after the DASH-P and DASH-CF		

Appendix 4

Definition of unprocessed meats and outcomes assessed by each study

Meta-analyses and new observational studies investigating unprocessed meat intake and risk of CVD-related outcomes

Study	Red meat		White meat		All unprocessed meat		Outcomes				
	Yes/No	Definition	Yes/No	Definition	Yes/No	Definition	Incident CVD[1]	Incident CHD[1]	Incident total stroke	Incident IS	Incident HS

Meta-analyses											
Micha (2010), systematic review and meta-analyses	Y	Unprocessed meat from beef hamburgers, lamb, pork, or game.	N	N/A	N	N/A	N	Y	Y	N	N
Chen (2013), systematic review and meta-analyses	Y	Unprocessed meat from beef, veal, pork, mutton, and lamb.	N	N/A	N	N/A	N	N	Y	Y	Y
Abete (2014), systematic review and meta-analysis	Y	Fresh meat from beef, veal, lamb, pork, hamburgers, and meatballs	Y	Poultry (chicken and turkey), and rabbit.	N	N/A	Y	Y	N	N	N
New observational studies											
Bernstein[1] (2010), prospective cohort study (NHS)	Y	Not defined	Y	Chicken with and without skin.	N	N/A	N	Y	N	N	N
Von Ruesten (2013), prospective cohort study (EPIC-Potsdam)	Y	Beef, hamburger/meat loaf, Bolognese sauce, pork, smoked pork, veal, lamb, rabbit	Y	Poultry (turkey and chicken)	N	N/A	Y	N	N	N	N

Haring (2014), prospective cohort study (ARIC)	Y	Not defined	Y	Poultry (but not further defined)	N	N/A	N	Y	N	N	N
Haring (2015), prospective cohort study (ARIC)	Y	Not defined	Y	Poultry (but not further defined)	N	N/A	N	N	Y	Y	Y

IS, ischemic stroke, HS, Haemorrhagic stroke.

[1] Some cohorts investigated incident total CVD (including both fatal and non-fatal events), whereas others investigated CVD mortality only.

[2] Some cohorts investigated incident total CHD (including both fatal and non-fatal events), whereas others investigated CHD mortality s only.

New observational studies investigating unprocessed meat intake and risk of heart failure related outcomes

Study	Red meat		White meat		All unprocessed meat		Outcomes	
	Yes/No	Definition	Yes/No	Definition	Yes/No	Definition	Incident HF	HF mortality
Kaluza (2014), prospective cohort study (Cohort of Swedish Men)	Y	Pork, beef/veal and minced meat. Authors noted specifically that minced meat is generally prepared without food additives in Sweden and hence considered as unprocessed red meat.	N	N/A	N	N/A	Y	Y
Kaluza (2015), prospective cohort study (Swedish	Y	Pork, beef/veal and minced meat. Authors noted specifically that minced meat is generally prepared without food additives in	N	N/A	N	N/A	Y	N

Mammography Cohort)		Sweden and hence considered as unprocessed red meat.						

New observational studies investigating unprocessed meat intake and weight gain

Study	Red meat		White meat		All unprocessed meat	
	Yes/No	**Definition**	**Yes/No**	**Definition**	**Yes/No**	**Definition**
Vergnaud (2010), prospective cohort study (EPIC-PANACEA)	Y	Beef, veal, pork and lamb	Y	Poultry (chicken, and in some cohorts, turkey and rabbit)	N	N/A
Smith (2015), (Nurses' Health Study, Nurses' Health Study II and Health Professionals Follow-Up Study)	Y	Hamburger, beef, lamb and pork	N	N/A	N	N/A

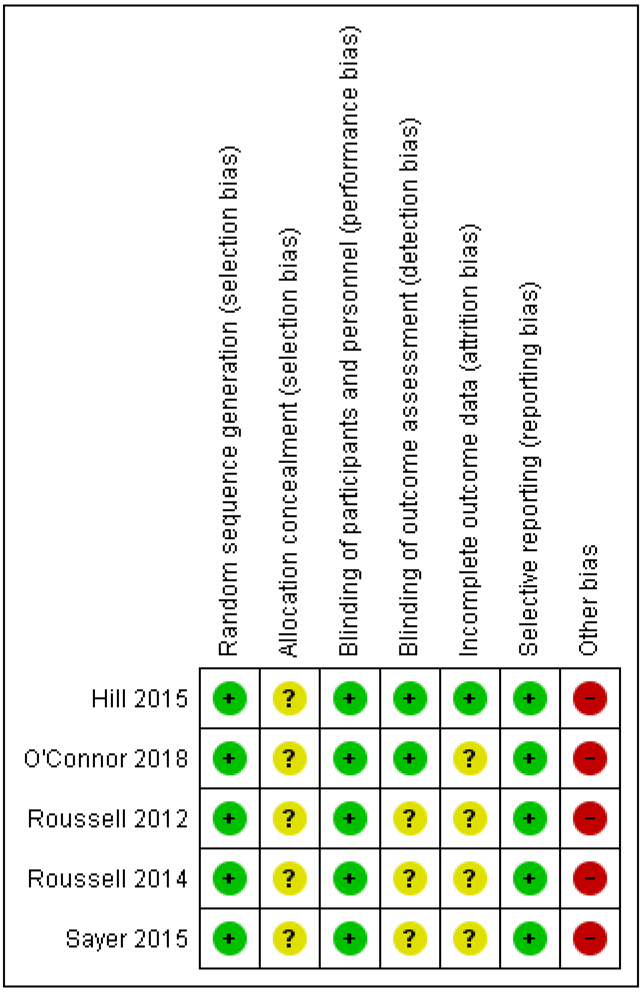
Appendix 5

TABLE 1
BOLD study diets: energy, nutrient composition, and food-group servings[1]

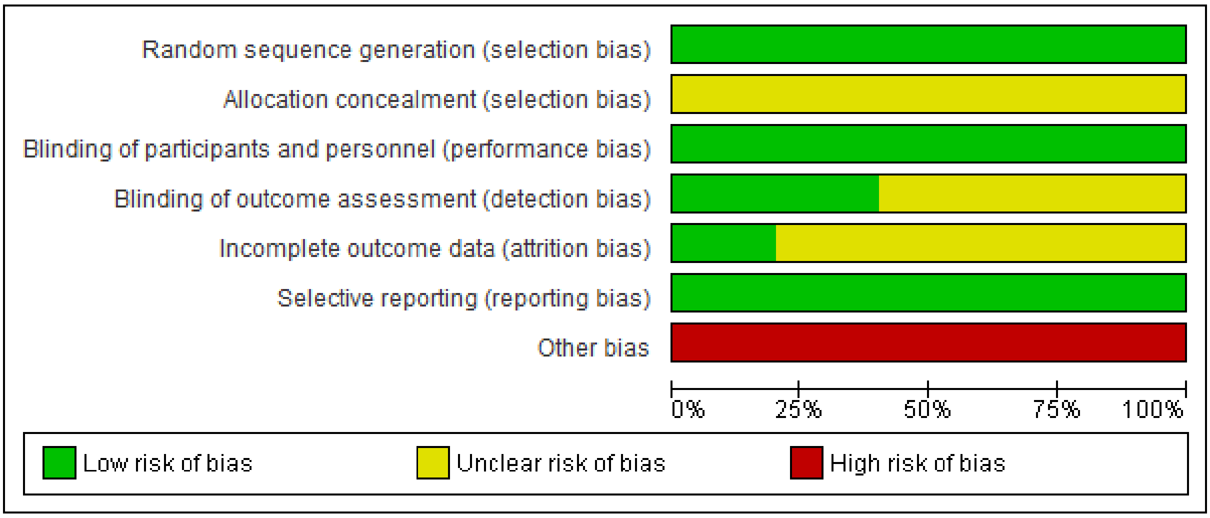
	Diets			
	HAD	DASH	BOLD	BOLD+
Nutrient targets				
Calories	2097	2106	2100	2104
Protein (g; percentage of kcal)	17 (91.7)	18 (98.4)	19 (99.6)	27 (145.6)
Carbohydrates (g; percentage of kcal)	50 (268.1)	55 (298.3)	54 (287.4)	45 (243.7)
Fat (g; percentage of kcal)	33 (77.0)	27 (64.4)	28 (65.8)	28 (66.6)
Cholesterol (mg)	287	188	168	193
SFA (g; percentage of kcal)	12 (27.9)	6 (15.2)	6 (15.4)	6 (14.5)
PUFA (g; percentage of kcal)	7 (15.5)	8 (18.9)	7 (16.5)	7 (16.1)
MUFA (g; percentage of kcal)	11 (25.9)	9 (21.8)	11 (25.2)	12 (29.3)
Fiber (g)	24	36	32	38
Sodium (mg)	3243	2982.8	2712	3344
Potassium (mg)	3259	4247	3998	4417
Calcium (mg)	993	1140	936	1060
Magnesium (mg)	308	403	392	429
Food groups (servings/d)				
Fruit and juices (cups)	3.1	4.1	4.5	3.4
Vegetables (cups)	3.2	4.3	3.9	4.6
Grains (oz)	8.3	4.5	5.6	5.3
Low-fat dairy products (cups)	1.2	2.3	1.8	4.7
High-fat dairy products (cups)	0.7	0.1	0.0	0.0
Legumes, nuts, seeds, and other vegetable protein (oz)	0.6	2.1	1.3	4.2
Beef (oz)	0.7	1.0	4.0	5.4
Poultry, pork, and fish (oz)	3.7	3.7	1.0	1.0
Egg and egg-product substitutes (oz)	0.24	0.2	0.1	0.9
Fats and oils (g)	5.4	4.0	4.3	1.4

[1] On the basis of 2100 kcal/d. Average across a 6-d menu cycle. All values were determined by using Nutritionist Pro software (Axxya Systems LLC). BOLD, Beef in an Optimal Lean Diet; BOLD+, Beef in an Optimal Lean Diet plus additional protein; DASH, Dietary Approaches to Stop Hypertension; HAD, healthy American diet; SFA, saturated fatty acid.

Appendix 6



Risk of bias summary: review authors' judgements about each risk of bias item for each included study in Question 3



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies in question 3

Appendix 7

TABLE 3
Prescribed daily and weekly food group servings for the median energy intake level[1]

	Med-Red	Med-Control
Servings of fruit/d,[2] *n*	4	4
Servings of vegetables/d,[3] *n*	7	8
Dark green vegetables	1	2
Red and orange vegetables	1	1
Legumes	1	1
Starchy vegetables	1	1
Other vegetables	3	3
Servings of grains/d,[4] *n*	4	5
Whole grains	4	4
Refined grains	0	1
Protein-rich foods/wk,[5] g		
Red meat	476	196
Poultry	112	420
Seafood	336	336
Whole eggs	2	3
Nuts, seed, soy[6]	560	616
Servings of dairy/d,[7] *n*	3	2
Olive oil/wk,[8] g	247	247
14-point Mediterranean Diet Assessment Tool Score (20)	12	13

[1]Food group servings presented for representative 2492 kcal Med-Red and Med-Control diets averaged across a 7-d menu cycle. Med-Control, Mediterranean-style eating pattern with ~200 g lean, unprocessed red meat/wk; Med-Red, Mediterranean-style eating pattern with ~500 g lean, unprocessed red meat/wk.

[2]Half a cup or 1 medium fresh fruit.

[3]Half a cup of fresh or 1 cup of cooked vegetables.

[4]28 g = half a cup or 1 oz.

[5]28 g = 1 oz; cooked weights.

[6]28 g = 1 tbsp of nut butter, 0.5 oz of nuts or seeds, or ~1 oz-equivalent.

[7]1 cup of milk or yogurt.

[8]4.5 g = 1 tsp.

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