Total, red and processed meat consumption and human health: an umbrella review of observational studies

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Abstract

Meat consumption has represented an important evolutionary step for humans. However, modern patterns of consumption, including excess intake, type of meat and cooking method have been the focus of attention as a potential cause of rise in non-communicable diseases. The aim of this study was to investigate the association between total, red, and processed meat with health outcomes and to assess the level of evidence by performing a systematic search of meta-analyses of prospective cohort studies. Convincing evidence of the association between increased risk of (i) colorectal adenoma, lung cancer, CHD and stroke, (ii) colorectal adenoma, ovarian, prostate, renal, and stomach cancers, CHD and stroke, and (iii) colon and bladder cancer was found for excess intake of total, red, and processed meat, respectively. Possible negative associations with other health outcomes have been reported. Excess meat consumption may be detrimental to health, with a major impact on cardiometabolic and cancer risk.

Introduction

The inclusion of meat in the diets of human ancestors certainly contributed to human evolution and brain development (Milton 2003). Besides the obvious nutritional advantages in terms of vitamins, minerals, and protein content, primates consuming meat invested a shorter time for eating after the discovery of fire and cooking, resulting in improvement of their social and manual skills needed for hunting compared to their solely vegetarian counterpart (Carmody & Wrangham 2009). Over the centuries, fresh meat has been typically consumed occasionally, representing a rich course in Southern European regions, while some other populations had a higher consumption of preserved meats whether living in geographical areas with more severe weather (Larsen 2003; Mann 2018). Nowadays, meat consumption is no more affected by nationality or seasonality; meat is generally always available in developed countries and probably over consumed since its introduction into fast foods (Cocking et al. 2020; Henchion et al. 2021). Health surveys and investigations aiming to test the association between meat consumption and health outcomes revealed that excess intake of meat may be detrimental for cardiometabolic diseases and certain cancers (O'Keefe & Cordain 2004). Thus, a great deal of effort has been done to determine whether and how meat could affect human health.

Current research differentiates between red meat, white meat, and processed meat: red meat refers to mammalian muscle meat (i.e., beef, veal, pork, lamb, horse, etc.) rich in myoglobin and heme iron (from which derive the red color); white meat refers to the white counterpart (i.e., chicken, turkey, and other birds); while processed meat refers to red meat or either red or white meat that has been transformed through salting, curing, smoking, or other processes aiming to improve its preservation and, lately, to enhance its flavor (Klurfeld 2015). Notably, the processing procedures include the use of additives, such as sodium, nitrites, and phosphates, which have been the focus of major interest for their potentially detrimental effects on health (Srour & Touvier 2020). Overall, several meta-analyses have been conducted on this matter and various scientific organizations have provided rather discordant opinions: while in part agreeing that excessive consumption of processed meat would lead to certain adverse health outcomes, the overall level of evidence, especially concerning red meat, has been questioned as in contrast with the high biological value of proteins and essential nutrients (Wyness 2016). The aim of this study is to provide a summary of existing meta-analyses exploring the relation between total, red, and processed meat consumption and various health outcomes; an attempt to measure the level of evidence for the retrieved results is also provided.

Methods

Study selection

A systematic search in Medline and Embase electronic databases of meta-analyses on meat consumption and various health outcomes was conducted until January 2017. The search strategy included: [(meat OR poultry OR chicken OR lamb OR pork) AND (meta-analysis OR meta-analyzed OR pooled analysis)]. Inclusion criteria were: (i) meta-analyses only including observational studies (prospective or case-control studies); (ii) quantitative analysis with the availability of measure of association [effect size as risk ratio (RR), odds ratio (OR), or hazard ratio (HR)]. Exclusion criteria were: (i) meta-analyses of RCTs with outcomes of intermediary biomarkers of disease (i.e., blood lipids, blood pressure, etc.) or (ii) intermediary clinical conditions (i.e., variation in body weight/BMI, etc.). Hand searching of reference lists was also undertaken. Any discrepancy on the inclusion/exclusion decision was solved through discussion.

Data extraction

From each meta-analysis included, the following information was extracted: name of the first author and year of publication, outcome, number of studies included in the meta-analysis, study design of included studies (i.e., case-control/cross-sectional and prospective), total number of population, number of cases, type of exposure, measure of exposure [including highest versus lowest (reference) category of exposure or dose-response incremental servings per day (linear)], effect sizes.

Data evaluation and evidence synthesis

Where more than one meta-analysis was conducted on the same outcome, including the same study design, and the same population group, the concordance for the main outcome of interest, including direction and magnitude (overlapping confidence interval) of the association was evaluated. For further analyses, the most recent/exhaustive study was considered. The pooled analyses of the highest versus the lowest (reference) category of exposure and dose-response analyses were evaluated. Direction and magnitude of the association, heterogeneity (I2) of results, and subgroup/stratified analyses for potential confounding factors were considered to have indication of the level of evidence. Criteria used for evidence categorization were modified from the Joint WHO/FAO Expert Consultation (Degrees of evidence by the Joint WHO/FAO Expert Consultation. http://www.who.int/nutrition/topics/5_population_nutrient/en/#diet 5.1.2 Accessed November 2015) (Table 1). Briefly, the relation between exposure and outcomes was categorized as following: suggestive/limited/contrasting evidence, when there was availability of solely meta-analyses of case-control studies, limited prospective cohort studies included in meta-analyses (n <3), or evident contrasting results from meta-analyses with the same level of evidence; possible evidence, when there was availability of meta-analyses with lack of information on/significant heterogeneity (I2 >50%) or identification of potential confounding factors (i.e., different findings in subgroups); probable association, when there was availability of meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained (and evidence of dose-response relation further investigated); convincing association, when there was concordance between meta-analyses of RCTs and observational studies. Lack of fulfillment of the previous criteria was considered as insufficient evidence.

Results

Study selection

Out of 399 articles identified through the database search, 215 were excluded based on title and 97 after abstract evaluation (Figure 1). Twenty-eight studies were further excluded because meta-analyses of RCT (n = 1), narrative/systematic reviews without quantitative evaluation of the association between exposure and outcome (n = 10), pooled analysis of prospective cohort studies (n = 3), and investigating biomarkers (n = 14). Thus, a total number of 23 studies on total meat (Boyd et al. 1993; Sandhu et al. 2001; Norat et al. 2002; Faramawi et al. 2007; Aune et al. 2009; Kolahdooz et al. 2010; Micha et al. 2010; Wallin et al. 2011; Chan et al. 2011; Wang & Jiang 2012; Chen et al. 2013; Salehi et al. 2013; Zhu et al. 2013; Larsson & Orsini 2014; Zhu et al. 2014; Xu et al. 2014; Luo et al. 2014; Abete et al. 2014; Liu & Lin 2014; Alexander et al. 2015; Ge et al. 2015; Fang et al. 2015; Wu et al. 2016), 52 studies on red meat (Boyd et al. 1993; Sandhu et al. 2001; Norat et al. 2002; Larsson & Wolk 2006; Faramawi et al. 2007; Bandera et al. 2007; Alexander & Cushing 2009; Huxley et al. 2009; Aune et al. 2009; Kolahdooz et al. 2010; Micha et al. 2010; Smolińska & Paluszkiewicz 2010; Alexander, Mink, et al. 2010; Alexander, Morimoto, et al. 2010; Wallin et al. 2011; Chan et al. 2011; Alexander et al. 2011; Pan et al. 2011; Larsson & Wolk 2012; Paluszkiewicz et al. 2012; Wang & Jiang 2012; Kaluza et al. 2012; Chen et al. 2013; Huang et al. 2013; Xu et al. 2013; Choi et al. 2013; Aune et al. 2013; Salehi et al. 2013; Zhu et al. 2013; Qu et al. 2013; Fallahzadeh et al. 2014; Larsson & Orsini 2014; Zhu et al. 2014; Luo et al. 2014; Song et al. 2014; Xue et al. 2014; Li et al. 2014; Abete et al. 2014; Guo et al. 2015; Alexander et al. 2015; Saneei et al. 2015; Yang et al. 2015; Fang et al. 2015; Bylsma & Alexander 2015; Caini et al. 2016; Wang et al. 2016; Solimini et al. 2016; Yang et al. 2016; Zhao et al. 2016; Li et al. 2016; Wu et al. 2016; Zhao et al. 2017) , and 47 studies on processed meat consumption (Sandhu et al. 2001; Norat et al. 2002; Huncharek et al. 2003; Larsson et al. 2006; Larsson & Wolk 2006; Faramawi et al. 2007; Alexander & Cushing 2009; Huxley et al. 2009; Aune et al. 2009; Kolahdooz et al. 2010; Micha et al. 2010; Alexander, Miller, et al. 2010; Alexander, Mink, et al. 2010; Alexander, Morimoto, et al. 2010; Wallin et al. 2011; Chan et al. 2011; Pan et al. 2011; Larsson & Wolk 2012; Wang & Jiang 2012; Kaluza et al. 2012; Chen et al. 2013; Huang et al. 2013; Xu et al. 2013; Choi et al. 2013; Aune et al. 2013; Salehi et al. 2013; Qu et al. 2013; Fallahzadeh et al. 2014; Larsson & Orsini 2014; Xu et al. 2014; Luo et al. 2014; Xue et al. 2014; Li et al. 2014; Abete et al. 2014; Wei et al. 2015; Guo et al. 2015; Saneei et al. 2015; Yang et al. 2015; Fang et al. 2015; Bylsma & Alexander 2015; Wang et al. 2016; Solimini et al. 2016; Yang et al. 2016; Zhao et al. 2016; Li et al. 2016; Wu et al. 2016; Zhao et al. 2017) and various health outcomes was selected for evaluation.

Characteristics of the studies on total meat consumption and health outcomes

The main characteristics of the studies exploring the risk associated to high vs. low total meat consumption for 10 unique outcomes from 8 non-overlapping meta-analyses and the risk associated to linear consumption for 9 unique outcomes from 7 non-overlapping meta-analyses are shown in Figure 2 and Supplementary Table 1, respectively. Higher intake of total meat was associated with an increased risk of colorectal and colon cancer, stroke, and all-cause mortality (Figure 2); a linear association was found for all outcomes investigated, including coronary heart disease (CHD), type-2 diabetes mellitus (T2DM), various cancers (colorectal, colon, rectal, ovarian, and breast cancers), all-cause and cardiovascular disease (CVD) mortality (Supplementary Table 1). Two meta-analyses conducted on a limited number of prospective cohort studies (<3) and case-control studies also reported a potential association of high total meat intake and endometrial cancer (significant among case-control studies but not in the only prospective one) (Bandera et al. 2007), inflammatory bowel disease (Ge et al. 2015), and nasopharynx cancer (Xu et al. 2014). Most studies reported limited information on potential confounding factors: however, higher risk of colorectal cancer was significant only among European cohorts (Chan et al. 2011), while higher risk of all-cause mortality only among US ones (Larsson & Orsini 2014). Subgroup analyses by sex showed no significant association with risk of colorectal, colon, and rectal cancers (Chan et al. 2011).

Characteristics of the studies on red meat consumption and health outcomes

A summary of the main characteristics of the studies investigating the risk estimates for the highest vs. the lowest category of red meat consumption for 19 unique outcomes extracted from 16 non-overlapping meta-analyses in Figure 3 and the risk estimates of 14 outcomes from 12 non-overlapping meta-analyses for linear consumption of red meat are reported in Supplementary Table 2. The risk associated with high vs. low consumption of red meat included breast and lung cancers, stroke, CVD mortality, and T2DM, although with relatively high heterogeneity (>50%) between studies (Figure 3); a significant linear association was also reported for colorectal (and colon) cancer and adenomas, breast cancer, pancreatic cancer, stroke, and T2DM (Supplementary Table 2). Limited evidence was also found for higher intake of red meat and increased risk of endometrial cancer (Bandera et al. 2007), nasopharyngeal carcinoma (Li et al. 2016), and ischemic rather than hemorrhagic stroke (Yang et al. 2016). When controlling for potential confounding factors, certain variables substantially modified the retrieved associations: for instance, increased risk of colorectal cancer was observed in European but not US or Asian cohorts (Chan et al. 2011), while other outcomes, such as all-cause mortality (Larsson & Orsini 2014), became significant when considering the same geographical area; in contrast, higher red meat intake was associated with increased risk of bladder and esophageal cancer in US cohorts but not in other regions (Zhu et al. 2014; Li et al. 2014). Moreover, increased risk of lung cancer and CVD mortality was significant only in the subgroup analysis restricted to women while all-cause mortality (Larsson & Orsini 2014) and pancreatic cancer (Zhao et al. 2017) risk was significant when restricted to men.

Characteristics of the studies on processed meat consumption and health outcomes

An overview of the main characteristics of the studies included and the risk estimates of various health outcomes for the highest versus the lowest category of processed meat consumption are reported for 19 unique outcomes extracted from 16 non-overlapping meta-analyses in Figure 4 and the risk estimates of 15 outcomes from 12 non-overlapping meta-analyses for linear consumption are reported in Supplementary Table 3. Higher intake of processed meat was associated with significantly increased risk of TD2M, all-cause mortality, various cancers (including prostate, gastric, colorectal, colon, rectal, renal, and ovarian cancers) and cardiovascular outcomes (including stroke and CVD mortality) (Figure 4). Similar findings with lower heterogeneity between studies (with exception of T2DM reporting >50% of heterogeneity) were reported when considering a linear association with increasing intake of processed meat (50 g/d or 1 serving/d increase) (Supplementary Table 3). Among meta-analyses with not sufficient evidence, an increased risk of colorectal adenomas (Aune et al. 2013), nasopharyngeal (Li et al. 2016), oral cavity, and oropharynx cancers (Xu et al. 2014), associated with higher intake of processed meat was also reported. Controlling the results for potential confounding factors revealed that the increased risk of esophageal (Zhu et al. 2014), bladder (Li et al. 2014), pancreatic (Zhao et al. 2017) cancers and glioma (Wei et al. 2015) associated with higher processed meat consumption was significant only in US cohorts while breast cancer (Guo et al. 2015) only in European ones; some outcomes [such as CVD mortality (Abete et al. 2014) and colon cancer (Chan et al. 2011)] were significant in women only, while others (gastric (Zhu et al. 2013), lung (Xue et al. 2014), and pancreatic (Zhao et al. 2017) cancers) only in men. The analyses restricted to subgroups by sex resulted in no significant associations of processed meat intake and colorectal and rectal cancers in both men and women (Chan et al. 2011).

Summary of evidence

A detailed description of the evaluation of the evidence level is reported in Supplementary Table 4. Possible evidence of increased risk has been found for (i) adenoma of colorectum, lung cancer, CHD and stroke was found for higher intake of total meat; (ii) adenoma of colorectum, ovarian, prostate, renal, and stomach cancers, CHD and stroke for higher intake of red meat; and (iii) colon and bladder cancer for higher intake of processed meat (Table 1). Increased risk of other outcomes, including breast and colorectal cancers, T2DM, and mortality was deemed as limited mainly due to heterogeneity between results and potential otherwise inexplicable confounding factors (i.e., results were significant only in certain geographical regions or differed by sex). No probable nor convincing associations were found. Insufficient or no evidence of association has been reported for all other outcomes investigated (Table 1).

Discussion

In this umbrella review of meta-analyses investigating the relation between total, red, and processed meat consumption and various health outcomes, revealing rather limited evidence weakened by large heterogeneity across studies and geographical differences when considering grouping cohorts by regions. The reasons for such discrepancies between results are rather unclear: we may hypothesize that the differences by nationality may reflect different overall dietary patterns in which meat is consumed (for instance, hamburger with concomitant consumption of refined sugars from sugar-sweetened beverages and hydrogenated trans fats vs. lean meat with vegetables) as well as preferences for different cooking methods (for instance, a different impact of fried bacon, roasted beef, or long-cooked meat). However, a possible impact of high total, red, and processed meat on some cardiovascular and cancer outcomes have been observed. The rationale behind the detrimental effects of excess meat consumption in the diet on various health outcomes includes several mechanisms. Most studies stressed the concept that meat processing plays a central role in the detrimental effects on colorectal cancer risk: the conversion of nitrates and nitrites contained in processed meat into N-nitroso-compounds, which can act as multi-site carcinogens through the formation of covalent adducts with DNA bases (Alisson-Silva et al. 2016). Moreover, exposure to high temperature during cooking processes lead to the formation of known mutagens, such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), some of which have been associated with increased risk of colorectal adenomas (Hammerling et al. 2016). Interestingly, contrary to the common misconception that a diet rich in meat is mostly hazardous for cancer risk, in the present evaluation of the evidence we found evidence that both red and processed meat may comparably also be associated with a higher risk of CVD. Several specific mechanisms may explain this association: concerning processed meat, sodium (and specifically, NaCl) may play a detrimental role on endothelial health and raise blood pressure (Micha et al. 2013). However, irrespectively of the processing level, the saturated fat content of meat (particularly characterized by long-chain saturated fatty acids) is under investigation as a potential trigger of low-grade sub-clinical inflammatory processes and potentially contribute to rise in post-prandial blood LDL (Astrup et al. 2020). Moreover, lipid oxidation occurring after the passage of meat through the various gastrointestinal compartments and further promoted by heme iron, high content in PUFA, and lack of antioxidants, may play a role in endothelial dysfunction and subsequent increased risk of CVD (Wu et al. 2019). Another hypothesized indirect cardiotoxic mechanism related to meat consumption may involve the transformation of L-carnitine into trimethylamine (TMA) by the gut microbiota and, subsequently, metabolized to trimethylamine-N-oxide (TMAO) in the liver: TMAO has been suggested to be involved in the atherogenesis processes, vascular inflammation, and increased platelet activity (Delgado et al. 2021).

The level of evidence reported in this umbrella review is lower than conclusions of expert scientific committees due to the stronger weight we imputed to heterogeneity of results among cohort studies (particularly evident when considering T2DM) and inexplicable differences across geographical regions (mostly concerning colorectal cancer and CVD outcomes). Scientific societies on cardiovascular health, such as the American College of Cardiology and American Heart Association, suggest limiting consumption of red and processed meat to ameliorate blood lipids and reduce the risk of CVD (Eckel et al. 2014). Experts from the American Diabetes Association and the expert panel of Diabetes UK also concluded in their recommendations to reduce meat-products for the prevention and management of T2DM (American Diabetes Association 2018; Dyson et al. 2018). Similar concerns have been reported by the World Cancer Research Fund/American Institute for Cancer Research and the Continuous Update Project, with attention to the consumption of red and, especially processed meat and increased risk of colorectal cancer (Vieira et al. 2017). In all cases, we negatively weighted the various potential confounding factors contributing to the heterogeneity of the results and leading to an overall weakening of the level of evidence. The interpretation of such findings does not undermine the actual evidence of the retrieved associations between higher meat intake with increased risk of health conditions, but would rather suggest that other factors related to meat intake (i.e., unexplored confounding factors, effect modifiers, genetic differences among individuals, correlated variables, etc.) may play a synergistic role to define a pool or pattern of factors actually leading to the increased risk of disease. This hypothesis is supported by results from our previous study showing that red meat consumption in cohort studies globally correlates with several health risk factors, including higher BMI, higher prevalence of smokers, lower prevalence of high physical activity and university studies (Grosso et al. 2017). A recent ecological study showed that red meat had no significant impact on life expectancy in low-income or lower-middle-income countries (Ranabhat et al. 2020). A systematic review focused on studies conducted in Middle Eastern and North African countries showed an inverse association between (unprocessed) beef meat intake and colorectal cancer risk (Mint Sidi Deoula et al. 2020) and a multicenter case-control study involving the five largest university hospitals in Morocco investigated the differential association of traditional (decreased risk) vs. westernized (increased risk) processed meat products and colorectal cancer (S Deoula et al. 2020). Another individual study conducted on 21 low-, middle-, and high-income countries showed a rather null association between unprocessed red meat consumption and mortality or major CVD (Iqbal et al. 2021). Finally, concerning mechanistic studies, a case-control study conducted in non-smokers revealed the potential role of genes for S-glutathione transferase (GST), which are responsible for detoxification processes (including antioxidant activity) in the association between meat consumption and colorectal cancer risk (Klusek et al. 2019).

Albeit only preliminary, there is increasing awareness that other factors may play a role independently or together with higher meat consumption and human health. Further studies investigating intermediate outcomes and mechanistic processes in humans (i.e., gut microbiota modification, alteration of immunitary pathways, etc.) are needed to provide stronger evidence of the potential associations, ideally eliminating known confounding factors (such as, obesity, smoking habits, and scarce physical activity).

Another hypothesis that could explain the overall negative effects of meat consumption on human health, although with great heterogeneity between individuals, is the role of dietary fats on the immune system and inflammation (Ruiz-Núñez et al. 2016). There is consistent evidence from the scientific literature that intake of saturated fatty acids may trigger a number of pathways leading to local (gut level) and systemic low-grade inflammation, which in turn may affect endothelial health, cardiovascular risk, and ultimately the central nervous system through activation of the gut microbiota and pro-inflammatory processes (Ceppa et al. 2019; Salvucci 2019). Earlier meta-analyses of RCTs showed no significant differences in blood lipids levels comparing beef consumption to poultry and/or fish consumption (Maki et al. 2012) as well as consumption of ≥0.5 servings of total red meat/d on blood lipids, lipoproteins or blood pressure (O'Connor et al. 2017). However, a more recent meta-analysis showed that substituting red meat with high-quality plant protein sources, but not with fish or low-quality carbohydrates, may lead to favorable changes in blood lipids and lipoproteins (Guasch-Ferré et al. 2019). The findings from our recent work show substantial benefits on cardiometabolic outcomes of healthy alternative foods to meat, such as whole grains (Tieri et al. 2020), legumes and nuts (Martini et al. 2021). This may be explained by considering the different quality of fat contained in food groups, mostly omega-3 and omega-6 from vegetable sources, together with a higher fiber content

(Siri-Tarino et al. 2015; Fritsche 2015). It is under evaluation whether short-chain saturated fatty acids provided also from animal sources (i.e., dairy products and fish) may produce anti-inflammatory actions in the human body (Lordan et al. 2018). Whether confirmed by this pathway of action, the level of systemic low-grade inflammation may play a central role in nearly all non-communicable diseases, with a substantially stronger impact on the overall diet rather than individual components determining the final effect on the immune system (Stromsnes et al. 2021). Although evidence from observational studies supports the potential positive (Godos et al. 2020; Lee et al. 2020) or null effects (Marventano et al. 2020) on cardiovascular health, further research is needed to provide a stronger rationale for such potential benefits.

The present study has several limitations that should be discussed. First, the results are based on the original results of the meta-analyses of prospective studies included for evaluation, thus the same limitations applicable to observational studies should be considered (i.e., recall bias, reverse causation, under/over-reporting of meat intake, etc.). Second, the classification of the type of meat may not be univocal across individual prospective studies and across meta-analyses (i.e., some studies specified “red processed meat” while others included all types of processed meats). Similarly, total meat may include different types and proportions of meats (i.e., red, white, and processed) that may mislead the proper comparability of results.

In conclusion, excess meat consumption may be detrimental to health, potentially impacting both cardiometabolic and cancer risk. The heterogeneity of results does not allow to establish a clear ideal recommended frequency of consumption. Meat is a nutrient-dense food that significantly contributes to the nutritious dietary quality if compared to completely lacking in the average diet (McEvoy et al. 2012). Healthier dietary sources of protein with clear health benefits are an advisable dietary choice, especially if compared to processed meats. However, the inclusion of moderate consumption of lean, unprocessed red meats in a balanced dietary pattern and a healthy lifestyle may not necessarily produce a harmful effect.

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Declaration of interests

The authors declare no conflicts of interest.

Figure legend

Figure 1. Flow chart of study selection.

Figure 2. Summary results from meta-analyses of prospective cohort studies on total meat consumption on various health outcomes included in umbrella review.

Figure 3. Summary results from meta-analyses of prospective cohort studies on red meat consumption on various health outcomes included in umbrella review.

Figure 4. Summary results from meta-analyses of prospective cohort studies on processed meat consumption on various health outcomes included in umbrella review.

Supplementary material legend

Supplementary Table 1. Summary results from meta-analyses investigating continuous linear exposure to total meat consumption and health outcomes.

Supplementary Table 2. Summary results from meta-analyses investigating continuous linear exposure to red meat consumption and health outcomes.

Supplementary Table 3. Summary results from meta-analyses investigating continuous linear exposure to processed meat consumption and health outcomes.

Supplementary Table 4. Variables investigated to address the strength of evidence from selected meta-analyses on total meat, red meat and processed meat consumption and health outcomes.

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Table 1. Level of evidence for the association between meat consumption and health outcomes.

Level of evidence*	Criteria§	Total meat	Red meat	Processed meat
Convincing	Meta-analyses of prospective cohort studies with evidence of dose-response relation, no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	None.	None.	None.
Probable	Meta-analyses of prospective cohort studies with no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	None.	None.	None.
Possible	Meta-analysis of prospective cohort studies with no heterogeneity and lack of information on potential confounding factors.	Association with increased risk of adenoma (colorectum), cancer (lung), CHD (any), stroke (total).	Association with increased risk of adenoma (colorectum), cancer (ovarian, prostate, renal, stomach), CHD (any), stroke (total).	Association with increased risk of cancer (colon, bladder).
Limited	Meta-analysis of prospective cohort studies with presence of significant heterogeneity (I^2 >50%) or identification of potential confounding factors (i.e., different findings in subgroups).	Association with increased risk of cancer (breast), mortality (CVD), T2DM.	Association with increased risk of cancer (breast, colon#, colorectum#, rectum#), mortality (all-cause, CVD), T2DM.	Association with increased risk of cancer (colorectum#), CHD (any), mortality (all-cause, cancer), stroke (total).
Insufficient	Meta-analysis of case-control studies, limited prospective cohort studies included in meta-analyses (n <3), or evident contrasting results from meta-analyses with the same level of evidence.	Association with increased odds of cancer (nasopharynx), inflammatory bowel disease, and stroke (ischemic).	Association with increased odds of cancer (naso-oropharynx).	Association with increased odds of inflammatory bowel disease.

No evidence	Meta-analyses of prospective cohort studies with evidence of dose-response relation, no heterogeneity, no potential confounding factors identified, and eventual disagreement of results over time reasonably explained [otherwise declassed as possible].	No association with risk of Barret's esophagus, cancer (bladder, colon, colorectum, esophagus, endometrial, liver, NHL, ovarian, pancreas, prostate, renal, rectum, stomach), mortality (all-cause, cancer), stroke (hemorrhagic).	No association with risk of Barret's esophagus, cancer (bladder, esophagus, glioma, liver, lung, NHL, pancreas), mortality (CHD), stroke (ischemic, hemorrhagic).	No association with risk of cancer (breast, esophagus, rectum, stomach), mortality (CHD), T2DM.

*all the associations should be biologically plausible; potential confounding factors should be taken into account.
§ modified from the Joint WHO/FAO Expert Consultation
# presence of potential confounding factors
Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; NHL, non-Hodgkin lymphoma; T2DM, type-2 diabetes mellitus.

Figure 1

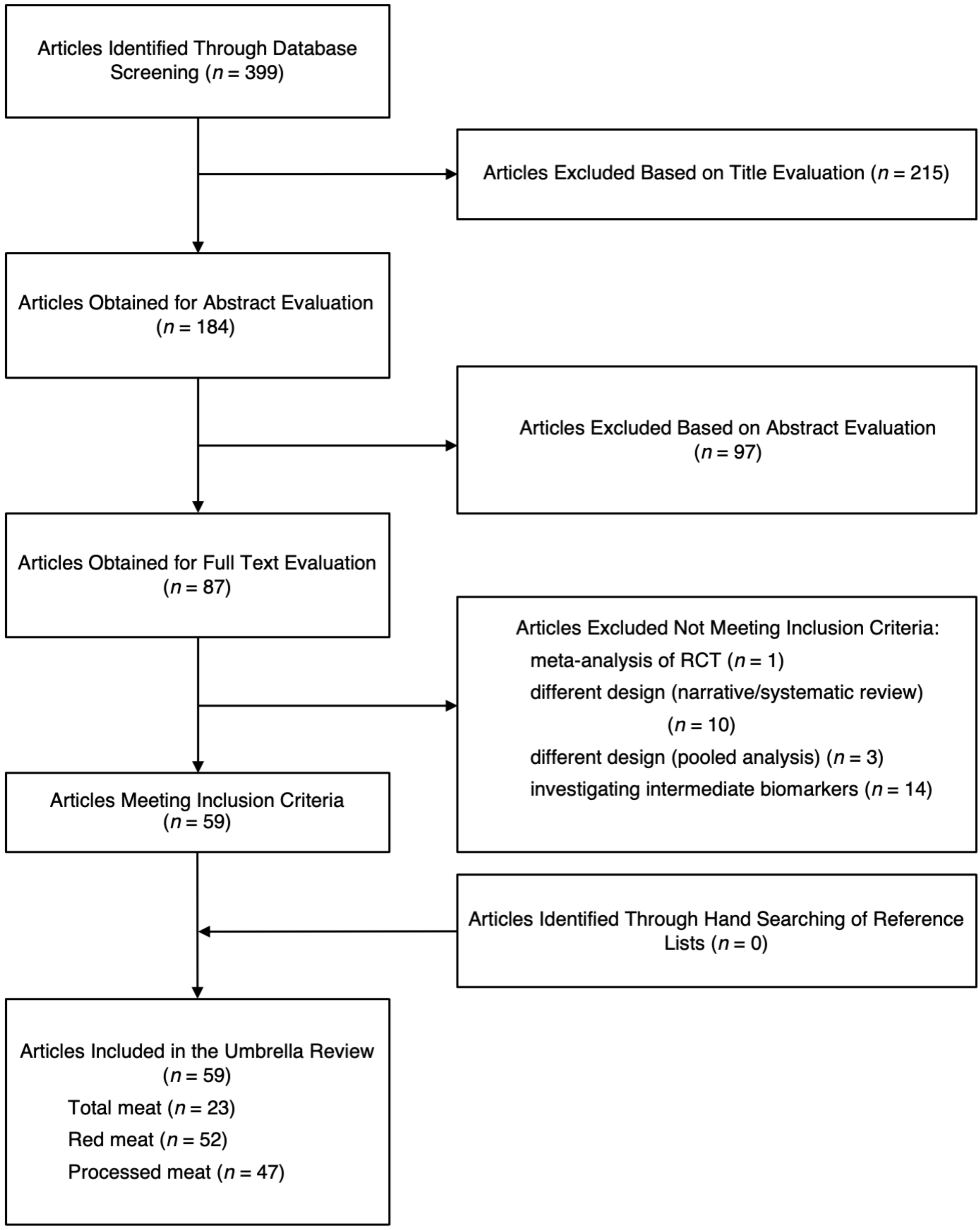
Articles Identified Through Database Screening (n = 399)
Articles Excluded Based on Title Evaluation (n = 215)
Articles Obtained for Abstract Evaluation (n = 184)
Articles Excluded Based on Abstract Evaluation (n = 97)
Articles Obtained for Full Text Evaluation (n = 87)
Articles Excluded Not Meeting Inclusion Criteria:
meta-analysis of RCT (n = 1)
different design (narrative/systematic review) (n = 10)
different design (pooled analysis) (n = 3)
investigating intermediate biomarkers (n = 14)
Articles Meeting Inclusion Criteria (n = 59)
Articles Identified Through Hand Searching of Reference Lists (n = 0)
Articles Included in the Umbrella Review (n = 59)
Total meat (n = 23)
Red meat (n = 52)
Processed meat (n = 47)

Figure 2

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
Esophageal cancer	4	789,557	2,564	0.94 (0.67, 1.32)	60%	Zhu et al. 2014
Gastric cancer	13	3,387,802	15,596	1.00 (0.90, 1.12)	24%	Fang et al. 2015
Breast cancer	8	691,383	19,912	1.05 (0.95, 1.16)	63%	Wu et al. 2016
Colorectal cancer	27	NA	NA	1.11 (1.03, 1.19)	33%	Alexander et al. 2015
Colon cancer	16	NA	NA	1.11 (1.04, 1.18)	0%	Alexander et al. 2015
Stroke	4	202,121	5,721	1.15 (1.05,1.25)	0%	Chen et al. 2013
T2DM	5	445,323	6,525	1.17 (0.92, 1.48)	86%	Aune et al. 2009
Bladder cancer	4	128,471	922	1.17 (0.83, 1.50)	0%	Wang et al. 2012
Rectal cancer	13	NA	NA	1.17 (0.99, 1.39)	51%	Alexander et al. 2015
All-cause mortality	4	719,361	99,808	1.29 (1.24, 1.35)	65%	Larsson et al. 2014

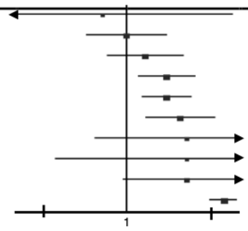

Figure 3

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
Gastric cancer	8	1,006,898	1,670	1.00 (0.82, 1.20)	33%	Fang et al. 2015
CHD mortality	4	230,663	1,234	1.02 (0.72, 1.46)	70%	Abete et al. 2014
Renal cancer	4	1,417,703	2,903	1.02 (0.91, 1.15)	No	Alexander et al. 2009
Prostate cancer	10	541,970	25,007	1.02 (0.92, 1.12)	61%	Bylsma et al. 2015
Cancer mortality	5	1,144,264	45,738	1.03 (0.89, 1.18)	78%	Wang et al. 2016
Rectal cancer	10	NA	NA	1.03 (0.88, 1.21)	20%	Alexander et al. 2015
Colorectal cancer	17	NA	NA	1.05 (0.98, 1.12)	8%	Alexander et al. 2015
Colon cancer	11	NA	NA	1.06 (0.97, 1.16)	0%	Alexander et al. 2015
Bladder cancer	5	1,494,283	4,814	1.08 (0.97, 1.20)	No	Li et al. 2014
NHL	4	1,026,163	5,181	1.08 (0.92, 1.26)	33%	Solimini et al. 2016
Breast cancer	14	1,588,890	31,552	1.10 (1.02, 1.19)	62%	Guo et al. 2015
All-cause mortality	5	732,333	61,494	1.10 (0.98, 1.22)	83%	Larsson et al. 2014
Pancreatic cancer	16	3,135,215	8,735	1.12 (0.98, 1.28)	52%	Zhao et al. 2017
Stroke	4	245,853	8,844	1.14 (1.05, 1.24)	0%	Yang et al. 2016
Ovarian cancer	3	586,100	1,018	1.15 (0.97, 1.36)	No	Kolahdooz et al. 2010
CVD mortality	7	1,615,868	42,530	1.16 (1.03, 1.32)	82%	Abete et al. 2014
T2DM	10	433,070	12,226	1.21 (1.07, 1.37)	58%	Aune et al. 2009
Lung cancer	6	1,564,549	16,070	1.21 (1.14, 1.28)	No	Xue et al. 2014
Esophageal cancer	3	1,137,288	1,162	1.22 (0.89, 1.68)	40%	Zhu et al. 2014

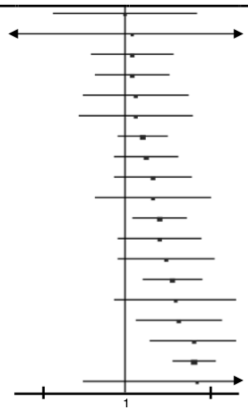

Figure 4

Outcome	No. of studies	No. of subjects	No. of cases	RR (95% CI)	I^2	Ref.
NHL	3	937,753	4,982	1.01 (0.91, 1.11)	0%	Solimini et al. 2016
Prostate cancer	11	568,147	27,705	1.05 (1.01, 1.10)	4%	Bylsma et al. 2015
Bladder cancer	5	1,051,404	3,927	1.08 (0.96, 1.20)	No	Li et al. 2014
Breast cancer	12	1,493,931	28,669	1.08 (1.01, 1.15)	58%	Guo et al. 2015
Lung cancer	5	1,560,213	15,892	1.09 (0.99, 1.19)	No	Xue et al. 2014
Pancreatic cancer	14	2,898,736	8,092	1.09 (0.96, 1.23)	51%	Zhao et al. 2017
Glioma	3	869,685	939	1.10 (0.88, 1.37)	0%	Wei et al. 2015
Gastric cancer	13	2,002,100	3,243	1.15 (1.03, 1.29)	8%	Fang et al. 2015
Colorectal cancer	18	2,085,221	67,673	1.17 (1.09, 1.25)	12%	Chan et al. 2011
Stroke	4	202,121	8,119	1.17 (1.09, 1.17)	0%	Yang et al. 2016
CVD mortality	6	1,186,761	35,537	1.18 (1.05, 1.32)	73%	Abete et al. 2014
Colon cancer	11	NA	NA	1.19 (1.11, 1.29)	0%	Chan et al. 2011
Renal cancer	3	1,383,505	2,889	1.19 (1.03, 1.37)	No	Alexander et al. 2009
Rectal cancer	9	NA	NA	1.19 (1.02, 1.39)	20%	Chan et al. 2011
All-cause mortality	5	1,143,696	125,803	1.23 (1.17, 1.28)	57%	Larsson et al. 2014
Esophageal cancer	3	1,137,288	1,162	1.25 (0.83, 1.86)	63%	Zhu et al. 2014
Ovarian cancer	3	525,043	730	1.26 (1.02, 1.56)	No	Kolahdooz et al. 2010
T2DM	9	380,606	9,999	1.41 (1.25, 1.60)	53%	Aune et al. 2009
CHD mortality	3	64,109	716	1.52 (0.50, 4.66)	81%	Abete et al. 2014