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REVIEW

A summary of meat intakes and health burdens

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This review summarizes published meta-analysis outcomes on the associations between meat intakes and burden of diseases. A novel assessment process was developed, combining selected Cochrane Review measures, AMSTAR checklist, and other quality measures identified by authors during preliminary phases of the review process. Meat intakes have been found to be statistically significant associated with 21 burden of diseases. A total of 37 risk-outcome best dose–response estimations were identified, all were positively associated, and 21 of them with low to moderate, or insignificant heterogeneity. The highest dose–responses per 50 g increases in processed meat intake at 95% confident levels were 1.81 (1.32, 2.48) for esophageal cancer, 1.71 (1.34, 2.19) for stomach cancer, 1.42 (1.07, 1.89) for CHD, 1.32 (1.19, 1.48) for diabetes, and 1.24 (1.13, 1.35) for colon cancer incidences, and 1.24 (1.09, 1.40) for CVD mortality. The highest dose–responses per each 65 g increases in total red meat intake were 1.36 (1.16, 1.58) for endometrial cancer, 1.25 (1.10, 1.41) esophageal cancer, and 1.22 (1.16, 1.23) for lung cancer incidences. In addition, 14 statistically significant associations in terms of high vs low meat intake relative risks were also identified. Total red meat intakes were found negatively associated with CVD and cancer mortalities, and poultry meat intakes were found negatively associated with all-cause and cancer mortalities, and rectal cancer incidences in low meat consumption Asian countries. Current global and dietary Comparative Risk Assessments may underestimate burden of diseases attributed to meat intakes. More investigation is needed in low-meat consumption countries.

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INTRODUCTION

Driven by an expanding global population with increasing disposable incomes, along with globalization and changing food preferences, global meat consumption has more than doubled in the past two decades and demand for meat is expected to increase rapidly.[1,2] High meat intake has long been linked to increased risk of non-communicable diseases (NCDs), mainly cardiovascular diseases (CVDs), cancers and diabetes. Meanwhile, the International Agency for Research on Cancer recently reclassified processed meat as Group 1 (carcinogenic) and red meat as Group 2A (probably carcinogenic) cancer risks.[3] Globally, it is estimated that NCDs are responsible for more deaths than all other causes combined.[4] In 2008 NCDs accounted for 63% of global deaths, and are expected to increase by a further 44% by 2030.[4,5] The World Health Organization have identified diet as a major behavior risk factor for NCDs, a risk that could be minimized through well-understood, cost-effective and feasible interventions.[4]

Comparative risk assessment of burden of disease is a decision-making tool for estimating the fractions of burden of disease attributable to changes in exposure distributions.[6–8] In a recent comparative risk assessment of global burden of diseases,[9] high processed meat intake was ranked the 22nd leading risk factor and contributed to 840857 deaths worldwide in 2010, while high red meat intake contributed to 38092 deaths. However, in this report meat intake assessments were assessed only regarding colon and rectal cancers, diabetes and coronary heart disease, and the literature sources of the relative risks used[10–12] in the evaluation were not up to date.[13–16] Also processed meat have been found significantly associated with a range of other burden of diseases, including all-cause, CVD and cancer mortalities,[16–18] risks of stroke[19,20] and other cancer.[21–32] Comparative risk assessment was also used to evaluate burden of diseases attributable to decreased exposure to dietary meat intakes in counterfactual scenarios[33–36] with results suggesting that shifting from a predominantly meat to plant-based diet could reduce CHD, stroke, total cancer, diabetes and colorectal cancer risks, and as well as greenhouse gas emissions. Again, comparative risk assessments in these studies only reflected a fraction of the total health impacts, and the evaluation outcomes were mostly not comparable, because different risk factors and dose–responses were used to evaluate the same disease outcomes.[37]

In a comparative risk assessment of burden of diseases attributable to dietary shift, study population baseline dietary intake levels, dietary shift assumptions, risk factors for each disease outcome and dose–response for each risk factor-disease outcome relationship are major inputs, and the evaluation outcome measures being burden of the associated diseases. While in the past three decades over a thousand studies have investigated the associations of meat, and plant-based food with individual NCDs, no summary report on dose–response relative risks covering the full range of potential burden of diseases associated with specific meat types was found. Consistent and comparable information on health outcomes, risk factors, dose–response relative risks and intervention designs at population levels are needed in comparative risk assessment of burden of diseases attributable to dietary alternatives in order to support healthy and sustainable dietary policy-making, planning and promotion. Decision-makers and professionals also need good information on the uncertainties and limitations in

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decision-making evaluations. This review aimed to identify statistically significant risk factors, best identifiable relative risk inputs, as well as associated diseases attributable to meat intakes from published meta-analyses for future comparable and better quality comparative risk assessment of burden of diseases attributable to meat intakes.

METHODS

Meat definitions in this review

Red meat: meat derived from bovine, ovine, pig and other mammalian species.

Poultry meat: meat derived from fowl, such as chickens, turkeys, ducks and geese.

Processed meat: meat products having a minimum of 30% meat that has undergone a method of processing other than boning, slicing, dicing, mincing or freezing,[38] including salted, smoked, cured/dried or fermented meats such as ham, sausage and biltong and luncheon meats.

Total meat: includes poultry and red meat. In some studies this may also have included fish, seafood, and egg products.

INCLUSION CRITERIA FOR STUDIES

Study types

Meta-analyses provide more robust estimates when compared to individual observational studies, and given the uncertainty of any meat component being a true causal factor, only meta-analyses examining the direct associations between human diseases and fresh and/or processed poultry and/or red meat were considered for this review. Estimates of specific biological components that do not reflect the total effects of actual intakes were not included. Studies were included in the review if they quantified the pooled relative risks directly associated with intake level ranges, or levels in grams or servings which could be converted to grams of specific meat groups. Meta-analyses of studies investigating the following were excluded:

1. Associations of diseases with sub-food-group intakes under the red meat, poultry meat, fruit and vegetable groups.
2. Associations of diseases with total white meat. However white meat such as fish, seafood and egg products may be included in some study estimates of total meat.
3. Associations of diseases with food biomarkers.
4. Associations of disease biomarkers with foods.
5. Associations of diseases with general dietary patterns.
6. Associations of disease biomarkers with general dietary patterns.
7. Associations of diseases with different cooking methods.

Types of outcome measures

Two major categories of outcome measures were considered:

1. Incidence and/or mortality relative risks (RR), odds ratios (OR) or hazard ratio (HR) over a time span for high vs low food intakes with 95% confidence interval (CI), with *P*-value provided.
2. Incidence and/or mortality relative risks (RR), odds ratios (OR) or hazard ratio (HR) over a time span per gram(s) of meat with 95% confidence interval (CI), with *P*-value provided.

LITERATURE SEARCH

To identify relevant publications, systematic searches were conducted according to Cochrane guidelines[39] in PubMed, Ovid, EBSCOhost, Google Scholar databases, Australian Institute of Health and Welfare and World Cancer Research Fund International websites without pre-specified limits. A combination of terms used in the search included 'food', 'meat', 'health', 'cardiovascular disease', 'CVD', 'cancer', 'diabetes', 'mortality', and "meta-analysis'. Within the Cochrane Database the terms 'meat' in title, abstract or key words were searched. Potential abstracts were retrieved and screened. Identified potential full-texts were then retrieved for further analysis. Additional potential full-texts identified from reference lists of screened reports were also searched, and where possible retrieved and screened. All studies meeting the selection criteria were included in the review.

DATA EXTRACTION FROM EACH META-ANALYSIS

Descriptive data on authors, year of the meta-analysis publication, study design, number of component studies, countries involved and publication year range of component studies, intake meat types, types of disease outcomes, association outcome orientations (positive, negative or insignificant), pooled relative risks at 95% confidence level, and heterogeneities were extracted. If the characteristics of the component studies were not provided in any meta-analysis, the original full-text of the component studies were retrieved.

IDENTIFICATION OF STATISTICALLY SIGNIFICANT RISK-OUTCOME PAIRS AND THE BEST ESTIMATES

At 95% confidence level if the *P*-value of an estimation is < 0.05, the association was regarded as statistically significant, else insignificant. For a risk-outcome pair where multiple meta-analyses were identified:

1. If all $P < 0.05$, then the outcome of the meta-analysis which included the most up-to-date component studies were taken as the best estimate,
2. If both $P < 0.05$ and $P \geqslant 0.5$ coexist, characteristics and inclusion criteria of each identified meta-analysis were examined and compared against each other. On the basis of the common specific characteristics of component studies included in the Meta-analyse identified by the authors during the preliminary phases of the review process, following decision rules were used:

   a If a meta-analysis captured all the component studies of the other meta-analyses then the outcome of the meta-analysis was taken as the best estimate.
   b If the latest meta-analysis did not captured all component studies in other meta-analyses:
      i If the number of component studies included in each of the meta-analysis < 5, then the investigations were regarded as inconclusive.
      ii If the number of component studies included in any of the meta-analyses $\geqslant 5$, and no valid reason of exclusion were found:
         1. The outcome of the meta-analysis that covered at least 80% of the most up-to-date component studies captured in other meta-analyses was taken as the best estimate.
         2. Otherwise the investigations were considered as inconclusive.

IDENTIFICATION OF THE BEST DOSE–RESPONSE

Statistically significant risk-outcome pairs were further assessed to identify the best identified dose–responses or the best identified high vs low intake relative risk estimates in case dose–responses were not provided. GRADE is a well-developed system for assessing the quality of scientific evidence in systematic reviews.[40] Whereas AMSTAR is a measurement tool specifically

established to assess the methodological quality of systematic reviews. Given that this study is a systematic review of systematic reviews which included meta-analyses and AMSTAR assesses whether systematic reviews conducted are of high quality, AMSTAR is used in this study. AMSTAR not only evaluates whether the scientific quality of the included studies were assessed but also whether they were used appropriately in formulating conclusions, as well as whether the methods used to combine the findings of studies were appropriate.[41] Out of a maximum AMSTAR score = 11, AMSTAR quality levels were assigned as follow: high $\geqslant$ 9, 9 $\leqslant$ moderate $\geqslant$ 6, questionable $<$ 6 and assessed.

For a risk-outcome pair:

1. If only one meta-analysis was found, estimate from this meta-analysis was taken as the best identified estimate/dose–response.
2. If multiple meta-analyses were found in a risk-outcome pair, the best identified estimate/dose–response priorities were given to the following characteristics.

   a The meta-analysis outcome providing specific dose–measure which can be converted into game (g) instead of measuring range.
   b The meta-analysis that included the most up-to-date component studies captured in other meta-analyses.
   c The meta-analysis providing specific heterogeneity (I^2) and $P_{Heterogeneity}$ value.
   d The estimate with the lower I^2-value and/or higher $P_{Heterogeneity}$ value.
   e The estimate with higher AMSTAR score.

For each best identified dose–response, ratio and assigned weight percentage of association orientations of component studies, and number of component studies adjusted for total energy intakes were also record.

PRESENTATION OF MAIN FINDINGS

Structured narrative presentation of the results, and in figures and tables. Given that processed meat is often taken in smaller serving size, dose–responses were normalized to per serving increases: per 50 g/day[3] increase for processed meat and per 65 g/day increase for red meat,[42] and other meat.

RESULTS

Included reports

Initially 706 abstracts were identified, of which 645 were excluded as irrelevant, not meeting the inclusion criteria, or duplicates, and 61 full-text reports were retrieved. An additional six full-text reports were identified from reference lists of these reports. A total of 67 full-text reports were retrieved and evaluated, 15 of which did not fully meet the selection criteria and were excluded. The remaining 52 reports[10–32,43–71] were included in the final review (Figure 1). All reports were published between 2001 and 2015. In most, pooled high vs low food intake relative risks were estimated. However, exact quantities of 'high' and 'low' intakes in component studies were not uniform, and often undefined. Component studies included were predominantly conducted among high meat consumption populations in America and Europe, whereas few component studies were conducted in low meat consumption populations in Asia. Each meta-analysis included between two to 50 component studies, and high and/or statistically significant heterogeneity often reported. Each meta-analysis included component studies adjusted for different combinations of between one to $>$20 different confounders. In multiple meta-analyses that examined a specific risk-outcome pair, a high level of duplication of component studies was seen, particularly in the most recent published meta-analyses often included most of the component studies included in meta-analyses published in earlier years (often one or two component studies differences). Most meta-analyses reported consistent outcomes regardless the publication years and study qualities. Few meta-analyses reported full adjustment for total energy.

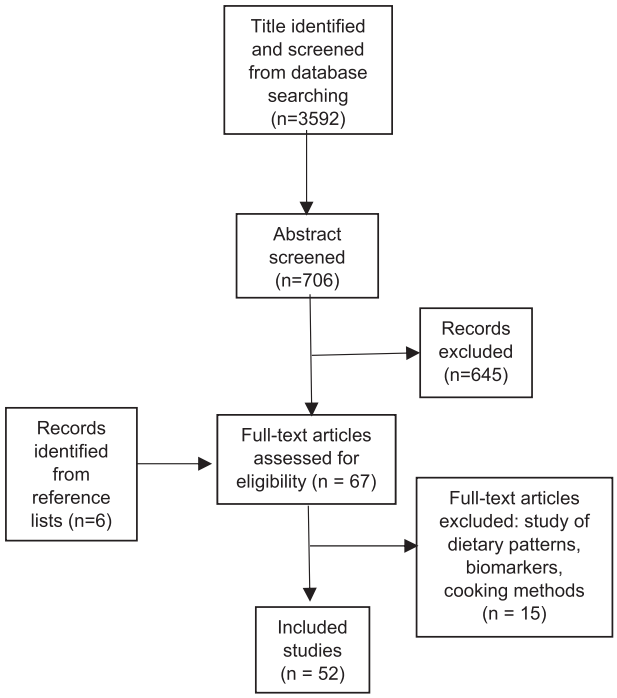


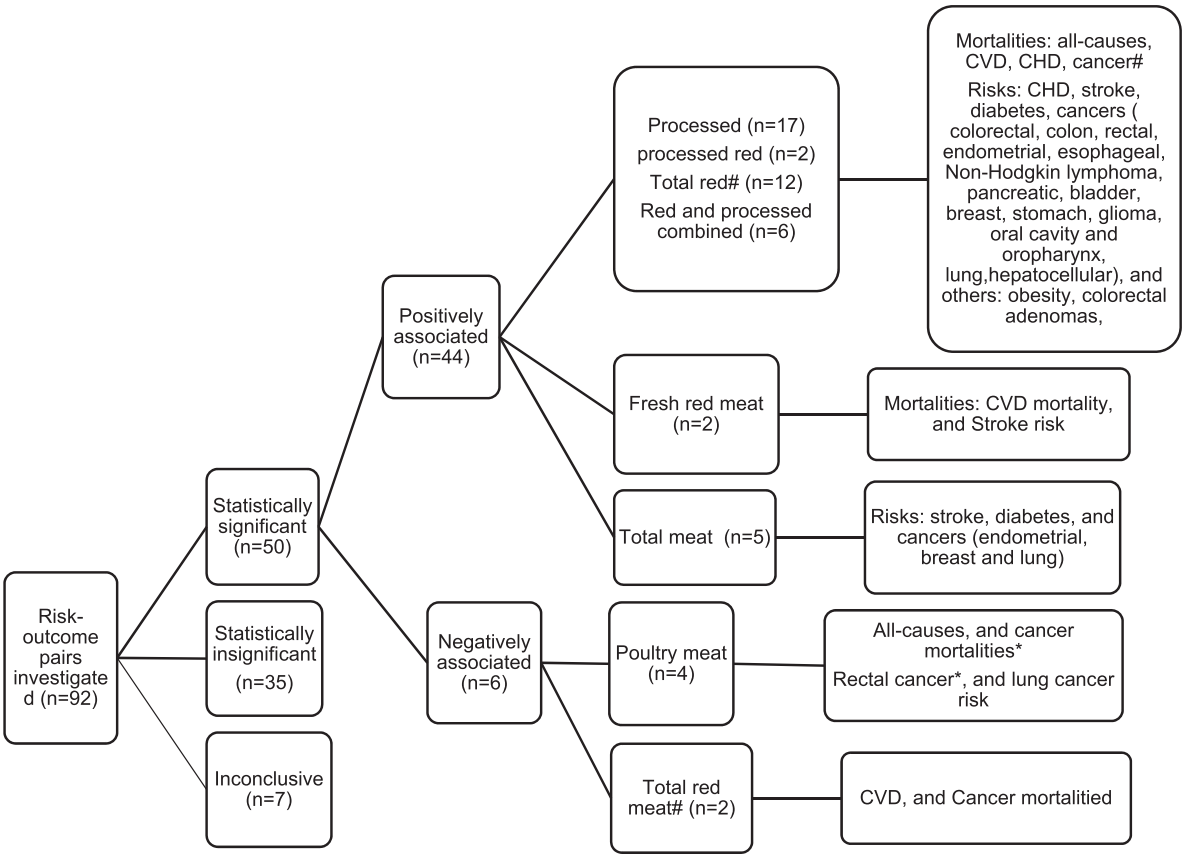
Figure 1. Literature searching flow chart.

Identified statistically significant risk-outcome pairs

Within the 52 meta-analysis study reports reviewed (Supplementary Information A1), a total of 92 risk-outcome associations were investigated (Figure 2), of which 50 risk-outcomes were assessed as statistically significant. As some reports investigated multiple associations of multiple food groups, the sum of the number of reported associations presented in tables, figures and texts may exceed the total number of reviewed reports. Processed meat was involved in 42 statistically significant positive associations and linked to 21 different burden of diseases (Table 1). Only two positive associations were reported between fresh red meat intakes and one each for CVD mortalities and stroke incidences. Five positive associations were found between total meat intakes and stroke, diabetes, endometrial cancer, breast cancer and lung cancer incidences. Poultry meat was negatively associated with lung cancer incidences. Among low meat consumption populations in Asia, poultry meat intakes were negatively associated with all-cause and cancer mortalities[55] and rectal cancer incidences.[62]

The best identified dose–responses

A total of 37 risk-outcome pairs provided dose–responses from 24 reports (Table 2). The best identified dose–responses were identified from 17 reports[12–14,16–26,31,53,70] and seven reports[10,15,54,61,65,66,72] were excluded (reasons of exclusion were stated in Table 2). All the best identified dose–responses were obtained from methodological high quality systematic reviews, with AMSTAR score $\geqslant$ 9, except three estimates from Feskens *et al.*[13] and one from Larsson *et al.*[53] which AMSTAR score = 7



total red meat was +ve associated to CVD mortality in (Wang *et al*.[18]) including component studies of 2US 2 US and 1 Japan , and -ve associated with men in (Lee *et al*.[55]) including component studies of 8 Asian countries; +ve associated to cancer mortality in (Wang *et al*.[18]) including component studies of 2US , and -ve in women in (Lee *et al*.[55]) including component studies of 8 Asian countries.

*in low meat consumption populations

Figure 2. Number of investigated associations between meat intakes and burden of diseases.

(Table 3, Figure 3). Sixteen of these best identified dose–responses estimations, involving CVD and cancer mortalities, stroke incidences, and colorectal, colon, endometrial, pancreatic, breast and stomach cancer incidences, which presented low and or insignificant heterogeneity of $I^2 < 40\%$, and $P_{Heterogeneity} > 0.1$ respectively. Five of these best identified dose–responses estimations, involving diabetes, and colorectal, colon, and esophageal cancer incidences presented moderated heterogeneity of $30\% < I^2 < 60\%$.[73] Three best identified dose–responses did not provide heterogeneity information and the other 13 presented substantial heterogeneities. All estimates were biased toward high-meat consumption populations, especially in Europe and America, except those from Lee *et al*.[55] and Pham *et al*.[62] which examined low-meat consumption populations in Asia. However no statistically inconsistent outcome was found except the association between total red meat and cancer mortalities, where Lee *et al*.[55] found negative association for women in low meat consumption population in Asian countries while Wang *et al*.[18] found positive association in high-meat consumption population in the US. This may reflect a benefit-to-harm threshold effect of amount of meat consumed with outcomes. Only seven of the best identified dose–responses were fully adjusted for total energy intakes.

Comparisons of processed meat intake best identified dose–responses revealed the highest dose–response was an 81% increases in esophageal cancer[23] per each 50 g increases in processed red meat intakes, following by 71% increases in stomach cancer,[53] 42% increases in CHD,[12] 37% increases in esophageal cancer,[22] 32% increases in diabetes,[13] 24% increases in colon cancer incidences[16] and 24% increases in CVD mortalities[17] per each 50 g increases in processed meat intakes. The highest dose–response per each 65 g increases in total red meat intake were 36% increases in endometrial cancer,[21] 25% increases in esophageal cancer[23] and 22% increases in lung cancer[31] incidences. Each 65 g increases in total meat intake also associated with 22% increases in endometrial cancer (Bandera *et al*.[21]), 15% increases in stroke,[12] 10% increases in diabetes incidences,[13] respectively (Table 3, Figure 3).

High vs low intakes

A total of 14 statistically significant associations from nine reports[30,32,49,55,56,60,62,63,69] provided high vs low intake relative risks but no dose–responses (Table 4, Figure 4), eight were positively associated with incidences of lung, breast and bladder, oral cavity and oropharynx cancer, glioma, and Non-Hodgkin lymphoma, as well as obesity. The highest high vs low intake relative risk was 91% increased oral cavity and oropharynx cancer incidences[32] for high processed meat intakes, followed by 39% increased breast cancer[60] and 35% increased lung cancer incidences[30] for high total meat intakes, and 32% in obesity[63] for high red and processed meat intakes. The remaining six negative association involved poultry, and total red meat intakes in low meat consumption populations in Asia. For these studies, the highest reported decreases in risk was 20% decreased rectal cancer when compared high vs low poultry intakes,[62] 7–15%

Table 1. Invested meat intake risk-outcome pairs and assessment outcomes

Association	*Processed meat*	*Fresh red meat*	*Processed red meat*	*Total red*	*Red and processed meat*	*Poultry meat*	*Total meat*
Incidence							
All-cause mortality	+ve	insig		+ve			insig
CVD mortality	+ve	+ve		+ve		insig	insig
CHD mortality	insig	insig					insig
Cancer mortality	+ve	insig		+ve			insig
CHD	+ve			insig	insig		
Stroke	+ve	+ve		+ve	+ve		+ve
Diabetes	+ve	insig		+ve	+ve	insig	+ve
Kidney cancer	insig			insig			
Colorectal cancer	+ve			Inc	+ve	insig	insig
Colon cancer	+ve			+ve	+ve		insig
Rectal cancer	Inc			Inc	+ve		insig
Endometrial cancer				+ve		insig	+ve
Esophageal cancer	+ve		+ve	+ve		Inc	Inc
Non-Hodgkin lymphoma			+ve	+ve			
Ovarian cancer	Inc			Inc		insig	insig
Pancreatic cancer	+ve			insig			
Bladder cancer	+ve			insig		insig	insig
Thyroid Cancer							insig
Breast cancer	+ve			+ve			+ve
Prostate cancer	insig			insig			
Stomach cancer	+ve			+ve			
Glioma	+ve			insig			
Oral Cavity and Oropharynx Cancer	+ve			insig			insig
Lung cancer	+ve			+ve		−ve	+ve
Colorectal adenomas	+ve			+ve			
Hepatocellular carcinoma	insig			insig			insig
obesity					+ve		
Investigation outcomes in low meat consumption countries							
All-cause mortality						−ve	
CVD mortality				-ve in men			
Cancer mortality				-ve in women		−ve	
Rectal cancer						−ve	

+ve: statistically positively associated; −ve: statistically negatively associated; insig: statistically insignificant association. Inc: inconclusive-mixed results including both statistically significant and insignificant association results.

decreased mortalities when compared high vs low total red, or poultry meat intakes in low meat consumption populations.[55]

DISCUSSION

Summary of main results

Meat and meat products have long been suspected risk factors for CHD, stroke, diabetes and colorectal cancer. This review used a combination of published systematic review tools along with selection algorithm developed during the review process identified and assessed 52 meta-analysis reports of the associations between meat intakes and burden of diseases published between 2001 and 2015. It assimilated studies and found that different types and combination of meat intakes were statistically positively associated with 21 different burden of diseases (Tables 3 and 4). The association between meat intakes and burden of diseases may be negative among low-meat consumption populations (Tables 1 and 4). The review outcomes suggest current comparative risk assessment of burden of diseases and dietary evaluations[9,33–36] may have underestimated the burden of disease attributed to meat intakes.

Potential biases in the review process

The published systematic review tools used in this review are designed to minimize potential biases and well-validated. The quality assessment protocol and the algorithm used were tailored to capture the specific characteristics of interest in the targeted meta-analyses, and were clearly defined to ensure consistent systematic evaluation of each meta-analysis. The broad range of databases and combination of search terms with and without the 'meta-analysis' term ensured as many relevant studies were identified as possible and minimized exclusion of relevant studies that met the well-defined selection criteria. Additional hand-searching compensated for insufficiencies in the database searches. Direct impacts of dietary meat were reviewed in preference to biological components such as the serum cholesterol concentration and saturated fat used in current comparative risk assessments in dietary shift studies,[34,35,74] and disease incidence and/or mortality instead of biomarker risk factor, minimizing uncertainty that any food constituent is a true causal factor, and providing utility for non-specialists. Not declaring conflict of interest, and/or including gray literature searching were the most common areas, where the assessed studies lost AMSTAR scores. However, because of the high level of duplication in component studies among the competing meta-analyses, including higher number of the most recent analyses were given the priorities. Additional clearly defined procedures to handle inconsistencies also further ensure the quality of the best identified dose–responses. Therefore, every effort has been made to minimize potential bias and ensure integrity.

Table 2. Included reports providing meat intake dose–response and reasons of the best identified dose–response selections

Burdens	*Meat types*	*Identified Studies provided Dose–response AMSTAR score (#)*	*Studies selected as best estimates*	*Studies excluded reasons*
Mortality				
All-cause	Processed	(Abete *et al.*[9,17]) (Wang *et al.*[11,18])	(Wang *et al.*[18])	Abete *et al.* has lower AMSTAR score
	Total red	(Wang *et al.*[11,18])	(Wang *et al.*[18])	
CVD	Processed	(Abete *et al.*[9,17]) (Wang *et al.*[11,18])	(Abete *et al.*[17])	Both included same components exact Wang *et al.* included a report published in 1999 vs Abete *et al.* included another report 2005, Abete missing AMSTAR score (missing questions 2, 4) did not contribute to the differences
	Fresh red	(Abete *et al.*[9,17]) (Wang *et al.*[11,18])	(Abete *et al.*[17])	
	Total red	(Wang *et al.*[11,18])	(Wang *et al.*[18])	
Cancer	Processed	(Wang *et al.*[11,18])	(Wang *et al.*[18])	
	Total red	(Wang *et al.*[11,18])	(Wang *et al.*[18])	
Incidences				
CHD	Processed	(Micha *et al.*[11,12])	(Micha *et al.*[12])	
Stroke	Processed	(Chen *et al.*[9,20]) (Micha *et al.*[11,12]) (Kaluza *et al.*[9,19])	(Chen *et al.*[20])	Chen *et al.* included Micha *et al.* Kaluza *et al.* no specific dose but dose range
	Fresh red	(Chen *et al.*[9,20]) (Micha *et al.*[11,12]) [in] (Kaluza *et al.*[9,19])	(Chen *et al.*[20])	
	Total red	(Kaluza *et al.*[9,19])	(Kaluza *et al.*[19])	
	Red and processed	(Chen *et al.*[9,20])	(Chen *et al.*[20])	
	Total meat	(Micha *et al.*[11,12])	(Micha *et al.*[12])	
Diabetes	Processed	(Feskens *et al.*[7,13]) (InterAct Consortium[14]) (Pan *et al.* 2013) (Micha *et al.*[11,12])	(Feskens *et al.*[13])	Feskens *et al.* included Pan *et al.*, InterAct Consortium, Micha *et al.*
	Total red	(Feskens *et al.*[7,13])	(Feskens *et al.*[13])	
	Total	(Feskens *et al.*[7,13]) (InterAct Consortium[14])	(Feskens *et al.*[13])	Feskens *et al.* included InterAct Consortium
	Red and processed	(InterAct Consortium[14])	(InterAct Consortium[14])	
Colorectal cancer	Processed	(Alexander *et al.*[15,44,45])[8] (Chan *et al.*[9,16]) (Larsson and Wolk[7,54]) (Norat *et al.*[7,61]) (Sandhu *et al.*[8,65]) (WCRFI-AICR[10]) (unclear)	(Chan *et al.*[16])	Alexander *et al.* included studies unclear, others less up to date, and have lower AMSTAR score
	Red and processed	(Chan *et al.*[16])	(Chan *et al.*[16])	
Colon cancer	Processed	(Chan *et al.*[9,16]) (Larsson and Wolk[7,54]) (Norat *et al.*[7,61])	(Chan *et al.*[16])	
	Total red	(Chan *et al.*[9,16]) (Larsson and Wolk[7,54]) ([7,61] (Smolinska and Paluszkiewicz[8,66])	(Chan *et al.*[16])	Smolinska and Paluszkiewicz heterogeneity unclear, others less up to date, and have lower AMSTAR score.
	Red and processed	(Chan *et al.*[16])	(Chan *et al.*[16])	
Rectal cancer	Red and processed	(Chan *et al.*[16])	(Chan *et al.*[16])	
Endometrial cancer	Total red	(Bandera *et al.*[10,21])	(Bandera *et al.*[21])	
	Total meat	(Bandera *et al.*[10,21])	(Bandera *et al.*[21])	
Esophageal cancer	Processed	(Huang *et al.*[10,22])	(Huang *et al.*[22])	
Esophageal cancer	Processed red	(Qu *et al.*[10,23])	(Qu *et al.*[23])	
	Total red	(Huang *et al.*[10,22]) (Qu *et al.*[10,23])	(Qu *et al.*[23])	Huang *et al.* included less component studies (7 vs 11) and higher heterogeneity
Pancreatic cancer	Processed	(Larsson and Wolk[9,24])	(Larsson and Wolk[24])	
Breast cancer	Processed	(Guo *et al.*[9,25])	(Guo *et al.*[25])	
	Total red	(Guo *et al.*[9,25])	(Guo *et al.*[25])	
Stomach cancer	Processed	(Larsson *et al.*[7,53])	(Larsson *et al.*[53])	
	Total red	(Song *et al.*[10,26])	(Song *et al.*[26])	
Lung cancer	Processed	(Xue *et al.*[11,31])	(Xue *et al.*[31])	
	Total red	(Xue *et al.*[11,31])	(Xue *et al.*[31])	
Colorectal adenomas	Processed	(Xu *et al.*[10,70]	(Xu *et al.*[70])	
	Total red	(Xu *et al.*[10,70])	(Xu *et al.*[70])	

BID: the best identified dose–response.

Table 3. Characteristics of the best identified dose–responses of meat intakes and burden of diseases

Meta-analysis Studies	*Health outcomes*	*Number of studies and countries included*	*Study years*	*Number of studies adjusted for energy intakes*	*Heterogeneity I^2 %, $P_{Heterogeneity}$*	*RR (95% CI), /50g processed meat, /65g meat*	*AMSTAR Scores, max. 11*	*Significant: insignificant ratio, and weight (%)*[a]
Processed meat								
(Wang *et al.*[18])	All causes mortalities	3 US, 2 EU	1999–2013	2	75, <0.01	1.15 (1.11, 1.19)	11	5:3[93]
(Abete *et al.*[17])	CVD mortalities	3 US, 1 Australia, 2 Asia, 3 EU	2005–2013	1	76.4, 0.001	1.24 (1.09, 1.40)	9	4:2[71]
(Wang *et al.*[18])	Cancer mortalities	3 US, 2 EU	1999–2013	1	0, 0.450	1.08 (1.06, 1.11)	11	5:2[99]
(Micha *et al.*[12])	CHD incidences	2 US, 2 EU, 1 Australia	1999–2009	3	$P=0.04$	1.42 (1.07, 1.89)	11	4:2[95]
(Chen *et al.*[20])	stroke incidences	1 US, 1 EU, 1 Asia	2003–2012	2	23, 0.268	1.11 (1.02, 1.20)	9	3:2[68]
(Feskens *et al.*[13])[b]	Diabetes incidences	8 US, 12 EU, 1 Australia	2001–2012	21	89	1.32 (1.19, 1.48)	7	Not provided
(Chan *et al.*[16])	Colorectal cancer incidences	4 US, 4 EU, 1 Australia	1999–2009	7	12.2, 0.333	1.18 (1.10, 1.28)	9	3:6[70]
(Chan *et al.*[16])	Colon cancer incidences	4 US, 3 EU, 1 Asia, 1 Australia	1994–2001	7	0, 0.649	1.24 (1.13, 1.35)	9	4:6[59]
(Huang *et al.*[22])	Esophageal cancer incidences	4 US, 3 EU	1997–2012	4	71,0, 0.002	1.37 (1.03, 1.81)	10	Not provided
(Larsson and Wolk[24])	Pancreatic cancer incidences	3 US, 3 EU, 1 Asia	2002–2009	5	0, 0.46	1.19 (1.04, 1.36)	9	1:8[13]
(Guo *et al.*[25])	Breast cancer incidences	7 studies, 4 US, 3 EU	2007–2013	6	$P>0.1$	1.09 (1.03, 1.16)	9	Not provided
(Larsson *et al.*[53])	Stomach cancer incidences	2 US, 1 Canada, 2 EU, 2 Asia, 2 South America	1985–2004	4	28.6, 0.19	1.71 (1.34, 2.19)	7	Not provided
(Xue *et al.*[31])	Lung cancer incidences	5 America, 4 EU, 2 Asia	1997–2012	6	significant	1.20 (1.11, 1.29)	11	Not provided
(Xu *et al.*[70])	Colorectal adenomas incidences	6 US	1998–2012	4	74.2, <0.002	1.30 (1.03, 1.64)	10	Not provided
Processed red meat								
(Qu *et al.*[23])	Esophageal cancer incidences	3 US, 4 EU, 4 Asia, 1 South America, 1 Iran	1988–2012	4	56.5, 0.006	1.81 (1.32, 2.48)	10	4:8[34]
Fresh red meat								
(Abete *et al.*[17])	CVD mortalities	3 US, 1 EU, 1 Asia	2009–2013	1	Men: 32.5, 0.205 Women: 75.5, 0.003	Men: $n=5$ 1.13 (1.08, 1.19) Women: $n=5$, 1.16 (1.05, 1.28)	9	Not provided
(Chen *et al.*[20])	stroke incidences	1 US, 1EU, 1 Asia	2003–2013	2	0, 0.923	1.07 (1.02, 1.13)	9	0:5 (100)
Total red meat								
(Wang *et al.*[18])	All causes mortalities	2 US	2009–2012	1	78.5, 0.003	1.11 (1.09, 1.13)	11	4:0 (100)
(Wang *et al.*[18])	CVD mortalities	2 US, 1 japan	2009–2012	1	60.3, 0.027	1.12 (1.09, 1.16)	11	2:4[95]
(Wang *et al.*[18])	Cancer mortalities	2 US	2009–2012	1	0, 0.614	1.08 (1.06, 1.09)	11	4:0 (100)
(Kaluza *et al.*[19])	Stroke incidences	1 US, 1 EU, 1 Asia	2003–2013	2	0, 0.59	1.06 (1.04, 1.09)	9	1:3[36]
(Feskens *et al.*[13])[b]	Diabetes incidences	1 US, 11 EU, 1 Asia, 1 Australia	2004–2012	14	not provided	1.08 (1.02, 1.14)	7	Not provided
(Chan *et al.*[16])	Colon cancer incidences	3 US, 3 EU, 2 Asia, 1 Australia	1994–2009	6	0, 0.646	1.09 (1.01, 1.17)	9	1:9[10]
(Bandera *et al.*[21])[b]	Endometrial cancer incidences	3 America, 2 Asia	1993–2006	5	46.2, 0.11	1.36 (1.16, 1.58)	10	3:2[69]
(Qu *et al.*[23])	Esophageal cancer incidences	4 America, 4 EU, 2 Asia, 1 Iran	1988–2012	4	51.7, 0.023	1.25 (1.10, 1.41)	10	4:6[52]
(Guo *et al.*[25])	Breast cancer incidences	6 US, 4 EU, 1 Asia	2004–2014	9	$P>0.1$	1.06 (1.03, 1.08)	9	Not provided
(Song *et al.*[26])	Stomach cancer incidences	4 America, 6 EU, 2 Asia, 1 Iran	1997–2012	5	73.8, <0.001	1.11 (1.03, 1.20)	10	10:9[65]
(Xue *et al.*[31])	Lung cancer incidences	5 America, 4 EU, 2 Asia	1997–2012	6	significant	1.22 (1.15, 1.29)	11	Not provided
(Xu *et al.*[70])	Colorectal adenomas incidences	9 US, 5 EU	1992–2012	10	76.8, <0.001	1.23 (1.10, 1.37)	10	Not provided
Red and processed meat								
(Chen *et al.*[20])[b]	Stroke incidences	1 US, 1 EU	2010–2012	2	0, 0.874	1.06 (1.03, 1.10)	9	1:3[36]
(InterAct Consortium[14])[b]	Diabetes incidences	10 EU	2014	10	not provided	1.12 (1.07, 1.17)	NA	3:5[49]
(Chan *et al.*[16])	Colorectal cancer incidences	7 US, 1 Canada, 3 Europe	1998–2010	10	56.2, 0.011	1.09 (1.03, 1.15)	9	2:9[70]
(Chan *et al.*[16])[b]	Colon cancer incidences	5 US, 1 Canada, 2 EU	1990–2010	8	59.6, 0.015	1.16 (1.06, 1.26)	9	5:3[69]
(Chan *et al.*[16])	Rectal cancer incidences	2 US, 1 Canada, 2 EU	2005–2010	3	18.2, 0.299	1.19 (1.08, 1.31)	9	2:3[38]
Total meat								
(Micha *et al.*[12])	stroke incidences	2 US	2003–2004	not provided	Not provided	1.15 (1.05, 1.26)	11	1:1[65]
(Feskens *et al.*[13])	Diabetes incidences	1 US, 10 EU, 2 Asia, 1 Australia	2001–2012	13	54	1.10 (1.04, 1.15)	7	Not provided
(Bandera *et al.*[21])[b]	Endometrial cancer incidences	3 US, 2 Asia,	1993–2008	5	77.6, <0.01	1.22 (1.01, 1.46)	10	2:3[21]

[a]Number of significant: insignificant component studies entries ratio, significant weight (%). [b]Fully adjusted for energy intake.

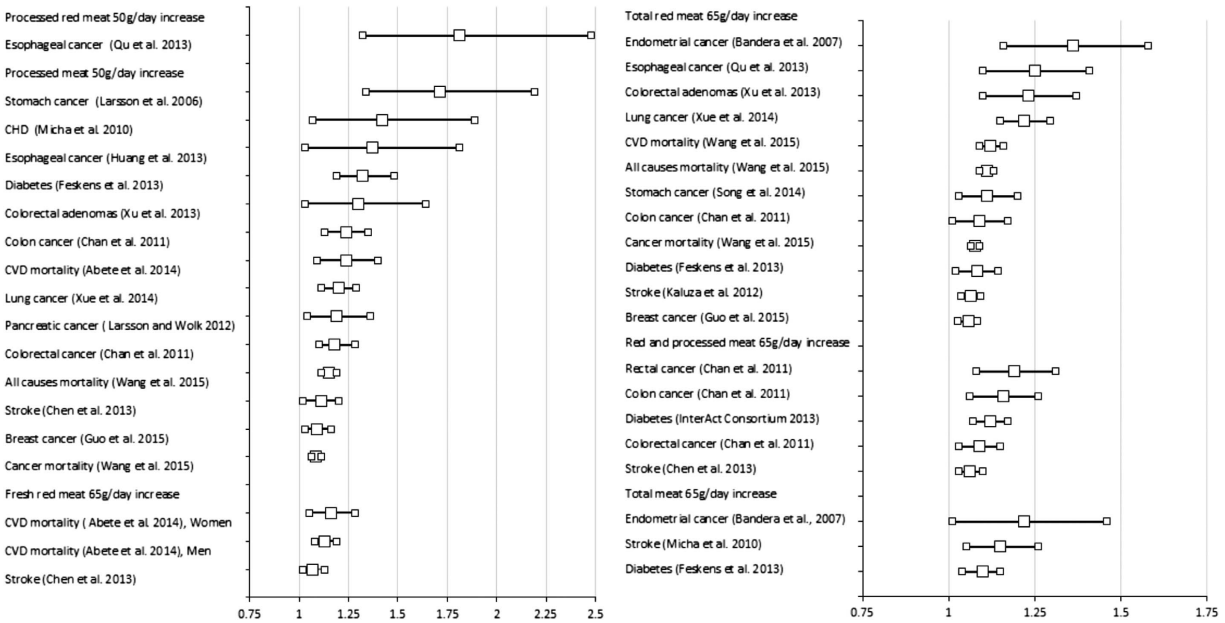


Figure 3. The best identified dose–responses relative risks of burden of diseases by meat intake types.

Table 4. Characteristics of relative risks of high vs low meat intakes and burden of diseases

Meta-analysis Studies	*Health outcomes*	*Studies number and countries included*	*Study years*	*Number of studies adjusted for energy intakes*	*Heterogeneity I^2 %, $P_{Heterogeneity}$*	*Relative risk/ Odds/ Hazard Ratio (95% CI)*
Processed meat						
(Li *et al.*[56])	Bladder cancer incidences	4 US, 3 EU, 1 Asia, 2 South America, 1 Canada	1991–2012	9	64.9, 0.002	1.22 (1.04, 1.43)
(Wei *et al.*[69])	Glioma incidences	10 US, 1 EU, 1 Australia, 1 Isreal, 1 white in 6 countries	1987–2010	2	22.4, 0.21	1.25 (1.08, 1.45)
(Xu *et al.*[32])	Oral Cavity and Oropharynx Cancer incidences	3 EU, 2 South America, 2 Middle East, 2 Asia	1992–2012	2	85.9, < 0.001	1.91 (1.19, 3.06)
Processed red meat						
(Fallahzadeh *et al.*[49])	Non-Hodgkin lymphoma incidences	6 US, 4 EU, 1 Canada	1999–2013	0	45.3, 0.04	1.17 (1.06, 1.29)
Total red meat						
(Lee *et al.*[55])	CVD mortalities	8 Asia	2013	8	not provided	men 0.87 (0.78, 0.98)
(Lee *et al.*[55])	Cancer mortalities	8 Asia	2013	8	not provided	women 0.85 (0.76, 0.94)
(Fallahzadeh *et al.*[49])	Non-Hodgkin lymphoma incidences	3 US, 4 EU, 1 Canada	2004–2013	0	59.4, 0.001	1.10 (1.02, 1.19)
Red and processed meat						
(Rouhani *et al.*[63])	Obesity incidences	3 US, 2 Asia	2006–2013	1	94.7, < 0.001	1.32 (1.13, 1.53)
Poultry meat						
(Lee *et al.*[55])	All-cause mortalities	8 Asia	2013	8	not provided	men 0.89 (0.81, 0.98) women 0.93 (0.86, 0.99)
(Lee *et al.*[55])	Cancer mortalities	8 Asia	2013	8	not provided	women 0.88 (0.79, 0.97)
(Pham *et al.*[62])	Rectal cancer incidences	5 Japan	unclear	unclear	insignificant	0.80 (0.67, 0.96)
(Yang *et al.*[30])	Lung cancer incidences	4 EU, 4 US, 2 South America, 1 Australia	1989–2011	3	34.7, 0.112	0.91 (0.85, 0.97)
Total meat						
(Namiranian *et al.*[60])	Breast cancer incidences	3 Eastern Mediterranean Region	2006–2010	unclear	unclear	1.39 (1.03, 1.87)
(Yang *et al.*[30])	Lung cancer incidences	12 America, 6 EU, 3 Asia, 1 Australia	1989–2011	5	75.7, < 0.001	1.35 (1.08, 1.69)

Limitations of the review

Not all statistically significant associations were reported with dose–responses. Given that different component studies had different definition of 'high' and 'low' intake levels, the exact meanings of 'high' and 'low' intakes levels in the pooled estimations were not clearly defined in meta-analysis studies.

According to the latest available Food Balance data,[2] among the 173 countries/or regions, in 2013, mean meat consumption (raw meat at commodity level, including bone and inedible) in the Low Income Food Deficit Countries was 7.96 kg/capita/year compared with 86.94 kg/capita/year in America, 77.34 kg/capita/year in Europe, the 173-country pooled mean 43.22 kg/capita/year,

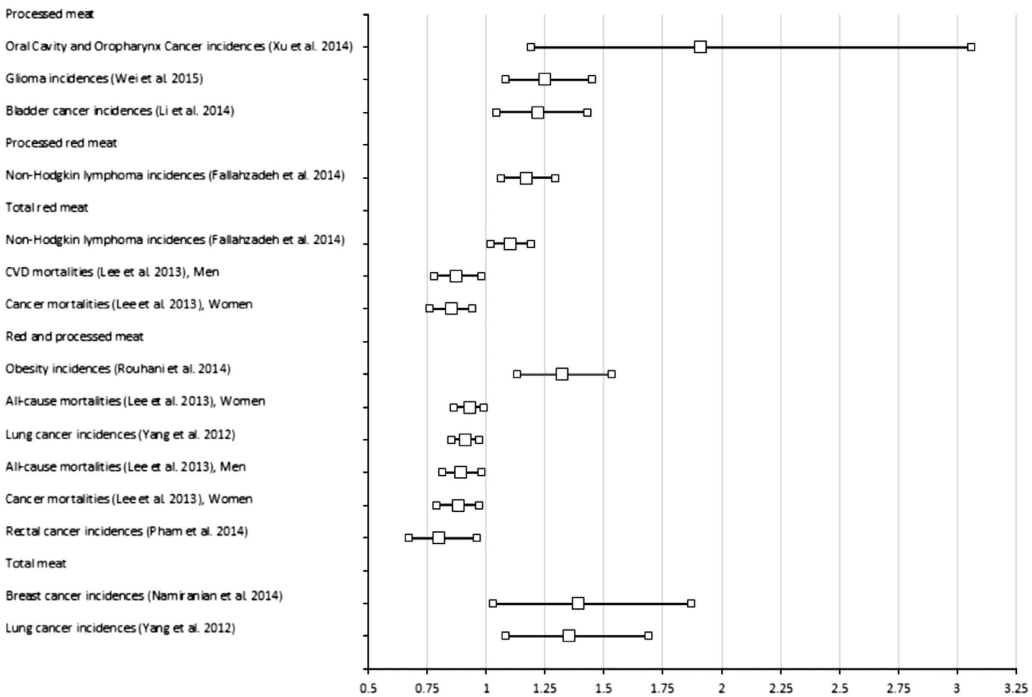


Figure 4. The best identified high vs low intake relative risks of burden of diseases by meat intake types.

32.55 kg/capita/year in Asia, and the lowest per capita meat consumption country India 3.69 kg/capita/year. Therefore 'high' meat intake (cooked, off-bone and inedible) population segments among populations of Low Income Food Deficit Countries may have intake levels equivalence to 'low' meat intake population segments among populations of high meat consumption countries such as in America and Europe. Currently the causal associations between meat intakes and burden of diseases are not fully understood. Most estimations were based on observations in regions dominated by high meat consuming populations' demographic and environmental characteristics, and dietary and nutrient absorption patterns. The effects of underlying disease-proneness or lifestyles differences of predominantly populations living in high meat consumption vs low meat consumption regions have largely been neglected. Livestock products are important sources of protein, energy and essential nutrients for healthy growth and development, especially for children and undernourished populations.[34,75–77] They are sources of protein, energy and nutrients such as all essential amino acids (lysine, threonine, methionine, phenylalanine, tryptophan, leucine, isoleucine and valine), iron, calcium, selenium, vitamin B12, zinc, phosphorus, niacin choline, riboflavin and various micronutrients.[75,78] Observation studies showed that in low-meat consumption populations increase meat intake is associated with reduced cerebrovascular disease mortalities;[79–81] cancer and CVDs incidences.[55,62,82] A cohort study[81] followed 58453 Japanese men and women aged 40–79 years at 1988 for 14.1 years found an increase saturated fatty acids intake reduce mortality from total stroke, intraparenchymal hemorrhage and ischemic subtypes. The outcome negative associations[55,62] shown in Table 1 or 4 are consistent with these studies.

Unless stated otherwise relative risks identified involved uncertainties associated with assuming log-linear relationships between exposures and disease outcomes. All relative risks identified are subject to diverse degrees of residual confounding, which are not fully understood, and may differ by ethnic, environmental and demographic characteristics, and which may also change with time. All relative risks were obtained from comparison of populations having different food intake levels, and did not include measures of the effect of any dietary interventions and the effects of past dietary patterns, and hence may be subject to considerable uncertainties in real world intervention practices. Assumptions, evaluation processes, biases and limitations of component studies in each meta-analyses were not assessed in this review. However, this would not affect the best identified dose–response selection outcomes because these quality variables were often not assessed in any of the identified meta-analyses, and where multiply meta-analyses existed for a specific risk-outcome pair investigation, unselective duplication in component studies (predominantly differing by only one or two studies) occurred in most cases. Other selection measures such as AMSTAR score, heterogeneity, specification of dose measure, and if the component studies were up-to-date were employed to ensure the best identified dose–responses in Table 3 are the best available choices.

Addition caveats for using the best identified dose–responses in Table 3:

1. Potential regional/population bias warrants caution especially where all component studies included in meta-analyses were conducted in only one specific country/region.
2. Heterogeneity issues warrant caution where $P_{\text{Heterogeneity}} < 0.1$ or $I^2 > 40\%$, or $P_{\text{Heterogeneity}}$ value was unavailable in meta-analyses.
3. Small-n potential bias should be assumed where the number of component studies included in any meta-analysis < 5.
4. The best identified dose–responses were based on observational component studies that adjusted for confounders but not for factors along causal pathways. Few best identified dose–responses were fully adjusted for total energy intake.
5. Components studies were adjusted for deferent combination of confounders, but not all the possible confounders, therefore overestimation of the effects may occur.

Implications for practice

This review presents a comprehensive summary of identified burden of diseases associated with meat intakes. In terms of four comparative risk assessment major inputs and outcomes this review identified all published statistically significant risk-outcome pairs (Table 1), and dose–responses relative risks (Table 2) mostly from high quality estimations and having at least AMSTAR scores $\geqslant 7$. The best identified dose–responses in Table 3 summarize the total effect of meat groups by taking the meat groups themselves and not their nutrient components as risk factors, and specific disease outcomes instead of their biomarker concentrations. This allows direct estimations of disease outcomes associated with meat intakes. It uncovered a fuller range of identified disease impacts from different combinations of meat intakes for future meat intake comparative risk assessments. Presenting the limitations and concerns and the exact quality context (number of studies and countries included in the estimations, component study years, number of studies adjusted for energy intakes, heterogeneity, number of significant vs insignificant component studies entries ratio and weight percentage) of the best identified dose–response estimations in Table 3 better inform policy-makers of the risks and uncertainties of using the data for future estimations. This review also suggests current global and dietary Comparative Risk Assessments have underestimated the burden of diseases attributed to meat intakes. Consequently, more attention is needed promoting lower and healthier meat intakes in high meat intake populations.

Implications for research

This review provides clear pointers to future studies on the association of meat intakes and burden of diseases. It identified evidence of statistically significant associations, and the uncertainties and limitations (Tables 3 and 4). A review of identified confounders inherent in each risk-outcome pair investigations (Supplementary Information) can help to guide future studies towards improved adjustment of important confounders and improve future evaluations. Further work is recommended to clarify associations where there are currently inconclusive outcomes. Given that the investigated association outcomes in high-meat consumption populations may different from those in low meat intake populations, more future investigations in low-meat consumption populations and in populations, where meat consumption is rising are recommended. Studying populations having similar characteristics in similar environments may minimize potential effects of variation in genetic or lifestyle. Population intervention studies can test the limitations of current observations. Although a body of research suggests vegetarian diet is associated with reduced burdens of a list of diseases,[83] other studies also found vegetarian diet as a risk factor for symptomatic gallstone disease and some other possible health risks.[84,85] A number of studies shows meat consumption is social, psychological, biological, cultural and habitual decisions.[86–94] Dietary guidelines from different countries and The World Cancer Research Fund International do not only included recommended overall meat intakes, but also give specific recommendations on red meat intake levels.[42,95–97] It is unclear if this is an indication of the importance of including a small amount of red meat in daily diet, or an expression of concern of over-consumption of red meat red meat, or else. Therefore in additional to comparing health outcomes of meat eaters against vegetarian sub-groups and pescatarians, comparing health outcomes of red meat intake population against zero red meat eating populations is another topic needing further investigations especially when red meat consumption contributes to significantly more greenhouse gas emissions than do white meat or plant-based food.[98] Given that traditional means of meat preservation (drying, salting, smoking and sausage) are widespread internationally, special attention should be paid at not only that risks associated with processed meat intakes are generally higher than unprocessed meat, more research work are also needed to investigated the potential health burden of pickled vegetables,[99] and other preserved food.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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