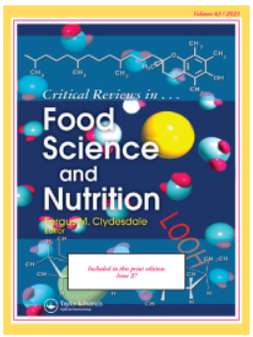

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Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/bfsn20

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To cite this article: Gidyenne Christine Bandeira Silva de Medeiros, Gabriela Xavier Barbalho Mesquita, Severina Carla Vieira Cunha Lima, David Franciole de Oliveira Silva, Kesley Pablo Morais de Azevedo, Isac Davidson Santiago Fernandes Pimenta, Ana Katherine da Silveira Gonçalves de Oliveira, Clélia de Oliveira Lyra, Daniel Guillén Martínez & Grasiela Piuvezam (2023) Associations of the consumption of unprocessed red meat and processed meat with the incidence of cardiovascular disease and mortality, and the dose-response relationship: A systematic review and meta-analysis of cohort studies, Critical Reviews in Food Science and Nutrition, 63:27, 8443-8456, DOI: 10.1080/10408398.2022.2058461

To link to this article: https://doi.org/10.1080/10408398.2022.2058461

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
2023, VOL. 63, NO. 27, 8443–8456
https://doi.org/10.1080/10408398.2022.2058461

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REVIEW

Associations of the consumption of unprocessed red meat and processed meat with the incidence of cardiovascular disease and mortality, and the dose-response relationship: A systematic review and meta-analysis of cohort studies

Gidyenne Christine Bandeira Silva de Medeiros[a,b,g], Gabriela Xavier Barbalho Mesquita[a], Severina Carla Vieira Cunha Lima[a,c], David Franciole de Oliveira Silva[b,c], Kesley Pablo Morais de Azevedo[b,g], Isac Davidson Santiago Fernandes Pimenta[b,g], Ana Katherine da Silveira Gonçalves de Oliveira[d,g], Clélia de Oliveira Lyra[a,b,c], Daniel Guillén Martínez[e,g], and Grasiela Piuvezam[b,f,g]

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ABSTRACT

Objectives: The aim of this study was to examine the associations of unprocessed red meat and processed meat consumption with cardiovascular disease (CVD) incidence and mortality, and the dose-response relationship.

Methods: Published literature was retrieved through a structured search of 10 electronic databases: MEDLINE/PubMed, Scopus, SciELO, LILACS, ScienceDirect, Web of Science, Cochrane (CENTRAL), WHOLIS, PAHO and Embase, without language or year of publication restrictions. In addition, we searched the references of published studies. This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes: The PRISMA Statement.

Results: Twenty-one prospective cohort studies were included in the systematic review. The CVDs evaluated in the inserted studies were stroke, heart failure (HF) and coronary heart disease (CHD). Considering the heterogeneity found in the studies, for the meta-analysis, 9 articles were included. The results presented in the meta-analysis of the association of consumption of unprocessed red meat and CVD indicated that there was a significant association with total stroke incidence (RR 1.10; 95%; CI 1.01 to 1.19; $p=0.02$). There was no association with Ischemic stroke incidence, nor CHD Mortality with consumption of unprocessed red meat. However, for Hemorrhagic Stroke Mortality the assessment in the consumption of unprocessed red meat showed an association of protection for women (RR 0.64; 95%; CI 0.45 to 0.91; $p=0.01$). As for the results of the meta-analysis of the association between consumption of processed meat and CVD, they indicated that there was a significant association with total stroke incidence (RR 1.17; 95%; CI 1.08 to 1.26; $p<0.0001$). There was no association with Ischemic stroke, nor with CHD Mortality with consumption of processed meat. Some studies that showed no association of risk, presented a significant linear trend dose response for the association of the consumption of unprocessed red meat (Bernstein et al. 2010; Nagao et al. 2012) or processed meat (Bernstein et al. 2012) and CVD.

Conclusion: According to the results found in the meta-analysis, the consumption of unprocessed red meat and processed meat are associated with the incidence of stroke, however, no positive association was observed in relation to mortality from CVD. This systematic review and meta-analysis protocol was registered on the PROSPERO (number: CRD42019100914).

KEYWORDS
Unprocessed red meat; processed meat; incidence; mortality; cardiovascular disease

Background

Population feeding patterns are changing and include the replacement of fresh or minimally processed foods with processed products (Baker and Friel, 2014; Monteiro et al. 2013; Moubarac et al. 2014). Of the products of animal origin, there has been an increase in the consumption of meat and processed meat products (USDA, 2018).

A study by the International Agency for Research on Cancer (IARC), linked to the World Health Organization (WHO), showed that the consumption of processed meat is associated with the incidence of colorectal cancer. In

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/10408398.2022.2058461

relation to the consumption of red meat, the scientific evidence shows a probable association between red meat and cancer, especially for colorectal cancer, pancreatic cancer and prostate cancer (Stewart et al. 2015).

The association between the consumption of red meat and cardiovascular diseases (CVD) has been observed in meta-analysis studies, with an emphasis on coronary heart disease (CHD), stroke and/or heart failure (HF) (Bechthold et al. 2019; Micha, Michas, Mozaffarian, 2012) A meta-analysis that evaluated the consumption of food groups and the risk of all-cause mortality showed that each additional daily dose of 100 g of red meat was positively associated with the risk of all-cause mortality (Schwingshackl et al. 2017).

Evidence addressing the relationship between CVD and meat consumption has pointed to positive associations. Thus, it is opportune to deepen and produce new evidence on this relationship between CVD and meat consumption, highlighting aspects that have not yet been evidenced, such as the differences between processed meats and unprocessed red meats, the differences between the distribution by sex, as well as the associations of dose response in the consumption of processed meats and unprocessed red meats and cardiovascular health and it is in this sense that the present systematic review and meta-analysis will be able to contribute with the clinical recommendations and with the health of the populations.

In terms of the relevance of evidence that links the consumption of red and processed meat as a risk factor for the development of chronic, non-communicable diseases (Wiseman, Thompson, Allen, 2018) and all-cause mortality (Schwingshackl et al. 2017), it is appropriate to investigate the association between the gradient of the consumption of meat and the different types of CVD. Therefore, the aim of this study was to examine the associations of the consumption of unprocessed red meat and processed meat with the incidence of cardiovascular disease and mortality, and the dose-response relationship.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes: The PRISMA Statement (Liberati et al. 2009). Further methodological details of the study have been published elsewhere (De Medeiros, et al. 2019). The study is registered in Prospero under the number CRD42019100914.

Search strategy

Literature published until February 04, 2021 was retrieved through a structured search of 10 electronic databases: MEDLINE/PubMed, Scopus, SciELO, LILACS, ScienceDirect, Web of Science, Cochrane (CENTRAL), WHOLIS, PAHO and Embase, without language or year of publication restrictions. In addition, we also searched the references of published studies.

We performed an exploratory search, then defined the search strategy to include the following items: diet as exposure; consumption of unprocessed red meat or processed meat; cardiovascular diseases as outcome; and type of study as prospective epidemiological studies (cohort longitudinal). A complete and detailed summary of the search strategies used for each database can be found in Supplementary Appendix 1.

Study selection

Four authors (GXBM, DFOS, KPMA, IDSFP) independently screened titles and abstracts to ascertain relevance; disagreements were resolved by consensus after discussion with a fifth researcher (GP).

To be eligible for inclusion, studies needed to (1) be a prospective epidemiological study (longitudinal cohort); (2) with population apparently healthy people; (3) have assessed the association between the consumption of red or processed meat and the incidence of or mortality by cardiovascular disease.

It was chosen to include longitudinal cohort studies because, according to Micha, Michas, Mozaffarian (2012), to understand the effects of meat consumption on the development of chronic diseases, prospective observational studies provide the most robust evidence available. In addition, due to lack of blinding, noncompliance, and crossing over time, the interpretation of any RCT would be limited.

Reviewers excluded records if: (1) it was a study of animals; (2) risk assessment was related to the consumption of nutrients (animal protein, fat); (3) risk assessment only related to the consumption of all meat, including white meat (poultry and fish); 4) the study does not specify CVD. No searches were performed in the gray literature.

Data extraction

Two reviewers (KPMA, GXBM) independently conducted data extraction of the methodological characteristics, follow-up and outcomes of the studies, using standardized forms; disagreements were solved by consensus or by a third reviewer (GP). The extracted risk estimates and confidence intervals were the highest consumption versus the lowest consumption (reference) of red meat, and the respective results of the dose-response test (p-trend).

Methodological quality assessment

Four researchers (GXBM, DFOS, IDSFP, and KPMA) evaluated the methodological quality of the studies using the Newcastle-Ottawa scale (NOS) (Wells et al. 2015) (Supplementary Appendix 2). Disagreements were solved by consensus or by a fifth reviewer (GP).

Data synthesis

Measures of association (RRs/HRs/ORs) and their respective confidence intervals (95% CIs) were collected in each study that evaluated the association between consumption of unprocessed red meat and processed meat (low vs high) and outcomes. evaluated (Ischemic stroke, hemorrhagic

stroke, total stroke, heart failure, coronary heart disease and CHD mortality).

For the quantitative synthesis, we adopted all measures (HRs, ORs and RRs) as results equivalent to the RR measure, in addition, the logarithmic transformation of the RRs was calculated to reduce the standardization of results through the inverse variance method (DerSimonian and Laird, 1986; Munn et al. 2015). The calculation of heterogeneity was conducted using Cochran's Q tests (X^2) and I^2. Finally, the random effects model was chosen because it is a more conservative method. All analyzes were performed in Cochrane's recommended software, Review Manager 5.3.

Definition of red meat and processed meat

We observed that, in the included studies, there was no uniformity in the definitions for unprocessed red meat and processed meat. According to the terms defined by the WHO and adopted by this systematic review, the term "unprocessed red meat" was also found as "fresh red meat" (Larsson, Virtamo, Wolk, 2011a, 2011b) and "red meat" (Del Gobbo et al. 2015; Haring et al. 2014; Nagao et al. 2012; Takata et al. 2013). The term "processed meat" was also found as "processed red meat" (Bernstein et al. 2012; Würtz et al. 2016), and one study used "red meat" as a synonym for "processed meat" (Nettleton et al. 2008). The definitions used by each study are described in supplementary Appendix 3.

Based on the IARC definitions (Stewart et al., 2015), in this systematic review, we used the following definitions:

- Unprocessed red meat: unprocessed muscle meat from mammals, such as beef, veal, pork, lamb, mutton, horse or goat, including minced and/or frozen meat. It is usually eaten cooked (Stewart et al., 2015).
- Processed meat: meat that has been processed by salting, curing, fermentation, smoking or other processes that enhance the flavor or improve preservation. Most processed meat contains pork or beef, but it can also contain other types of red meat, poultry, organ meat (such as liver) or meat byproducts such as blood. Processed meat includes products such as bacon, sausages, ham, chicken nuggets, poultry deli meats and other deli meats and pâté.

Results

Literature flow

Out of the 10.595 records retrieved from the research bases and the 5 records identified by a survey in the references of published systematic reviews and meta-analyzes, 59 full-text articles were assessed in detail as they reported evaluating the association of red meat consumption and the incidence of or mortality by cardiovascular disease. Twenty-one articles were selected and assessed for their methodological quality, using the NOS scale, and subsequently included in the systematic review (Al-Shaar et al. 2020; Amiano et al. 2016; Ascherio et al. 1994; Bernstein et al. 2010, 2012; Burke et al. 2007; Del Gobbo et al. 2015; Haring et al. 2014, 2015; Kaluza, Åkesson, Wolk, 2014, 2015; Larsson, Virtamo, Wolk, 2011a, 2011b; Nagao et al. 2012; Nettleton et al. 2008; Saito 2020; Sauvaget et al. 2003; Takata et al. 2013; Whiteman et al. 1999; Würtz et al. 2016; Yaemsiri et al. 2012). Considering the heterogeneity found in the studies, 9 articles were included in the meta-analysis (Al-Shaar et al. 2020; Amiano et al. 2016; Bernstein et al. 2012; Larsson, Virtamo, Wolk, 2011a, 2011b; Nagao et al. 2012; Saito 2020; Takata et al. 2013; Yaemsiri et al. 2012). The final PRISMA diagram is shown in Figure 1.

Characteristics of the studies

The 21 studies in the present review include publications from 1994 to 2020, involving cohort studies carried out on three continents: America, Europe and Asia. The studies had follow-ups that varied from 4 to 30 years. Considering the baseline, the research subjects in 17 articles were adults and the elderly (Al-Shaar et al. 2020; Amiano et al. 2016; Ascherio et al. 1994; Bernstein et al. 2012; Haring et al. 2014, 2015; Kaluza, Åkesson, Wolk, 2014, 2015; Larsson, Virtamo, Wolk, 2011a, 2011b; Nagao et al. 2012; Nettleton et al. 2008; Saito 2020; Takata et al. 2013; Whiteman et al. 1999; Würtz et al. 2016; Yaemsiri et al. 2012). In two studies, the sample was composed of adults under 60 years of age, but with participants who become older than 60 years of age during the follow-up of the cohort (Bernstein et al. 2012; Sauvaget et al. 2003); One study was of adolescents, adults and elderly subjects (Burke et al. 2007); One study was with elderly people as the subjects of the research (Del Gobbo et al. 2015). By means of multivariate analysis, 47,6% of the studies presented risk measures according to sex (Amiano et al. 2016; Ascherio et al. 1994; Bernstein et al. 2010, 2012; Kaluza, Åkesson, Wolk, 2014, 2015; Larsson, Virtamo, Wolk, 2011b, 2011a; Nagao et al. 2012; Takata et al. 2013; Würtz et al. 2016; Yaemsiri et al. 2012).s

In 21 studies, data collection on food consumption was performed through a Food Frequency Questionnaire (FFQ), and only one study used a Food History Questionnaire (Amiano et al. 2016). Three studies did not mention questionnaire validation (Burke et al. 2007; Larsson, Virtamo, Wolk, 2011b; Whiteman et al. 1999); whereas the other studies used validated instruments: four studies used validated questionnaires for food and nutrients (Amiano et al. 2016; Bernstein et al. 2012; Saito 2020; Takata et al. 2013), two used questionnaires validated only for food (Bernstein et al. 2010; Sauvaget et al. 2003) and 12 used questionnaires validated for nutrients and not for food (Al-Shaar et al. 2020; Ascherio et al. 1994; Del Gobbo et al. 2015; Haring et al. 2014, 2015; Kaluza, Åkesson, Wolk, 2014, 2015; Larsson, Virtamo, Wolk, 2011a; Nagao et al. 2012; Nettleton et al. 2008; Würtz et al. 2016; Yaemsiri et al. 2012).

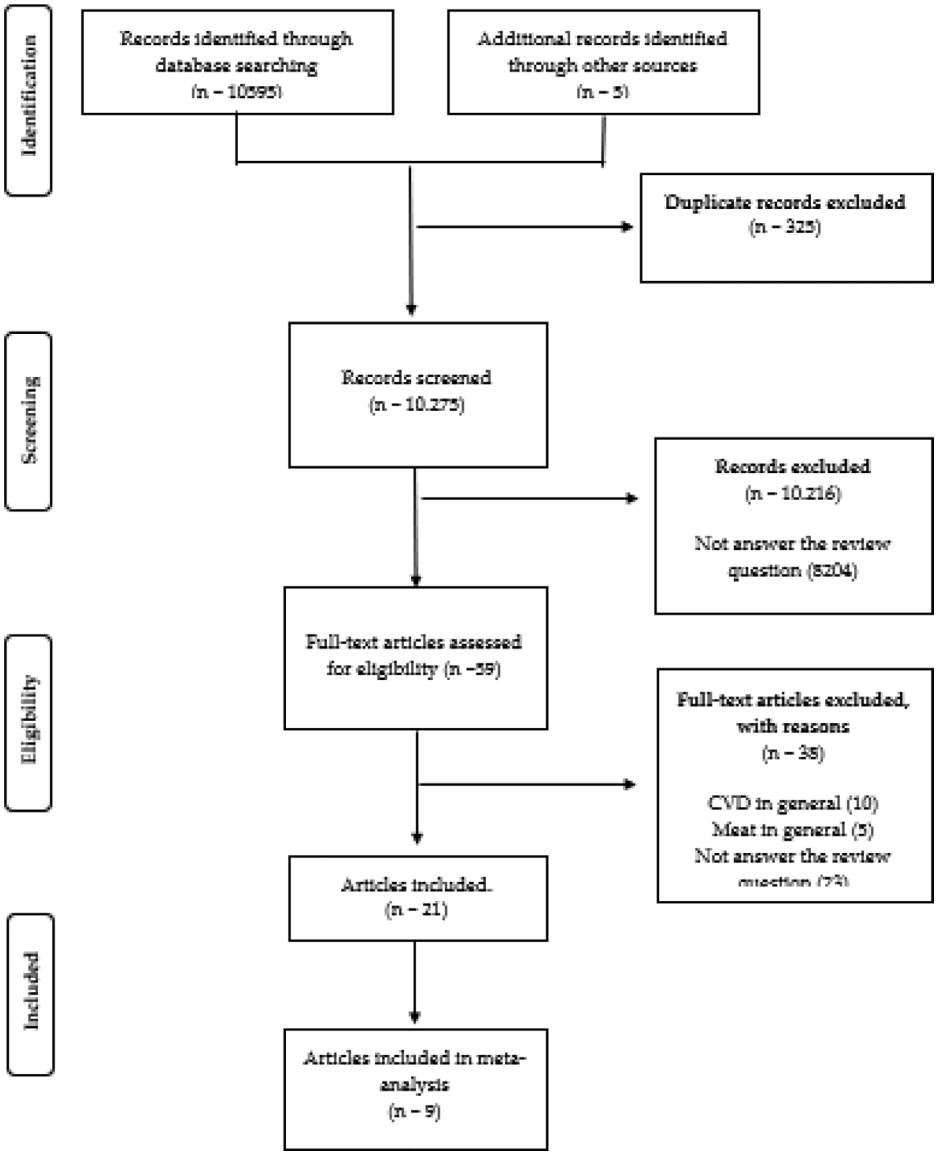

Figure 1. Flow chart of study selection, based on PRISMA (Liberati et al. 2009).

The analysis of the association between CVD and the consumption of red meat and processed meat showed the following results: 19 articles evaluated the association between the consumption of unprocessed red meat (Al-Shaar et al. 2020; Amiano et al. 2016; Ascherio et al. 1994; Bernstein et al. 2010, 2012; Del Gobbo et al. 2015; Haring et al. 2014, 2015; Kaluza, Åkesson, Wolk, 2014, 2015; Larsson, Virtamo, Wolk, 2011a, 2011b; Nagao et al. 2012; Sauvaget et al. 2003; Saito 2020; Takata et al. 2013; Whiteman et al. 1999; Würtz et al. 2016; Yaemsiri et al. 2012); 18 articles evaluated the association between processed meat consumption (Al-Shaar et al. 2020; Amiano et al. 2016; Bernstein et al. 2010, 2012; Burke et al. 2007; Del Gobbo et al. 2015; Haring et al. 2014, 2015; Kaluza, Åkesson, Wolk, 2014, 2015; Larsson, Virtamo, Wolk, 2011a, 2011b; Nagao et al. 2012; Nettleton et al. 2008; Sauvaget et al. 2003; Saito 2020; Whiteman et al. 1999; Würtz et al. 2016). The characteristics of the included studies are described in the Supplementary Appendix 4.

In 14 studies, the analysis of the meat consumption gradient was based on the categorization of the sample into quintiles; in the other articles, the categorization of the sample occurred randomly, with four studies categorizing by frequency of consumption and six by consumption portion. Consumption measures varied by weight, number of servings and frequency of consumption without quantification (Table 1).

The CVDs evaluated in the inserted studies were stroke, heart failure (HF) and coronary heart disease (CHD).

The risk results were found from the measurements of hazard ratios, relative risk or risk ratio (95% confidence intervals) of the incidence of and mortality by CVD according to the categories of unprocessed red meat and processed meat consumption in women, men and both, as presented in Tables 2 and 3, respectively.

Table 1. Categorization of the sample by consumption of unprocessed red meat and processed meat of each study inserted in the systematic review.

			Meat Consumption					
			Women		Men		Men and women	
Unprocessed red meat.	Categorization of the sample	Und	lowest	Highest or consumption amount	lowest	Highest or consumption amount	lowest	Highest or consumption amount
Al-Shaar et al. (2020)	quintiles	medium svg/day	–	–	0.14	1.09	–	–
Würtz (2016)	serving	g/week	–	150	–	150	–	–
Saito (2020)	quartiles	mean (±SE) g/day	3.1 ± 0.04	23.1 ± 0.2	5.5 ± 0.1	38.2 ± 0.3	–	–
Amiano et al. (2016)	quintiles	g/day	< 11.1	≥ 52.4	< 24.3	≥ 86	–	–
Bernstein et al. (2010)	quintiles	median svg/day	0.28	1.17	–	–	–	–
Nagao et al. (2012)	quintiles	median g/day	4.0	43.9	6.4	57.8	–	–
Sauvaget et al. (2003)	frequency	times/week	–	–	–	–	Never	Almost daily
Takata et al. (2013)	quintiles	median g/day	15.0	94.8	20.0	114.9	–	–
Bernstein et al. (2012)	quintiles	median svg/day	0.28	1.08	0.14	1.11	–	–
Del Gobbo et al. (2015) *	quintiles	–	–	–	–	–	NS	NS
Haring et al. (2014)	quintiles	median svg/day	–	–	–	–	0,1	1.1
Kaluza, Åkesson, and Wolk (2014)	serving	median g/day	–	–	17.0	83.2	–	–
Kaluza, Åkesson, and Wolk (2015)	serving	median g/day	14	58	–	–	–	–
Yaemsiri et al. (2012)	serving	medium svg/day	–	1	–	–	–	–
Larsson (2011b)	quintiles	g/day	–	–	< 33.5	> 83.1	–	–
Larsson, Virtamo, and Wolk (2011b)	quintiles	g/day	< 16.5	≥ 48.8	–	–	–	–
Ascherio et al. (1994)	frequency	times/month [a] times/week [b]	≤ 1[a]	≥ 4[b]	–	–	–	–
Whiteman et al. (1999)	frequency	days week	–	–	–	–	< 1	4-7
Haring et al. (2014)	quintiles	median svg/day	-	-	-	–	0.14	1.08
Processed meat.								
Al-Shaar et al. (2020)	quintiles	medium svg/day	–	–	0.02	0.71	–	–
Würtz (2016)	serving	g/week	–	150	–	150	–	–
Burke et al. (2007)	frequency	serves/month	–	–	–	–	≤4	> 4
Saito (2020)	quartiles	mean (±SE) g/day	2.1 ± 0.03	11.7 ± 0.1	1.3 ± 0.02	8.4 ± 0.1		
Amiano et al. (2016)	quintiles	g/day	< 12.0	≥ 46.0	< 21.5	≥72.6	–	–
Bernstein et al. (2010)	quintiles	median svg/day	0.00	0.43	–	–	–	–
Nagao et al. (2012)	quintiles	medium g/day	0.9	10.4	1.2	13.9	–	–
Nettleton et al. (2008)	serving	medium svg/day	–	–	–	–	–	1.1 (± 0.02)
Sauvaget et al. (2003)	frequency	times/week	–	–	–	–	Never	Almost daily
Bernstein et al. (2012)	quintiles	median svg/day	0.05	0.64	0.03	0.71	–	–
Del Gobbo et al. (2015) *	quintiles	median	–	–	–	–	NS	NS
Haring et al. (2014)	quintiles	median svg/day	–	–	–	–	0,00	1.1
Kaluza, Åkesson, and Wolk (2014)	serving	median g/day	–	–	15.5	89.7	–	–
Kaluza, Åkesson, and Wolk (2015)	serving	median g/day	16	60	–	–	–	–
Larsson et al (2011b)	quintiles	g/day	–	–	< 20.1	≥ 57.1	–	–
Larsson, Virtamo, and Wolk (2011b)	quintiles	g/day	< 12.1	≥ 41.3	–	–	–	–
Whiteman et al. (1999)	tercile	days week	–	–	–	–	< 1	4-7
Haring et al. (2014)	quintiles	median svg/day	-	-	-	–	0	1.07

svg – servings; NS – not show.
*Reported that it was analyzed in quintile but did not present the consumption values.

Methodological quality

The studies included feature scores ranging between six and nine, with a median of eight points in the total NOS score. The details of the assessment of each study are described in supplementary Appendix 2.

The assessment of methodological quality indicated that most studies had good quality. From these assessments, it was found that the representativeness of the exposed cohort, verification of exposure and adequacy of follow-up were the most problematic items in the studies.

Meta-analysis of the association of consumption of unprocessed red meat, processed meat and CVD

The feasibility assessment for the meta-analysis study showed the existence of heterogeneity in outcomes among the analyzed articles. The studies showed diversity in the presentation of variables related to the consumption of unprocessed red meat and processed meat, both in the unit of presentation and in the classification by sex. Furthermore, differences were highlighted in the methods used to assess the association between consumption and the incidence of CVD and consumption and mortality from CVD. From this perspective, analysis of consumption was observed through association with a specific portion and evaluations through comparison of meat consumption density (higher consumption and lower consumption). And finally, it was still found in some articles insufficient information to convert the values into a single unit.

Thus, in view of the identified heterogeneity, 9 articles were included in the meta-analysis that met the following parameters: studies that carried out an association between higher and lower meat consumption; studies that presented

Table 2. Hazard ratios, relative risk or risk ratio (95% confidence intervals) of incident cardiovascular disease (CVD) by categories of unprocessed red meat and processed meat consumption in women, men and both.

Women			Men			Women and Men		
Study	HR/RR(95% CI)	P for Trend	Study	HR/RR (95% CI)	P for Trend	Study	HR/RR (95% CI)	P for Trend
Total stroke								
Unprocessed red meat								
Amiano et al. (2016)	1.21 (0.79, 1.85)	0.10	Amiano et al. (2016)	0.81 (0.54, 1.21)	0.15	Haring et al. (2014)	1.24 (0.94, 1.63)	–
Bernstein et al. (2012)	**1.19 (1.02, 1.40)**	**0.04**	Bernstein et al. (2012)	1.11 (0.88, 1.39)	0.51			
Larsson et al. (2011b) [∞]	1.07 (0.91, 1.23)	0.31	Larsson et al. (2011a)	1.07 (0.93, 1.24)	0.77			
Processed meat								
Amiano et al. (2016)	0.81 (0.51, 1.27)	0.17	Amiano et al. (2016)	0.92 (0.64–1.32)	0.82			
Bernstein et al. (2012) NHS	1.10 (0.95, 1.27)	0.13	Bernstein et al. (2012) HPFS	**1.27 (1.03, 1.55)**	**< 0.01**			
Larsson et al. (2011b) SMC	1.18 (1.00, 1.38)	0.25	Larsson et al. (2011b) CSM	**1.23 (1.07, 1.40)**	**0.004**			
Ischemic Stroke								
Unprocessed red meat								
Amiano et al. (2016)	1.24 (0.74, 2.05)	0.13	Amiano et al. (2016)	0.80 (0.51, 1.25)	0.51	Bernstein et al. (2012)	**1.27 (1.06, 1.53)**	0.05
Larsson et al. (2011b)	1.12 (0.93, 1.34)	0.15	Larsson et al. (2011b)	1.02 (0.87, 1.20)	0.63			
Yaemsiri et al. (2012)	0.97 (0.63-1.48) *	-						
Processed meat								
Amiano et al. (2016)	0.82 (0.47, 1.42)	0.31	Amiano et al. (2016)	0.86 (0.57–1.29)	0.77	Bernstein et al. (2012)	1.15 (0.98, 1.35)	**0.03**
Larsson et al. (2011b)	**1.24 (1.04, 1.49)**	0.15	Larsson et al. (2011b)	**1.18 (1.01, 1.38)**	**0.03**			
Hemorrhagic stroke								
Unprocessed red meat								
Larsson, Virtamo, and Wolk (2011b) [+]	0.83 (0.48, 1.42)	0.29	Larsson et al. (2011b)	1.27 (0.90, 1.80)	0.26	Bernstein et al. (2012)	0.83 (0.55, 1.27)	0.57
Larsson, Virtamo, and Wolk (2011b) [++]	0.90 (0.42, 1.91)	0.61						
Processed meat								
Larsson, Virtamo, and Wolk (2011b) [+]	0.71 (0.42, 1.18)	0.20	Larsson et al. (2011b)	1.39 (0.97, 1.99)	0.15	Bernstein et al. (2012)	1.13 (0.76, 1.67)	0.25
Larsson, Virtamo, and Wolk (2011b) [++]	1.53 (0.73, 3.20)	0.27						
Heart failure								
Unprocessed red meat								
Kaluza, Åkesson, and Wolk (2015)	1.00 (0.89, 1.13)	0,80	Kaluza, Åkesson, and Wolk (2014)	0.99 (0.87, 1.13)	0.75	Del Gobbo et al. (2015)	0.94 (0.80, 1.10)	0.44
Processed meat								
Kaluza, Åkesson, and Wolk (2015)	**1.30 (1.05, 1.60)**	**0,002**	Kaluza, Åkesson, and Wolk (2014)	**1.28 (1.10–1.48)**	**0.01**	Nettleton et al. (2008)*	1.07 (0.97, 1.17)	–
						Del Gobbo et al. (2015)	1.21 (0.92-1.60)	0.19
Coronary heart disease								
Unprocessed red meat								
Bernstein et al. (2010)	1.13 (0.99, 1.30)	**0.02**	Al-Shaar et al. (2020)	**1.24 (1.12 – 1.37)**	**<0.001**	Haring et al. (2014)	1.13 (0.89, 1.44)	0,13
Würtz et al. (2016)*	1.08 (1.02 – 1.14)	-	Würtz et al. (2016) *	1.01 (0.98 – 1.03)	-	Ascherio et al. (1994) *	1.38 (0.77-2.29)	–
Processed meat								
Bernstein et al. (2010)	1.05 (0.93,1.17)	0.11	Al-Shaar et al. (2020)	**1.24 (1.12 – 1.36)**	**<0.001**	Haring et al. (2014)	1.04 (0.85, 1.29)	0.49
Würtz et al. (2016) *	1.05 (0.96 – 1.16)	–	Würtz et al. (2016) *	1.04 (1–1.08)	–			

HR/RR of End Multivariable Model

[*]It did not perform a dose-response test.

[**]To examine more extreme levels of red meat consumption, they categorized participants into deciles of red meat consumption.

[+]intracerebral hemorrhage;

[++]subarachnoid hemorrhage.

[∞]The RR (95% CIs) was per 1 serving/d, but the p for trend was evaluated from the categorization of the sample in quintile of consumption, being the unit median svg/day, the lowest quintile 0.42 and the highest 1.78.

[∞∞]Significant of HR: $p < 0,05$.

Table 3. Hazard ratios or relative risk (95% confidence intervals) of mortality cardiovascular disease (CVD) by categories of unprocessed red meat and processed meat consumption in women, men and both.

Women			Men			Men and Women		
Study	HR/RR (95% CI)	P for Trend	Study	HR/RR (95% CI)	P for Trend	Study	HR/RR (95% CI)	P for Trend
Total stroke								
Unprocessed red meat								
						Sauvaget et al. (2003)	1.01 (0.73, 1.38)	0.857
Processed meat								
						Sauvaget et al. (2003)	0.90 (0.61,1.33)	0.812
Ischemic Stroke								
Unprocessed red meat								
Takata et al. (2013)	0.84 (0.55, 1.28)	0.38	Takata et al. (2013)	1.22 (0.69, 2.15)	0.73			
Hemorrhagic stroke								
Unprocessed red meat								
Takata et al. (2013)	**0.57 (0.37, 0.87)**	0.01	Takata et al. (2013)	0.71 (0.43, 1.20)	0.32			
Saito (2020)	0.82 (0.43-1.54)	0.522	Saito (2020)	1.07 (0.65, 1.79)	0.574			
Processed meat								
Saito (2020)	1.24 (0.65-2.35	0.408	Saito (2020)	0.73 (0.44-1.21)	0,237			
Heart failure								
Unprocessed red meat								
			Kaluza, Åkesson, and Wolk (2014)	0.77 (0.47, 1.27)	0.40			
Processed meat								
			Kaluza, Åkesson, and Wolk (2014)	**2.43 (1.52–3.88)**	**<0.001**			
Red meat								
			Kaluza, Åkesson, and Wolk (2014)	1.30 (0.75–2.27)	0.03			
Coronary heart disease								
Unprocessed red meat								
Nagao et al. 2012	1.23 (0.82, 1.85)	0.32	Nagao et al. (2012)	0.7 (0.47, 1.04)	**0.04**	Whiteman et al. (1999)*	0.55 (0.31–0.99)	-
Takata et al. (2013)	1.28 (0.84, 1.96)	0.43	Takata et al. (2013)	**1.54 (1.02, 2.32)**	0.07	Takata et al. (2013)	**1.41 (1.05-1.89)**	**0.04**
Saito (2020)	0.94 (0.60-1.48)	0.856	Saito (2020)	0.89 (0.64-1.23)	0.280			
			Al-Shaar et al. (2020)	**1.35 (1.15, 1.58)**	**0.001**			
Processed meat								
Saito (2020)	0.95 (0.61-1.49)	0,680	Saito (2020)	0.84 (0.59-1.18)	0,219			
Nagao et al. (2012)	0.98 (0.59 – 1.62)	0.63	Nagao et al. (2012)	**0.56 (0.36 -- 0.88)**	**0.002**	Burke et al. (2007)*	**2.21 (1.05, 4.63)**	–
			Al-Shaar et al. (2020)	**1.29 (1.11, 1.50)**	0,05	Whiteman et al. (1999)*	1.28 (0.46–3.54)	–

HR indicates Hazard Ratios. RR indicates Risk Relative. The HR/RR is the of End Multivariable Model.
*It did not perform a dose-response test.

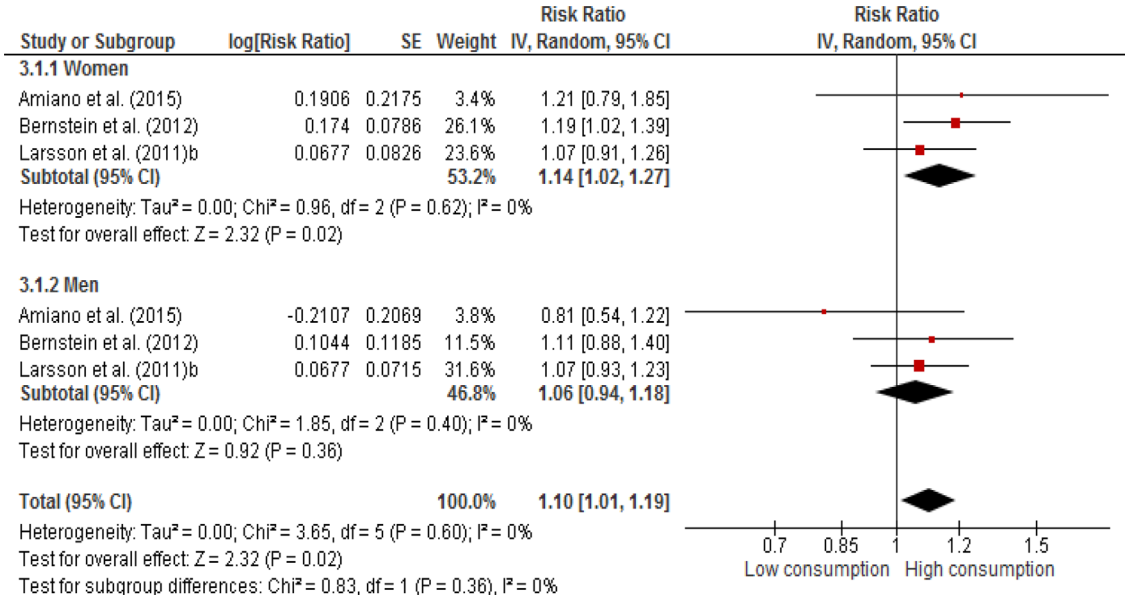

Figure 2. Forest plot of the risk of Total stroke incidence and unprocessed red meat consumption.

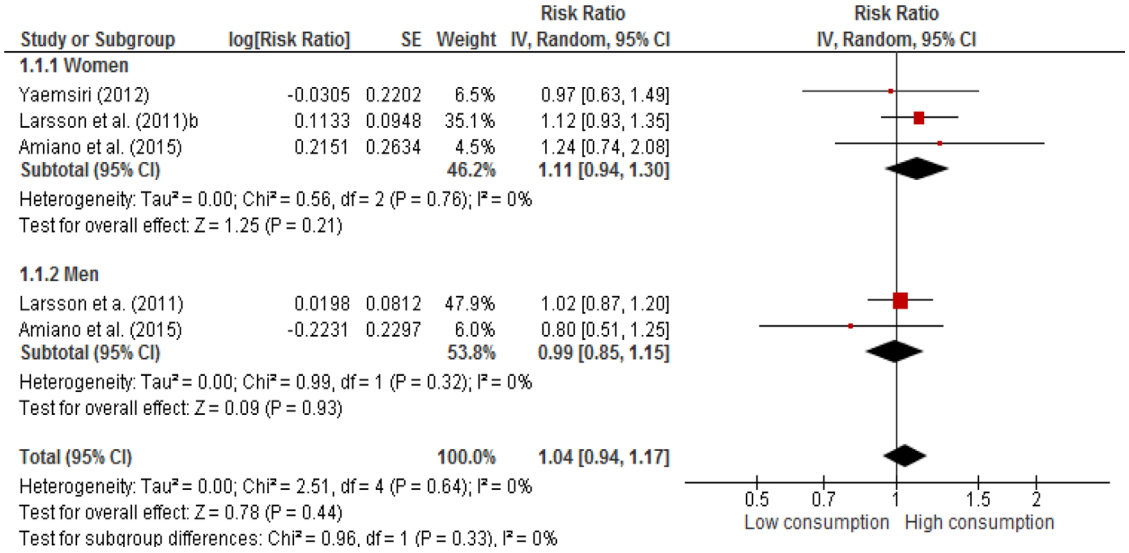

Figure 3. Forest plot of the risk of Ischemic stroke incidence and unprocessed red meat consumption.

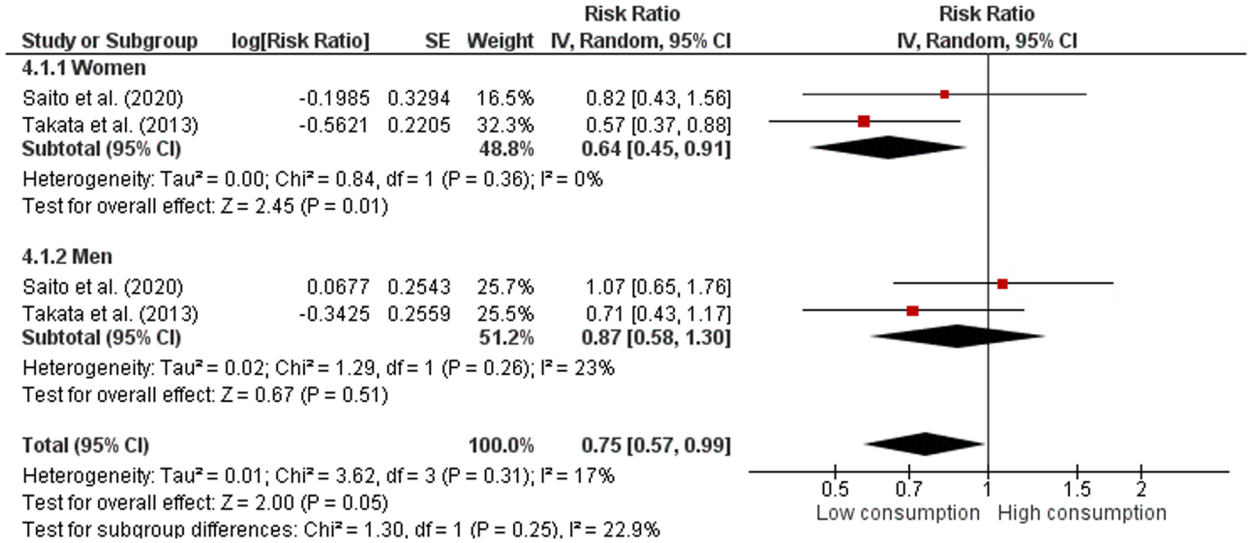

Figure 4. Forest plot of the risk of Hemorrhagic Stroke Mortality and unprocessed red meat consumption.

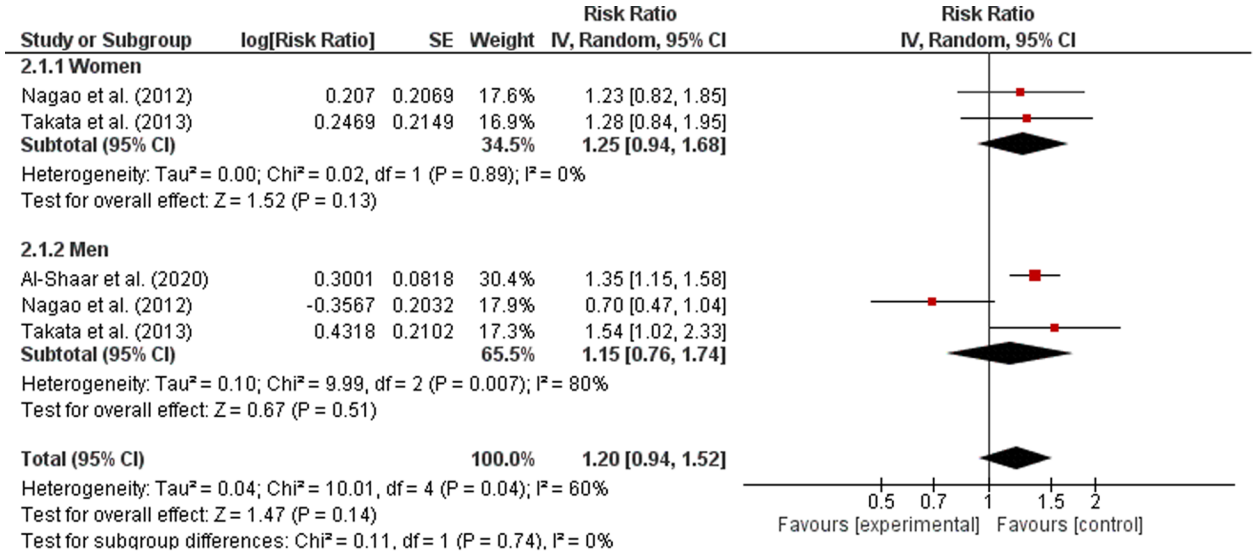

Figure 5. Forest plot of the risk of CHD Mortality and unprocessed red meat consumption.

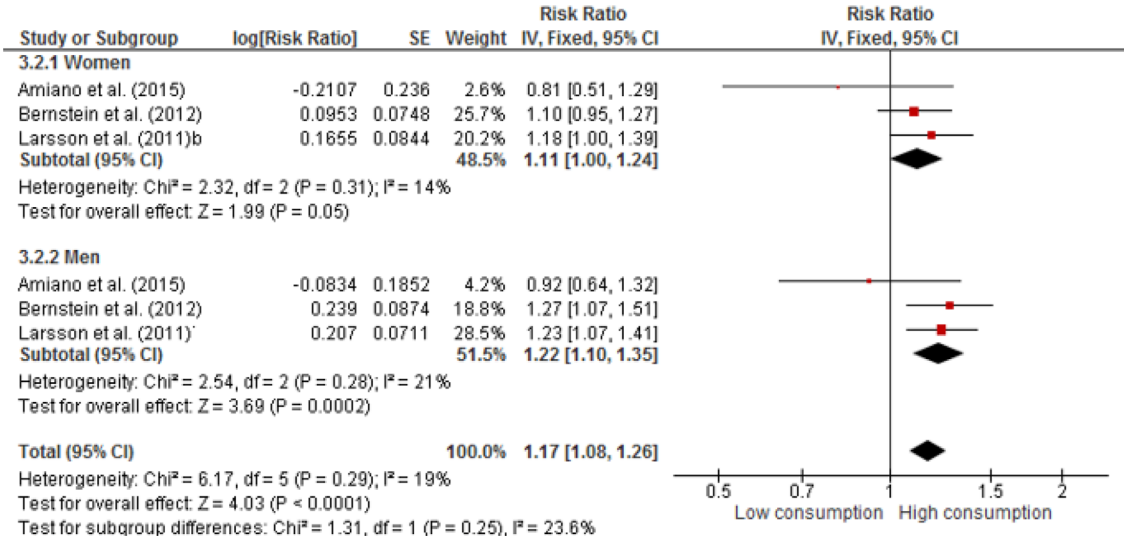

Figure 6. Forest plot of the risk of Total stroke incidence and processed meat consumption.

the evaluation of meat consumption in grams per day and studies in the data allowed the conversion of meat consumption into grams per day.

Among the articles included in the meta-analysis, in the evaluation of the association between the consumption of unprocessed red meat and total stroke incidence, three studies (four articles) were included (Amiano et al. 2016; Bernstein et al. 2012; Larsson, Virtamo, Wolk, 2011a, 2011b) (Figure 2); with Ischemic stroke, three studies were included (four articles) (Amiano et al. 2016; Bernstein et al. 2012; Larsson, Virtamo, Wolk, 2011a, 2011b) (Figure 3); with Hemorrhagic Stroke Mortality two studies were included (Takata et al. 2013; Saito 2020) (Figure 4); and with CHD Mortality three studies were included (Al-Shaar et al. 2020; Nagao et al. 2012; Takata et al. 2013) (Figure 5).

To evaluate the consumption of processed meat and total stroke incidence there were three studies (four articles) included in the metaanalysis (Amiano et al. 2016; Bernstein et al. 2012; Larsson, Virtamo, Wolk, 2011a, 2011b) (Figure 6); with Ischemic stroke incidence, two studies (three articles) were included (Amiano et al. 2016; Larsson, Virtamo, Wolk, 2011a, 2011b) (Figure 7); for CHD Mortality were three studies (Al-Shaar et al. 2020; Nagao et al. 2012; Saito 2020) (Figure 8).

The results of the meta-analysis showed a positive and statistically significant association between the consumption of unprocessed red meat and processed red meat with CVD, specifically for the two types of consumption the association occurred with the total stroke incidence respectively (RR 1.10; 95%; CI 1.01 to 1.19; $p=0.02$) (RR 1.17; 95%; CI 1.08 to 1.26; $p<0.0001$).

However, in the analysis, no positive associations were observed between the consumption of the two types of meat and Ischemic stroke incidence, nor CHD Mortality.

And for Hemorrhagic Stroke Mortality the assessment in the consumption of unprocessed red meat showed an

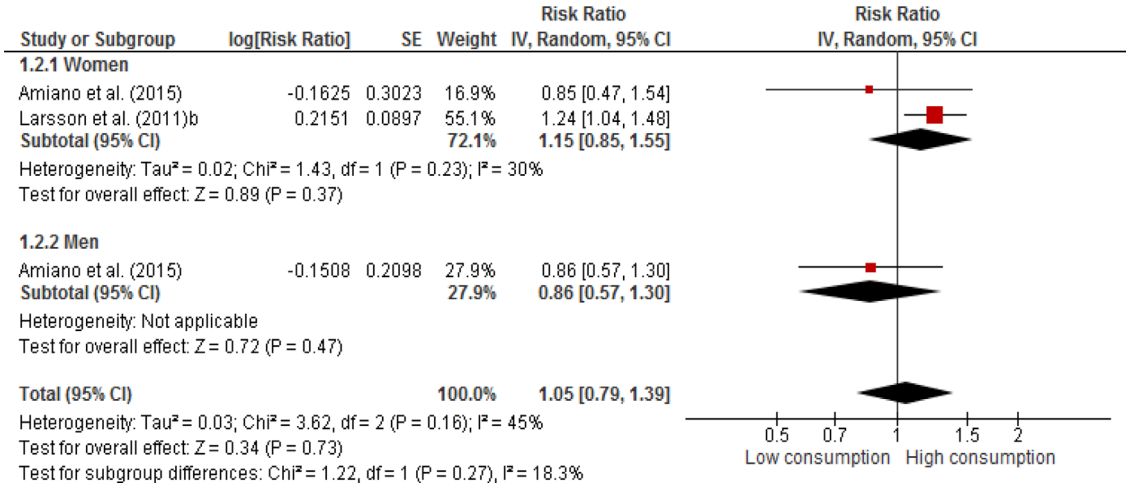

Figure 7. Forest plot of the risk of Ischemic stroke incidence and processed meat consumption.

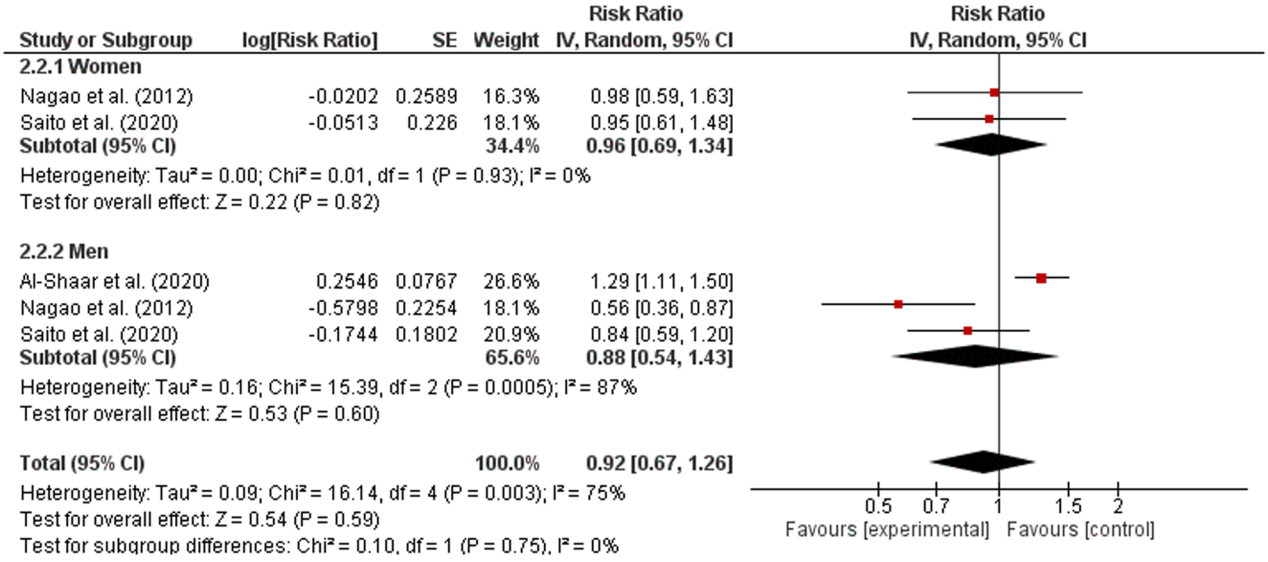

Figure 8. Forest plot of the risk of CHD Mortality and processed meat consumption.

association of protection for women (RR 0.64; 95%; CI 0.45 to 0.91; p = 0.01).

Unprocessed red meat consumption and CVD

Among the 13 studies that evaluated the association of the consumption of unprocessed red meat with the incidence of CVD, three studies found a positive association (Al-Shaar et al. 2020, Bernstein et al. 2012; Würtz et al. 2016). We point out that these three articles present a low risk of bias according to the NOS scale.

One of the studies showed association with total stroke and ischemic stroke in women, with a significant linear trend dose response for total stroke only (Bernstein et al. 2012); and the other two studies, found an association with CHD, one in women, but did not perform a dose-response test (Würtz et al. 2016), and other, in men with a significant linear trend dose response (Al-Shaar et al. 2020).

Regarding the association between the consumption of unprocessed red meat and CVD mortality, two studies (Al-Shaar et al. 2020; Takata et al. 2013) there was a risk association for CHD mortality in men, but one with a significant linear trend dose response (Al-Shaar et al. 2020), and another no (Takata et al. 2013).

In women, the consumption was associated as a protective factor for hemorrhagic stroke mortality, with a significant linear trend dose response (Takata et al. 2013). It is important to note that among the studies that tested negative, one study (Nagao et al. 2012) found a significant linear trend in dose response in men, but not in women.

These studies (Al-Shaar et al. 2020; Takata et al. 2013; Nagao et al. 2012) were evaluated with a low risk of bias, with scores between 8 and 9 out of 10.

Although few studies were included in the meta-analysis, the general result corroborates the other studies, showing a non-significant association for CVD found, with the exception of Total Stroke. However, the results of the dose-response test that show association call our attention.

A possible explanatory hypothesis for the association with the dose-response lies in the fact that the excessive consumption of red meat assumes an excessive consumption of proteins and fats, and therefore, an imbalance in the consumption of carbohydrates. Biochemistry research shows that this imbalance can lead to an excess of Acetyl-CoA molecules available for the citric acid cycle. Thus, the organism will tend to preserve the excess Acetyl-CoA, which starts to divert the molecules to the biosynthesis pathway of fatty acids, grouping themselves in triglycerides and fatty acids and, finally, being stored in adipose tissue (Nelson and Cox, 2017). Thus, the excess consumption of red meat, along with other risk factors, such as a lack of physical activity, sedentary behavior and alcohol consumption, can cause elevated cholesterol levels and blood pressure, which are risk factors for the development of CVD.

There are still questions about the association of CVD with the consumption of other nutrients present in meat, such as saturated fatty acids (SFA) and heme iron (Bronzato and Durante, 2017; Chowdhury et al. 2014; Lacroix, Cantin, Nigam, 2017; Quintana et al., 2018; Singh et al. 2013; Zhang et al. 2012). In this context, other environmental elements that relate the consumption of red meat with cardiovascular risk, such as the intestinal microbiome, have begun to be investigated (Bronzato and Durante, 2017), This research has identified the microbial metabolite of trimethylamine N-oxide as possibly being responsible, through the link between the microbiota and the synthesis of the pro-atherogenic compound, trimethylamine N-oxide (TMAO) of L-carnitine and choline, present in red meat (Koeth et al. 2013).

Processed meat consumption and CVD

Of the studies that evaluated the association of the consumption of processed meat (Al-Shaar et al. 2020; Amiano et al. 2016; Bernstein et al. 2010, 2012; Del Gobbo et al. 2015; Haring et al. 2014; Kaluza, Åkesson, Wolk, 2014, 2015; Larsson, Virtamo, Wolk, 2011, 2011b; Nettleton et al. 2008; Würtz et al. 2016) with the incidence of CVD, we observed that two studies showed an association with total stroke in men, with a significant linear trend dose response (Bernstein et al. 2012; Larsson, Virtamo, Wolk, 2011a, 2001b). We also found an association between the consumption of processed meat and the incidence of HF, with a significant linear trend dose response in both women (Kaluza, Åkesson, Wolk, 2015) and men (Kaluza, Åkesson, Wolk, 2014); and one study founds association with CHD (Al-Shaar et al. 2020) with a significant linear trend dose response in men.

In terms of the stroke subtypes (ischemic or hemorrhagic), the selected study found an association between processed meat consumption and ischemic stroke in both men and women, with a significant linear trend dose response in men (Larsson, Virtamo, Wolk, 2011a) but not in women (Larsson, Virtamo, Wolk, 2011 b). The study found no association with hemorrhagic stroke (Larsson, Virtamo, Wolk, 2011a, b). These studies were assessed as having a low risk of bias, receiving a score of 7 or 9/10.

Among the studies that evaluated the association of the consumption of processed meat (Al-Shaar et al. 2020; Burke et al. 2007; Kaluza, Åkesson, Wolk, 2014; Nagao et al. 2012; Sauvaget et al. 2003; Whiteman et al. 1999) with CVD mortality three studies demonstrated association. One presented a risk association for HF mortality in men, with a significant linear trend dose response (Kaluza, Åkesson, Wolk, 2014), the second found a risk association for CHD mortality, regardless of gender, but did not perform a dose-response test (Burke et al. 2007), and the third found a risk association for CHD mortality in men with a significant linear trend dose response (Al-Shaar et al. 2020).

On the other hand, a fourth study presented the consumption of processed meat as a protective factor for mortality from CHD in men, but not in women, with a linear tendency to respond to a significant dose (Nagao et al. 2012).

Again, studies that showed an association (risk or protection) were assessed as low risk of bias with scores ranging from 7 to 9.

As for the summary measure, it was only possible to perform meta-analysis for the consumption of unprocessed red meat and processed meat with CHD Mortality and the consumption of unprocessed red meat and Hemorrhagic Stroke Mortality. There was no significant risk association for CHD Mortality, and consumption of unprocessed red meat was presented as a protective factor for Hemorrhagic Stroke Mortality among women.

Comparing the compositions of unprocessed red meat and processed meat, the processed meat has a higher content of sodium and nitrate (Bronzato and Durante, 2017).

The dietary sodium is touted as one of the factors that promotes increased blood pressure (Smyth et al. 2015; WHO, 2003), which is one of the risk factors for CVD (Bronzato and Durante, 2017; Singh et al. 2013).

Nitrate and its by-products, such as peroxynitrite, have shown to be experimentally associated with endothelial dysfunction and atherosclerosis development (Bronzato and Durante, 2017; Forstermann, 2008).

In this context, as the number of studies is small and considering that studies indicate an association between the consumption of processed meats and cancer (Stewart et al. 2015), it becomes important to carry out new cohort studies, also paying attention to the different levels of processing that the meat may have undergone.

Dose response

When exploring the consumption doses evaluated in the studies included in this systematic review, we observed that there was no methodological standardization regarding doses sizes between studies. We also found that the value that was high consumption had important variability (Table 1). In addition, some studies present consumption in servings or frequency, and not by weight (in grams) (Al-Shaar et al. 2020; Bernstein et al. 2010, 2012; Haring et al. 2014; Sauvaget et al. 2003).

It is important to note that some studies of the review that showed no association, also called “negative studies”,

presented a significant linear trend dose response for the association of the consumption of unprocessed red meat (Bernstein et al. 2010; Nagao et al. 2012) or processed meat (Bernstein et al. 2012) and CVD. The dose-response test indicates that any increase in the level of exposure to a modifiable risk factor (e.g., the consumption of unprocessed meat or processed meat) increases the effect of this risk factor on a particular outcome (Patino and Ferreira, 2016).

Also, considering that results that showed no association may, hypothetically, show an absence of evidence of an association, and not evidence of an absence of effects on the risk of death or incidence of CVD, the results of this review indicate the need to reduce the consumption of unprocessed red meat and processed meat in dietary guidelines, based on foods aimed at preventing CVD.

Conclusion

The results found showed that the consumption of unprocessed red meat and processed meat are associated with the incidence of stroke, however, no positive association was observed in relation to mortality from CVD.

Studies that show an association between meat consumption and CVD incidence or mortality show different possible routes (excess protein and fat, microbiota, heme iron consumption), in addition to other aspects, such as the consumption of foods with saturated fats, cholesterol and simple. carbohydrates (Bronzato and Durante, 2017; Chowdhury et al. 2014; Koeth et al. 2013; Lacroix, Cantin, Nigam, 2017; Quintana et al., 2018; Souza et al. 2015; Zhang et al. 2012)

In this sense, studies that analyze food standards may be more suitable for determining risky feeding habits than studies that analyze the food alone.

In a recently published meta-analysis study, dietary patterns with low carbohydrate consumption, but with plant-derived sources of protein and fat (vegetables, nuts, peanut butter and wholegrain breads), were associated with lower all-cause mortality, whereas dietary patterns with animal-derived sources of protein and fat (lamb, pork and chicken) were associated with higher mortality (Seidelmann et al. 2018). In a follow-up study, Stewart et al. (2016), noted that the higher consumption of healthy foods can be more important for the secondary prevention of coronary artery disease than avoiding the unhealthy foods typical of Western diets.

Thus, complete diet analysis may play a more important role in determining the risk of CVD than the isolated analysis of individual nutritional constituents. However, there is evidence that the consumption of processed meats and red meat is associated with cancer (Wiseman, Thompson, Allen, 2018). Since the restriction of the consumption of red meat from dietary patterns of vegetable protein can reduce the intake of high-quality essential nutrients and proteins, it is important to evaluate the dose response of the consumption of these foods to CVD; this evaluation should consider, among other variables, the individuals' eating pattern, in order to define recommendations of these foods within a secure and cardioprotective dietary pattern.

As some studies have shown a dose-response association for CVD incidence and mortality, the importance of reducing the consumption of red meat, especially processed meat, is emphasized.

Therefore, the moderate consumption of red meat, within a cardio-protective dietary pattern and respecting the individual's characteristics, are important measures in the prevention of CVD.

Limitation

The studies that composed the present systematic review, being longitudinal observational studies, have the limitation that dietary intake was verified by means of food frequency questionnaires or food history interviews. In food validation studies, correlations between food frequency questionnaire data and food records, considered to be more accurate, rarely exceed 0.7. This limit is probably related to the fact that an individual's diet, with all its inherent complexity, cannot be fully captured by a structured questionnaire, although some of the errors are inevitably attributable to the comparison methods (Willett 2001).

Moreover, we note that the metrics used to measure the consumption of red meat were varied, and the taxonomies used for unprocessed red meat and processed meat were varied and may cause confusion.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

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