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Meta-analyses

Effect of red meat consumption on cardiovascular risk factors: A systematic review and Bayesian network meta-analysis of randomized controlled trials

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SUMMARY

Background & aims: The role of red meat in cardiovascular risk remains controversial. The aim of this systematic review and Bayesian network meta-analysis (NMA) of randomized controlled trials (RCTs) was to investigate the effects of red meat consumption on cardiovascular risk factors concerning different comparison foods.

Methods: A systematic search of RCTs was conducted from the inception to April 2024. Studies compared diets containing red meat to those replacing red meat with various foods. Comparison diets were classified into high-quality plant protein sources, animal protein, mixed animal and plant protein and carbohydrates. The effects of the dietary interventions on cardiovascular parameters were evaluated using a random-effects NMA, with an analysis of interactions between the intervention and control groups. The outcomes were the mean changes in blood lipids, blood pressure, and C-reactive protein (CRP) in the red meat group compared to the comparator group.

Results: Thirty-six RCTs were included in the analysis. Consuming plant proteins resulted in a greater reduction in total cholesterol (TC) levels (mean difference (MD) = −0.14; 95 % credible interval (CrI): −0.28 to −0.001, $p < 0.05$) and low-density lipoprotein cholesterol (LDL-C) levels (MD = −0.19; 95 % CrI: −0.36 to −0.03, $p < 0.05$) compared to red meat interventions. In contrast, interventions combining animal and plant proteins increased TG levels more than red meat interventions (MD = 0.21; 95 % CrI: 0.06 to 0.34, $p < 0.05$). The certainty of the evidence for all outcomes ranged from very low to low.

Conclusion: The findings of this NMA indicate that the effect of red meat on cardiovascular risk factors depends on the comparison food. Replacing red meat with plant protein sources was associated with favorable changes in TC levels and LDL-C.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, representing a significant public health challenge [1]. One of the topics of considerable debate in this context is the association between the consumption of red meat and an increased risk of CVD [2]. The nutritional benefits of red meat, such as its high protein, iron and essential nutrient content have been

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reported, which makes it an important dietary source in many cultures. Nevertheless, the role of red meat in the development of CVD remains uncertain, particularly when considering unprocessed red meat in comparison to processed meat, which has been more consistently linked to adverse health effects [3].

A systematic review and meta-analysis indicated that higher red meat consumption is associated with poorer cardiovascular health outcomes [4]. Conversely, another meta-analysis of randomized controlled trials (RCTs) concluded that consuming ≥ 0.5 servings of total red meat per day does not significantly affect blood lipids, lipoproteins or blood pressure [5]. Several studies in recent years have suggested that red meat consumption may have a positive impact on cardiovascular health [6,7]. Due to these disparate outcomes, different studies have questioned the advisability of limiting red meat consumption for cardiometabolic health [8–10]. A meta-analysis of RCTs by Guasch-Ferré et al. [4] reported that the effect of unprocessed red meat on various cardiovascular risk factors depended on the food included in the comparator group. In this way, the consumption of red meat did not result in a significant change in cholesterol levels compared to interventions based on the consumption of animal protein, including poultry and/or fish. However, when the comparator group consumed high-quality plant foods, higher effect sizes were observed for total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), indicating a potentially higher risk of CVD [4].

In previous meta-analyses, multi-arm studies were included as many times as there were possible comparisons [4,5]. Due to the unaddressed correlation between the estimated intervention effects from multiple comparisons, this situation introduces a unit of analysis error. One approach to overcoming a unit-of-analysis error for a study that could contribute to several correlated comparisons is to conduct a network meta-analysis (NMA) [11]. Those earlier meta-analyses also included non-RCTs [12–14]. Moreover, given that the previous publication did not incorporate the methodological suggestions proposed by Cochrane, and considering that additional RCT publications on this topic have been published after the review by Guasch-Ferré et al., [4] the results of this work could prove valuable in more accurately delineating the impact of unprocessed red meat consumption on cardiometabolic health outcomes. [11]. Therefore, the aim of this systematic review and Bayesian NMA of RCTs was to investigate the impact of red meat consumption on cardiovascular risk factors (lipid profile, blood pressure, and C-reactive protein (CRP)) in comparison with different foods consumed in the comparator group. The hypothesis proposed is that the impact of red meat on CVD risk factors would vary according to the comparison diet, suggesting a potential advantage of consuming high-quality plant protein sources.

2. Methods

2.1. Review design

A pre-established protocol-based systematic review with meta-analysis was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42024537865.

2.2. Definitions of red meat

The World Health Organization considers red meat to be the one derived from beef, veal, pork, lamb, mutton, horse, and goat that has not undergone any form of preservation other than refrigeration or freezing. As in a previous systematic review in this matter, this criterion was also considered in the present study to evaluate RCTs comparing the effects of red meat intake with other comparator groups in relation to CVD [16].

2.3. Search strategy and eligibility criteria

The following search strategy was used in MEDLINE, and adapted to other two databases (the Cochrane Library and Scopus): (“Meat”[MESH] OR “Meat Products”[MESH] OR “Red meat” OR “Beef” OR “Pork”) AND (“Hypertension”[MESH] OR “Cholesterol, LDL”[MESH] OR “Cholesterol, HDL”[MESH] OR “Blood Pressure”[MESH] OR “lipoproteins”[MESH] OR “Apolipoprotein B-100”[MESH] OR “C-reactive protein”[MESH]). The search strategy for each database is outlined in Table S1. There were no restrictions for any specific language, as recommended by international criteria [17]. The literature search was done from database inception up to 29 April 2024. Inclusion criteria are reported in Table 1.

2.4. Study selection and data extraction

Articles matching the above-mentioned criteria were selected based on a 2-level screening procedure (Fig. 1). After excluding duplicates, two researchers (MLM and ARR) independently conducted a screening selection based on title and abstract to determine their eligibility attending to selection criteria. Full text screening of research passing the previous level were then independently analyzed by the same researchers. At this point, information including authors’ names, publication year, study location, study design, sample size, follow-ups, age means, comparator interventions and key outcome measures (TC, LDL-C, high-density

Table 1
PICOS criteria used to define the research question.

Parameter	Inclusion Criteria
Patientpopulation (P)	Adults (> 18 years old), not pregnant
Intervention (I)	Dietary interventions prescribing different amounts of red meat
Comparators (C)	Dietary interventions substituting red meat consumption with different comparator foods
Outcomes (O)	$\geq$ 1 cardiovascular risk factors (i.e., total blood cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure or C-reactive protein)
Study design (S)	Randomized controlled trials with parallel or crossover designs

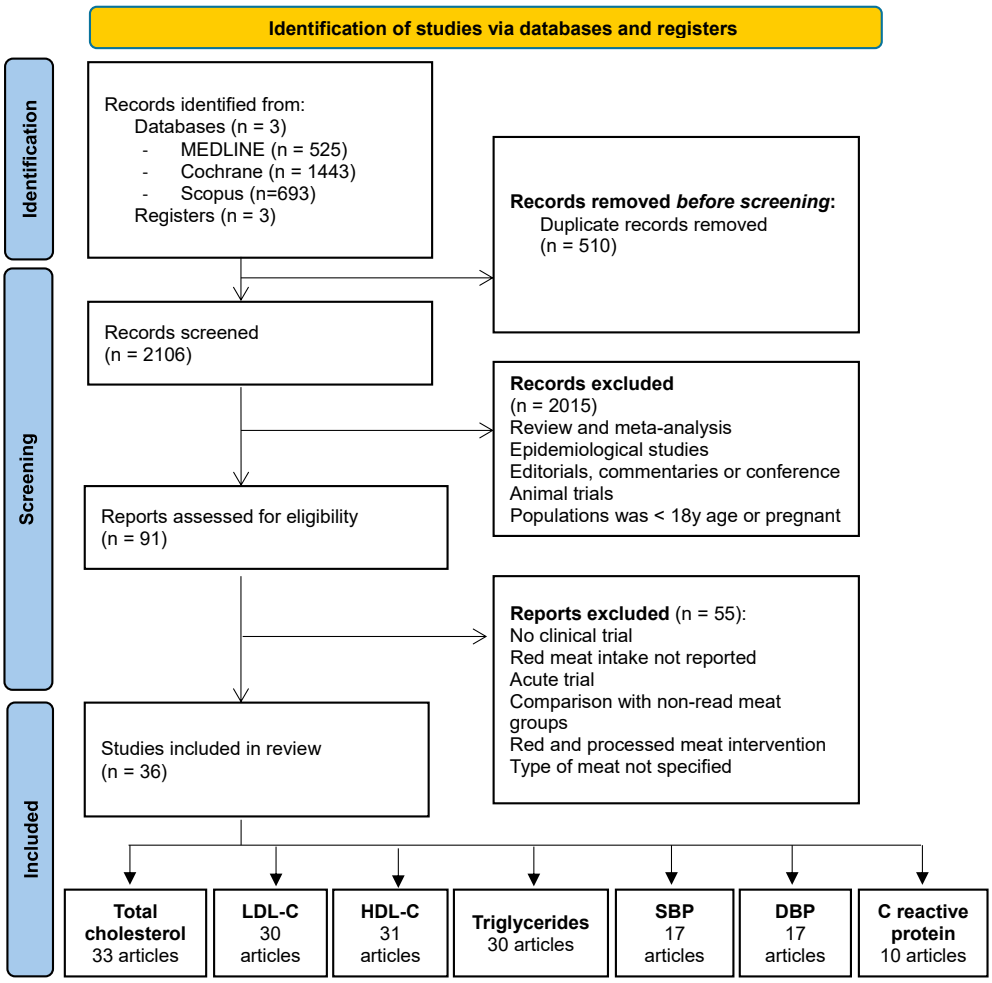

Fig. 1. Scheme of study selection. DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

lipoprotein cholesterol (HDL-C), triglycerides (TG), systolic blood pressure (SBP), diastolic blood pressure (DBP) and CRP were collected. This data can be found in Table 2. Additionally, reference lists of the included articles were also reviewed to potentially identify additional studies that met the reported criteria. Discrepancies in eligibility procedures at each stage were resolved by consensus within the research team (MLM, ARR, GB).

2.5. Methodological quality

The methodological quality of the included clinical trials was assessed using the PEDro scale, which evaluates the internal and external validity of individual studies [18]. It was originally developed by the Institute for Musculoskeletal Health at the University of Sydney and consists of 11 items that cover external validity (item 1 - specified study eligibility criteria), internal validity (items 2 - random allocation of patients, 3 - concealed allocation, 4 - measure of similarity between groups at baseline, 5 - patient blinding, 6 - therapist blinding, 7 - assessor blinding, 8 - fewer than 15 % dropouts, 9 -intention-to-treat analysis), and statistical reporting (items 10 - intergroup statistical comparisons, and 11 - point measures and variability data). The quality of studies was classified using the following cut-off points: excellent (9–10); good (6–8); fair (4–5); poor (< 4). Reliability on the independent use of the PEDro scale by two researchers (MLM and GB) was measured by inter-rater agreement and Cohen's kappa. Any lack of consensus was resolved through discussion between the two researchers (MLM and GB). Inter-rater reliability of 86 %, Scott's Pi of 0.814 and Cohen's kappa of 0.814 were found, considered almost perfect agreement.

2.6. Risk of bias and quality of evidence assessment

The risk of bias for the studies included was evaluated using the Cochrane risk of bias tool for RCTs or cluster RCTs (RoB 2.0) [19]. The risk of bias assessment was independently conducted by two researchers (GB and AR), and any discrepancies were resolved through consensus with a third investigator (MLM). This tool assesses five domains: the randomisation process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported outcome. Subsequently, the studies were categorized into three distinct groups: (1) low risk of bias: all domains were judged to have a low risk of bias; (2) some concerns: at least one domain raised some concerns, but no domain was rated as having a high risk of bias; (3) high risk of bias: at least one domain was rated as having a high risk of bias, or there were multiple domains with some concerns [19].

Table 2
Summary characteristics of the included studies.

Study	Country	Study design	Duration	Population/health status	Red meat intervention	Comparator intervention
Wiebe et al., 1984 [61]	Canada	Crossover randomized controlled trial	6 wk	8 healthy men with normal lipid profile (21 y)	Diet with 55 % of beef protein	Diet without beef protein (replaced by plant protein)
Wolmarans et al., 1991 [51]	South African	Crossover randomized controlled trial	12 wk	28 healthy adults (16 women/12 men) (35.8 ± 5.5 y)	Red meat diet (300 g/d in males and 225 g/d in females)	Fatty fish diet (280 g/d in males and 216 g/d in females)
Scott et al., 1994 [40]	USA	Randomized controlled trial	5 wk	38 men with hypercholesterolemia (20–55 y)	Beef diet (85 g of beef/d)	Chicken diet (85 g of chicken/d)
Davidson et al., 1999 [41]	USA	Randomized controlled rrial	32 wk	191 adults with hypercholesterolemia (84 women/107 men)	Lean red meat diet (170 g/d)	Lean white meat diet (170 g/d of poultry or fish)
Wolmarans et al., 1999 [53]	South Africa	Crossover randomized controlled trial	12 wk	52 adults with hypercholesterolemia (34 women, 36 men), (31.5 ± 9.6 y women; 35.1 ± 7.8 y men)	Lean beef (5 times/wk) and lean mutton (2 times/wk)	Skinless chicken (5 times/wk) and fish (2 times/wk)
Ashton et al., 2000 [56]	Australia	Crossover randomized controlled trial	8 wk	42 healthy men (45.8 y)	Lean red meat diet (150 g/d)	Tofu diet (290 g/d) in an isocaloric and isoprotein substitution
Beauchesne-Rondeau et al., 2003 [42]	Canada	Crossover randomized controlled trial	11 wk	17 men with hypercholesterolemia (50.1 ± 3.3 years)[a]	Lean beef diet	Lean fish diet, p oultry diet
Melanson et al., 2003 [43]	USA	Randomized controlled trial	12 wk	61 women with overweight (43.3 ± 7.8 y)	Hypocaloric lean beef diet and walking program	Hypocaloric chicken diet and walking program
Haub et al., 2005 [57]	USA	Randomized controlled trial	12 wk	21 men with overweight (65 ± 5 years)	Lacto-ovo vegetarian diet and beef (0.6 g protein/kg/d)	Lacto-ovo vegetarian diet and soy protein (0.6 g protein/kg/d)
Mamo et al., 2005 [73]	Australia	Randomizedc ontrolled trial	6 wk	20 adults with dyslipidemia (8 women/ 12 men)	High protein diet (25 % of total energy intake) derived from lean beef, veal and lamb	Low protein diet (14 % of total energy intake) with compensatory adjustments in carbohydrate
De Mello et al., 2006 [45]	Brasil	Crossover randomized controlled trial	12 wk	17 adults with diabetes type 2 and macroalbuminuria (3 women/14 men) (59 ± 11 y)	Red meat diet	Chicken diet
Hodgson et al., 2006 [70]	Australia	Randomized controlled trial	8 wk	60 participants (22 females and 38 males) with hypertension (≥ 20 y)	Lean red meat diet (200 g/d)	Control diet (red meat replaced by carbohydrate)
Hodgson et al., 2007 [95]	Australia	Randomized controlled trial	8 wk	60 adults with hypertension (22 women/38 men)	Lean red meat diet (200 g/d)	Control diet (red meat replaced by carbohydrate)
Mahon et al., 2007 [44]	USA	Randomized controlled trial	9 wk	54 women in the postmenopausal stage (58 ± 2 y)[a]	Lacto-ovo vegetarian diet and 250 kcal/d of beef	Lacto-ovo vegetarian diet and 250 kcal/d of (1) chicken or (2) non-meat carbohydrate
Nowson et al., 2009 [63]	Australia	Randomized controlled trial	14 wk	95 women in the postmenopausal stage with hypertension	Low-sodium DASH type diet (Vitality Diet) with 810 g/wk of raw lean red meat	Reference healthy diet red (meat replaced by breads/cereals and dairy products)
Navas-Carretero et al., 2009 [52]	Spain	Crossover randomized controlled trial	16 wk	25 young women with iron deficiency (18–30 y)	Red meat diet (5 portions/wk)	Oily fish diet (5 portions/wk)
Mateo-Gallego et al., 2011 [46]	Spain	Crossover randomized controlled trial	10 wk	36 women (71 [33–79] y)[b]	Red meat diet (lean breed lamb 3 times per wk)	Lean white meat (chicken 3 times per wk)
Murphy et al., 2012 [47]	Australia	Randomized controlled trial	24 wk	144 adults with overweight or obesity (48 ± 12 y)	Pork diet (7 servings/wk in men and 5 servings/wk in women)	Habitual diet (< 100 g of fresh pork per wk)
Roussell et al., 2012 [7]	USA	Crossover randomized controlled trial	20 wk	36 adults with hypercholesterolemia (21 women/15 men) (50 ± 1.4 y)[a]	Beef in an Optimal Lean Diet plus protein (153 g beef/d)	DASH diet with 28 g beef/d, beef in an Optimal Lean diet with 28 g beef/d, and Healthy America diet
Poddar et al., 2013 [62]	Australia	Randomized controlled trial	48 wk	73 adults with obesity (64 women/9 men) (48.4 ± 1.4 y)[a]	Standard diet group (lean ground beef 3 meals/wk)	Mushroom diet group (8 oz for meat at 3 meals/wk)
Daly et al., 2014 [68]	Australia	Randomized controlled trial	16 wk	100 healthy older women (73 y)	Progressive resistance training with lean red meat diet (~160 g/ d consumed 6 d/wk)	Progressive resistance training with control diet (1 serving of pasta or rice)
	Germany		6 wk		Red meat diet (200 g/d)	Whole grain diet

(*continued on next page*)

Table 2 (*continued*)

Study	Country	Study design	Duration	Population/health status	Red meat intervention	Comparator intervention
Foerster et al., 2014 [67]		Crossover randomized controlled trial		20 healthy adults (10 women/10 men) (40 ± 11.6 y)		
Hill et al., 2015 [64]	USA	Randomized controlled trial	23 wk	62 adults with overweight or obesity (34 women/28 men)	Beef in an Optimal Lean plus protein (196 g beef/d)	DASH diet with 12 g beef/d, b eef in an Optimal Lean with 139 g beef/d
Hosseinpour-Niazi et al., 2015 [60]	Iran	Crossover randomized controlled trial	16 wk	31 adults with type 2 diabetes (24 women/7 men) (58.2 ± 6.0 y)	Legume-free Therapeutic Lifestyle Change	Legume-based Therapeutic Lifestyle Change (two servings of red meat replaced with non-soy legume)
Sayer et al., 2015 [100]	USA	Crossover randomized controlled trial	12 wk	19 adults with hypertension (13 women/6 men) (61 ± 2 y)[a]	DASH diet with lean pork (55 % of total protein intake from lean pork)	DASH diet with pork (55 % of total protein intake from chicken and fish)
Sayer et al., 2017 [55]	USA	Randomized controlled trial	16 wk	120 adults with overweight or obesity adults (99 women/21 men) (37.6 ± 8.1 y)	High protein with ≥ 4 weekly servings of lean beef	High protein restricted in red meats
Hematdar et al., 2018 [59]	Iran	Randomized controlled trial	8 wk	64 adults with diabetes type 2 (46 women/18 men) (40–65 y)	Red meat diet (two servings 3 d/wk)	Soybean group (a cup of soybeans 3 d/wk),l egumes group (a cup of non-soy legumes 3 d/wk)
O'Connor et al., 2018 [48]	USA	Crossover randomized controlled trial	10 wk	41 adults with overweight or obesity adults (28 women/13 men) (46 ± 2 y)[a]	Mediterranean patterns with ~500 g/wk of lean, unprocessed beef or pork	Mediterranean patterns with poultry
Bergeron et al., 2019 [49]	USA	Crossover randomized controlled trial	12 wk	113 healthy adults (69 women/44 men) (43.5 ± 12 y)	High saturated fatty acid diet enriched with red meat	Low saturated fatty acid diet enriched with white meat or nonmeat protein
Porter Starr et al., 2019 [54]	USA	Randomized controlled trial	24 wk	80 adults with obesity (72 women/8 men) (64 ± 8 y)	High protein diet (enriched with beef and pork)	Normal protein diet
Wade et al., 2019 [69]	Australia	Crossover randomized controlled trial	16 wk	33 adults with hypertension, hypercholesterolemia and impaired glucose (23 women/10 men) (61 ± 7.1 y)	Mediterranean diet supplemented with 2–3 serves of fresh, lean pork	Low-fat control diet
Formica et al., 2020 [71]	Australia	Randomized controlled trial	24 wk	154 adults with severe obesity (BMI > 40 (kg/m^2)) (96 women/58 men) (70.7 ± 4.1 y)	Exercise plus lean meat group (two 80 g servings of red meat)	Exercise plus carbohydrate group (≈225 g of rice or pasta or potato)
Maki et al., 2020 [72]	USA	Crossover randomized controlled trial	8 wk	33 adults with overweight or obesity, prediabetes and/or metabolic syndrome (26 women/7 men) (44.4 ± 2.4 y)[a]	USDA Healthy US-Style Eating Pattern with an additional 150 g/d lean beef	USDA Healthy US-Style Eating Pattern with isocaloric replacement for carbohydrate
Fleming et al., 2021 [66]	USA	Crossover randomized controlled trial	16 wk	59 healthy adults (31 women/28 men) (49 ± 1.6 y)[a]	Fatty acid-matched Mediterranean diet with 156 g/d lean beef, 71 g/d lean beef 14 g/d lean beef	American diet with 71 g/d of beef
Hassanzadeh-Rostami et al., 2019 [58]	Iran	Randomized controlled trial	8 wk	64 adults with type 2 diabetes (46 women/19 men)	Red meat diet (2 servings 3 ds/wk)	Soybean diet (2 servings 3 d/wk), n on-soy legume (2 servings 3 days/wk)
Wang et al., 2023 [50]	USA	Crossover randomized controlled trial	9 wk	19 young healthy adults (8 women/11 men) (26 ± 4 y)	Healthy lacto-ovo vegetarian diet plus 3 oz/d of unprocessed lean red meat	Healthy lacto-ovo vegetarian diet, h ealthy lacto-ovo vegetarian diet plus 3 oz/d of processed lean red meat

[a] Mean and standard error.
[b] Median and interquartile range. BMI, body mass index; CRP, C-reactive protein; DASH, Dietary Approaches to Stop Hypertension; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; USDA, United States Department of Agriculture; VLDL, very low-density lipoprotein.

2.7. Data collection process and data items

The main objective of this Bayesian NMA was to determine the pre-post intervention changes in TC, LDL-C, HDL-C, TG, SBP, DBP and CRP when comparing red meat interventions with comparator diets. Thus, the reported effects result from the following equation: red meat change (post–pre) – comparator group change (post–pre). If necessary, TC, LDL-C, HDL-C and TG were converted to mmol/L dividing the reported mg/dL data by 38.67 (TC) and by 88.57 (TG), as previously conducted [4]. Additionally, change value in standard deviation (SD) was calculated by using the reported correlation factor representative of the change value SD in a previous systematic review, depending on intervention/comparator groups and the studied main outcome: TC: intervention = 0.79, control = 0.72; LDL-C: intervention = 0.76, control = 0.69; HDL-C: intervention = 0.87, control = 0.67; and TG = 0.67, control = 0.78) [4]. Concerning the other key outcome measures, blood pressure and CRP, a standardized 0.8 and 0.75 correlation factor was employed, respectively [21,22]. Furthermore, when the 95 % confidence interval (CI) was reported instead of SD, SD was calculated

with the following equation: "SD = [(upper limit CI / lower limit CI) / 2 × Z] × $\sqrt{n}$"; being Z = critical value of the standard normal distribution (1.96 as standard value). In the same manner, when the interquartile range (IQR) was reported instead of SD, SD was estimated by "SD = (Q3 - Q1) / 1.35". Similarly, when a standard error (SE) was reported instead of SD, SD was calculated with this estimation: "SD = SE × $\sqrt{n}$". Concerning the data of pre-post SD difference, it was reported as "SD = $\sqrt{[(A^2 + B^2)-(2 \times CF \times A \times B)]}$", being A = pre SD; B = post SD; and CF = correlation factor (0.7 was used as standard value for TC, LDL-C, HDL-C and TG; 0.8 for blood pressure and 0.75 for CRP) [21,22]. Finally, to estimate means when medians and IQRs were reported, we used the equation described by Wan et al. [23] as "mean = [first quartile (Q1) + median + third quartile (Q3)] / 3".

On the other hand, crossover studies were interpreted as follows: if washout periods were described and outcome measures were reassessed after them, those values were used as baseline data for the following intervention arm. When this was not reported, general given baseline data was also used as pre-values for the interventions following the first arm.

2.8. Network meta-analysis

Prior to the implementation of the NMA, an assessment was carried out of three basic assumptions following previous literature [24]: (i) to prevent potential bias in comparative analyses and to avoid the occurrence of heterogeneity and inconsistencies, a comprehensive assessment of the similarity and comparability of the studies included in the NMA was carried out; (ii) to corroborate the homogeneity of conditions across studies, a thorough check was made for the absence of heterogeneity within the results of pairwise comparisons. The magnitude and clinical significance of heterogeneity were quantified using the τ^2 statistic, classifying its impact as: low clinical relevance (< 0.04), moderate (0.04–0.14) or substantial (0.14–0.40); (iii) to verify that there were no significant inconsistencies between direct and indirect evidence, a consistency and transitivity check was performed. The side-splitting or node-splitting methodology was used to assess the validity of the similarity assumption or the presence of incoherence [25,26].

All statistical analyses were performed using R statistical software (version 4.4.0) from the R Core Team in Vienna, Austria, and RStudio (version 2024.04.1 + 748) from Posit in Boston, MA, USA. "BUGS*net*" (Bayesian inference Using Gibbs Sampling to conduct NETwork meta-analysis) package is a comprehensive R tool for conducting Bayesian NMA according to best practice and reporting guidelines [27]. Mean differences (MD) and SD were calculated to assess the effect of the red meat intervention and control groups independently for each RCT [28]. For analyses within the NMA, they were then combined into their respective groups (red meat, animal protein, plant protein, animal + plant protein and carbohydrate). The comparative evaluation of the effects of the interventions on TC, HDL-C, LDL-C, TG, SBP, DBP and CRP was conducted using NMA, with analysis of interactions between the intervention and control groups. For multi-arm studies, all experimental intervention groups within each study were combined into a single group, and all relevant comparator intervention groups were combined into a single comparator group [11]. Relative standardized mean differences (SMD) below −0.8 were considered clinically significant. The range between ±0.8 was defined as the "range of equivalence", indicating clinically insignificant differences between interventions [28]. In addition, data were converted to the same unit of measurement before reanalysis to assess the clinical impact on % TC, HDL-C, LDL-C, TG, SBP, DBP and CRP using MD. Similarly, and in line with previous reports, the effect size was interpreted based on known or estimated minimal clinically important difference (MCID) thresholds [29]. Inconsistency was assessed using the I^2 statistic, which ranges from 0 % to 100 %. The resulting I^2 values were classified as follows: not important (0–30 %), moderate (30–60 %), substantial (60–75 %) and significant (75–100 %) [30]. Finally, although the number of studies in the meta-analysis was below the recommended threshold of at least 10 per outcome [31], we still performed exploratory meta-regressions analyses using mixed-effects models. This analysis aimed to examine whether factors such as mean age, mean body mass index (BMI), intervention duration, risk of bias, conflict of interest, food provision (feeding and *ad libitum* trials), type of red meat (lean versus non-lean red meat) and dietary fat from red meat intake (expressed in both absolute (grams) and relative (percentage) values) might explain variability in the effect estimates. In the case of dietary fat from red meat intake, when not directly reported in the study, values were estimated using the United States Department of Agriculture (USDA) Food Database, considering the specific type of red meat used. Similarly, when red meat intake was reported as a range, the median value was used for the analysis [53]. In studies that reported separate intakes for men and women, the overall average intake was calculated by weighting the sex-specific values according to the proportion of male and female participants in each study [47,51].

2.9. Certainty of evidence

The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [20]. The Confidence in Network Meta-Analysis (CINeMA) framework was used to assess the certainty of evidence from simultaneous comparisons of multiple interventions [32]. CINeMA is a web-based application developed by the Cochrane Group that interfaces with an R back-end server [33]. Following the relevant protocol, each comparison was assessed for potential bias, including within-study bias, reporting bias, directionality, imprecision, heterogeneity and inconsistency. The confidence levels for each domain were initially assessed as high, but were later adjusted based on the specific methodological issues described below.

2.10. Within-study bias

After integrating the RoB 2.0 tool into the CINeMA framework, the bar chart generated by the system was evaluated. The confidence level of each comparison was then adjusted using the weighted average risk of bias method, assigning scores of −1, 0 and 1 for low, moderate and high risk of bias [32]. The resulting bias to be reported was determined by multiplying each percentage in the bar chart with its corresponding factor and summing the three components.

2.11. Reporting bias

The Risk of Bias due to Missing Evidence in Network Meta-Analysis (ROB-MEN) was also used to assess the reporting bias domain within CINeMA [34]. This tool integrates qualitative and quantitative methods, such as funnel plots, tests for small study effects or selection models, into a comprehensive assessment for comparative studies such as RCTs. In addition, following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [35], Bayesian funnel plots were used to assess publication bias by examining asymmetry between red meat interventions and controls. As these tests are not recommended for

comparisons involving fewer than 10 studies, it was decided to report “some concerns”.

2.12. Indirectness

This item assesses whether the available evidence applies to the clinical question [36]. The weighted average method was chosen for this, taking into account the bar chart provided by the framework.

2.13. Imprecision

The NMA combines indirect evidence with direct evidence to improve accuracy [37]. A SMD of 0.8 was set as an indicative value for a clinically important effect, and imprecision was assessed using 95 % credible intervals (CrIs) calculated using the maximum likelihood method. “No concerns” were recorded when the 95 % CrI was entirely on the effect side or within the range of equivalence. The confidence level was downgraded to “some concern” if the 95 % CrI spanned both the clinically important effect and the null effect. Comparisons were classified as “major concern” if the 95 % CrI limits extended beyond the range of equivalence.

2.14. Heterogeneity

Given the clinically significant effect threshold (SMD = −0.8), CINeMA assesses heterogeneity by checking for discrepancies between the prediction interval and the 95 % CrI of clinical relevance. Comparisons are classified as “some concern” if the prediction interval crosses into or out of the zone of clinical significance once, and as “major concern” if it crosses this region twice.

2.15. Incoherence

The ability of the NMA to provide similar estimates was assessed by using direct comparisons with indirect estimates. In addition, we evaluated the transitivity assumption to ensure that the only systematic difference between two groups is the treatment itself, without the influence of other confounding factors. Taking into account the inconsistency factor and applying the Systematic Investigation of Decision-making Evidence (SIDE) method [38], which separates direct and indirect estimates to detect significant differences in effect estimates, we noted ‘some concern’ when direct and indirect 95 % CrIs showed discrepancies in effect despite being aligned in the same direction. On the other hand, if the 95 % CIs showed disagreement because of a change in the direction of the effect, this was marked as “major concern”.

2.16. Confidence rating

The CINeMA domain levels were converted to the standard levels as follows: high confidence, meaning that the true effect is close to the estimated effect; moderate confidence, indicating that the true effect is likely to be close to the estimate but could differ substantially; low confidence, suggesting that the true effect could differ substantially from the estimate; and very low confidence, implying that the true effect is likely to differ substantially from the estimate. To avoid isolated judgments, the final report takes into account the interrelationships between the domains [39].

3. Results

3.1. Study selection and characteristics

The initial database search yielded 2661 records. After removing duplicates and screening titles/abstracts, 91 articles were assessed for eligibility (Table S2). Finally, 36 articles met the inclusion criteria and were analysed in the primary NMA (Fig. 1). The characteristics of the 36 RCTs included are detailed in Table 2. Among these studies, 18 employed crossover design and 24 studies were classified as industry-related due to sponsorship by the meat industry or declared conflicts of interest. The effect of red meat consumption was compared with animal protein (excluding red meat) in 16 studies, plant protein in 9 studies, animal and plant protein in 7 studies, and carbohydrate in 8 studies. This NMA included 2090 adults (mean age 39.68 ± 13.52 years; 56.81 % women). In the studies that compared red meat with other sources of animal protein, the following were used: white meat [40–49], processed red meat [50], fatty fish [51,52], lean fish [42], white meat and fish [53], and white meat, dairy, and eggs [54,55].

Of the studies with plant-based protein, 4 used soy or soy derivatives [56–59], 3 used non-soy legumes [58–60], 2 used a combination of legumes, nuts, and soy products [49,61,62], and 1 used mushroom protein [62]. In the studies that used animal and plant proteins, the following were included: vegetable and dairy proteins [45]; white meat and refined carbohydrates [44]; fish, margarine, and legumes [63]; white meat, fish, and legumes [64]; white meat, fish, legumes, and nuts [7]; white meat, fish, dairy, and vegetables [65]; and white meat, fish, eggs, nuts, and legumes [66]. In the case of studies that used carbohydrates as a comparator, the sources included whole grains [67], refined grains [68,69], refined grains and potatoes [70–72], or unspecified carbohydrate sources [66,73]. The details regarding dropouts, food provision, and adherence to interventions for the included studies are summarized in Table S3.

The RCTs were published between 1984 and 2023, and the duration of the intervention ranged from 5 weeks to 48 weeks. The mean, SD and mean difference for profile lipid, blood pressure and CRP in the red meat intervention and comparison diets are included in Tables S4–S10.

3.2. Network meta-analysis

Table S11 shows the random effects statistics stratified by comparison group. Compared to the red meat intervention, the consumption of plant-based proteins resulted in a more pronounced reduction in TC (MD = −0.14; 95 % CrI: −0.28 to −0.001, $n = 7$), HDL-C (MD = −0.06; 95 % CrI: −0.11 to 0.00, $n = 7$) and LDL-C levels (MD = −0.19; 95 % CrI: −0.36 to −0.03, $n = 7$), with significant differences between groups ($p < 0.05$) (Figs. 2 and 4). In the case of LDL-C levels, this reduction was superior to the MCID for this variable (MCID = 0.10). No significant differences were observed in HDL-C, TG, SBP, DBP and CRP levels (Figs. 3–8). In addition, interventions based on animal + vegetable proteinresulted in a greater increase in TG (MD = 0.21; 95 % CrI: 0.06 to 0.34, $n = 5$, $p < 0.05$) compared to red meat interventions, with no significant differences observed in TC, LDL-C, HDL-C, SBP or DBP. In the case of TG levels, this increase was superior to the MCID for this variable (MCID = 0.09). The dietary interventions based on carbohydrates resulted in no significant differences in TC, LDL-C, HDL-C, TG, SBP, DBP and CRP. Red meat consumption did not cause significant changes in TC, LDL-C, HDL-C, SBP, DBP and CRP compared to dietary interventions based on other sources of animal protein.

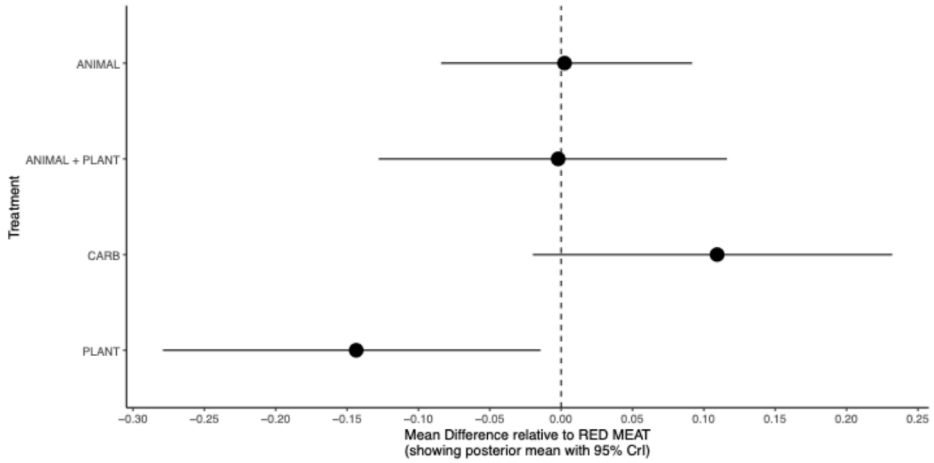

Fig. 2. Forest plot showing changes in total cholesterol (mmol/L) between the red meat intervention and the different comparison diets. Each row represents a specific diet, while the numbered point represents the corresponding mean difference, and the horizontal lines indicate 95 % credible intervals (CrI). The model was calculated using a random effects model. Studies included in each comparison were: animal protein [7,40–55], animal + plant protein [7,44,45,63,64,66,100], plant protein [49,50,56–58,60,62], and carbohydrate-rich foods [66–73].

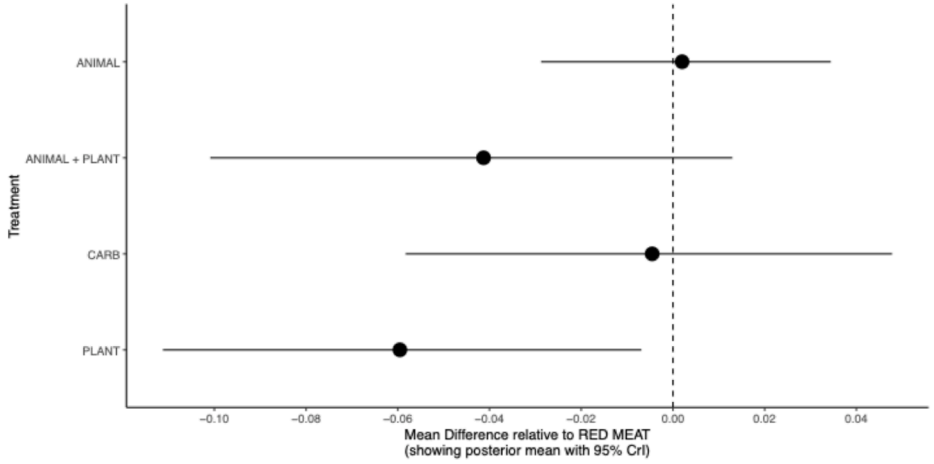

Fig. 3. Forest plot showing changes in high-density lipoprotein cholesterol concentrations (mmol/L) between the red meat intervention and the different comparison diets. Each row represents a specific diet, while the numbered point represents the corresponding mean difference, and the horizontal lines indicate 95 % credible intervals (CrI). The model was calculated using a random effects model. Studies included in each comparison were: animal protein [6,7,40–55], animal + plant protein [7,44,45,49,64,66,100], plant protein [49,50,56–58,60], and carbohydrate-rich foods [66,68–73].
Note: Negative mean differences indicate a decrease in HDL cholesterol concentrations relative to red meat, while positive values indicate an increase.

3.2.1. *Meta-regression analyses*

Additionally, focusing on outcomes with statistically significant differences in the main analyses, the exploratory meta-regression revealed that several study-level covariates significantly moderated the observed effects (Table S12). In the comparison of plant-based protein versus red meat, the effect on TC was significantly moderated by several variables. Higher mean BMI was associated with greater reductions in TC (unstandardized beta coefficient [B] = −0.60, 95 % CrI: −0.93 to −0.37), whereas longer intervention duration was linked to smaller reductions (B = 0.36, 95 % CrI: 0.16 to 0.62). Interventions with higher risk of bias tended to show greater TC reductions (B = −0.86, 95 % CrI: −1.57 to −0.14). Likewise, food provision (i.e., *ad libitum* trials) was related to greater TC decreases (B = −0.84, 95 % CrI: −2.78 to −0.06). In contrast, a higher fat content in red meat (grams) related to a smaller cholesterol-lowering effect of plant-based protein (B = 0.02, 95 % CrI: 0.01 to 0.03). Regarding HDL-C, the effect of plant-based protein compared to red meat was significantly moderated by risk of bias and the presence of conflicts of interest. A higher risk of bias was linked to attenuated reductions in HDL-C (B = 0.50, 95 % CrI: 0.05 to 0.88), while conflicts of interest were related to more pronounced reductions (B = −0.85, 95 % CrI: −1.69 to −0.39). No significant moderators emerged for LDL-C in this comparison.

In the comparison of animal and plant-based proteins combined versus red meat interventions, the reduction in TG was significantly shaped by multiple covariates. Higher mean age (B = −2.01, 95 % CrI: −2.55 to −1.44) and higher BMI (B = −0.86, 95 % CrI: −0.97 to −0.77) were linked to greater TG reductions. Similarly, higher fat content from red meat, both in grams (B = −0.11, 95 % CrI: −0.12 to −0.10) and as a percentage (B = −0.18, 95 % CrI: −0.19 to −0.17), and the use of non-lean red meat (B = −4.58, 95 % CrI: −5.13 to −3.78) corresponded to more pronounced reductions. Conversely, longer intervention duration (B = 0.59, 95 % CrI: 0.52 to 0.67), higher risk of bias (B = 5.41, 95 % CrI: 4.16 to 6.20), the presence of conflicts of interest (B = 6.56, 95 % CrI: 5.82 to 7.39), and food provision (B = 7.35, 95 % CrI: 6.52 to 8.17) were each related to smaller TG reductions, suggesting that

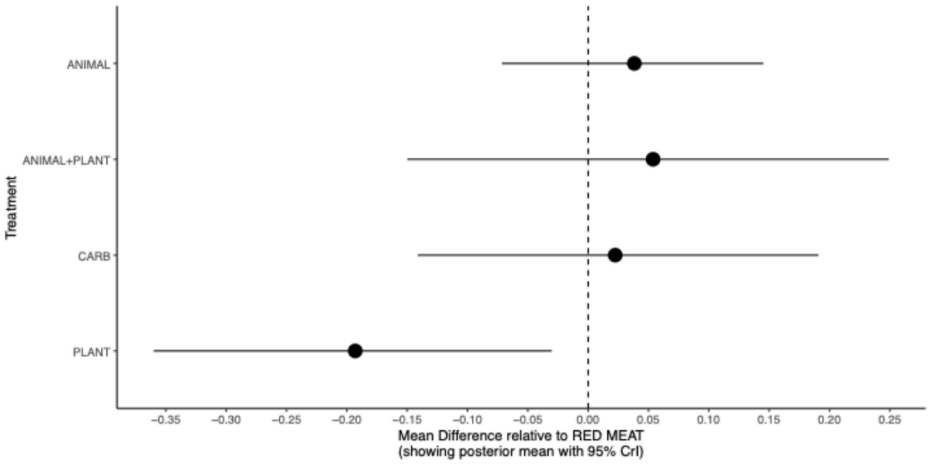

Fig. 4. Forest plot showing changes in low-density lipoprotein cholesterol concentrations (mmol/L) between the red meat intervention and the different comparison diets. Each row represents a specific diet, while the numbered point represents the corresponding mean difference, and the horizontal lines indicate 95 % credible intervals (CrI). The model was calculated using a random effects model. Studies included in each comparison were: animal protein [6,7,40–55], animal + plant protein [7,44,45,49,64,66], plant protein [49,50,57,58,60,62], and carbohydrate-rich foods [66,68–73].

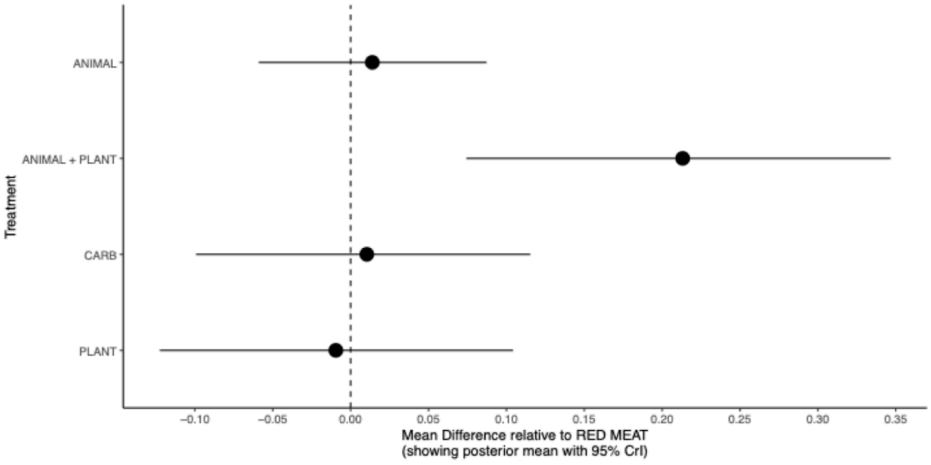

Fig. 5. Forest plot showing changes in triglycerides (mmol/L) between the red meat intervention and the different comparison diets. Each row represents a specific diet, while the numbered point represents the corresponding mean difference, and the horizontal lines indicate 95 % credible intervals (CrI). The model was calculated using a random effects model. Studies included in each comparison were: animal protein [6,7,40–55], animal + plant protein [7,44,45,49,64,66], plant protein [49,50,56–58,60], and carbohydrate-rich foods [66–73].

these factors may diminish the observed benefit of replacing red meat with mixed animal and plant protein sources.

3.3. Risk of bias

The interventions included in this systematic review received PEDro scores ranging from 4 to 8 points, with an average of 6.3 (SD = 0.98). A total of 29 interventions were assigned a good score and 7 received a fair score (Table S13). According to the RoB 2.0 tool 4 were rated as "low risk" of bias, 3 as "some concerns" of bias, and 27 as "high risk" (Fig. S1).

3.4. Certainty of the network meta-analysis evidence

The certainty of evidence for each outcome was evaluated using the GRADE criteria (Table S21). In general, the evidence for most outcomes was rated as very low to low. This downgrading was primarily due to concerns regarding risk of bias, inconsistency, and some degree of indirectness, which limited the certainty of the findings. When examining CINeMA, the confidence rating was "very low" for most of the different comparisons with red meat interventions in TC (75 %), TG (75 %), SBP (75 %), and DBP (75 %) (Table S14, Tables S17–S19). For HDL-C and CRP, the confidence ratings for comparisons with red meat was mostly "low" (50 %) (Table S15 and Table S20). The confidence ratings for LDL-C compared with red meat were "very low" (50 %), "low" (25 %) and "moderate" (25 %) (Table S16). The comparison between plant-based protein and meat yielded the highest confidence ratings: "moderate" for HDL-C, LDL-C, TG, SBP and CRP; and "low" for CT and DBP.

4. Discussion

This ground-breaking NMA offers a comprehensive assessment of the cardiometabolic impact of red meat consumption relative to a comparator food. Compared with the red meat, plant protein intake resulted in a greater reduction in TC, LDL-C and HDL-C levels. In the case of LDL-C, this effect was clinically important, as

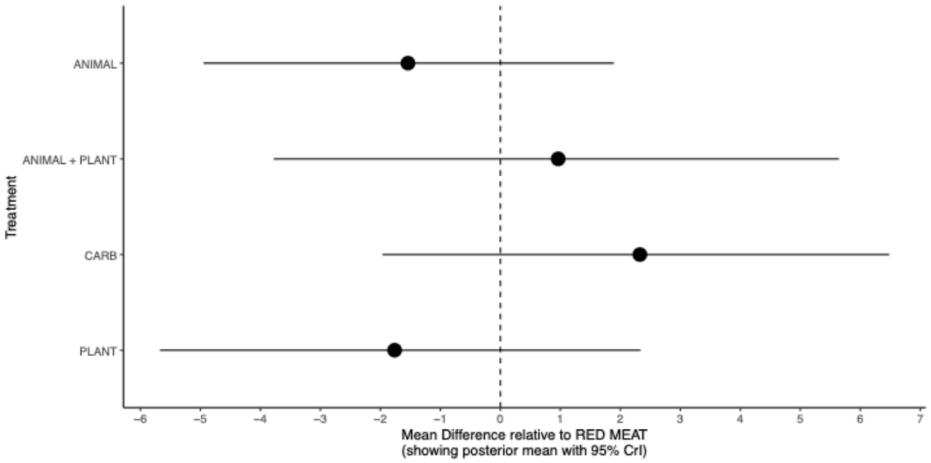

Fig. 6. Forest plot showing changes in systolic blood pressure (mmHg) between the red meat intervention and the different comparison diets. Each row represents a specific diet, while the numbered point represents the corresponding mean difference, and the horizontal lines indicate 95 % credible intervals (CrI). The model was calculated using a random effects model. Studies included in each comparison were: animal protein [47–50,53,55], animal + plant protein [63,64,100], plant protein [49,50,58,60,62], and carbohydrate-rich foods [68–72].

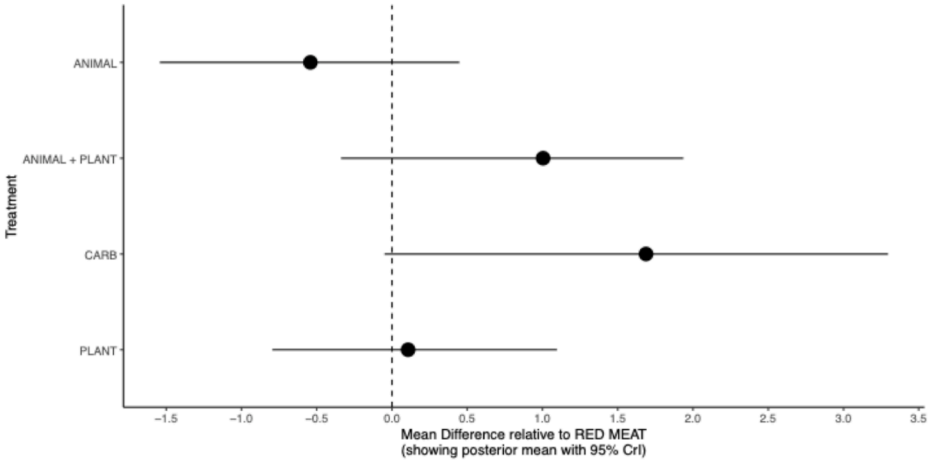

Fig. 7. Forest plot showing changes in diastolic blood pressure (mmHg) between the red meat intervention and the different comparison diets. Each row represents a specific diet, while the numbered point represents the corresponding mean difference, and the horizontal lines indicate 95 % credible intervals (CrI). The model was calculated using a random effects model. Studies included in each comparison were: animal protein [47–50,53,55], animal + plant protein [63,64,100], plant protein [49,50,58,60,62], and carbohydrate-rich foods [68–72].

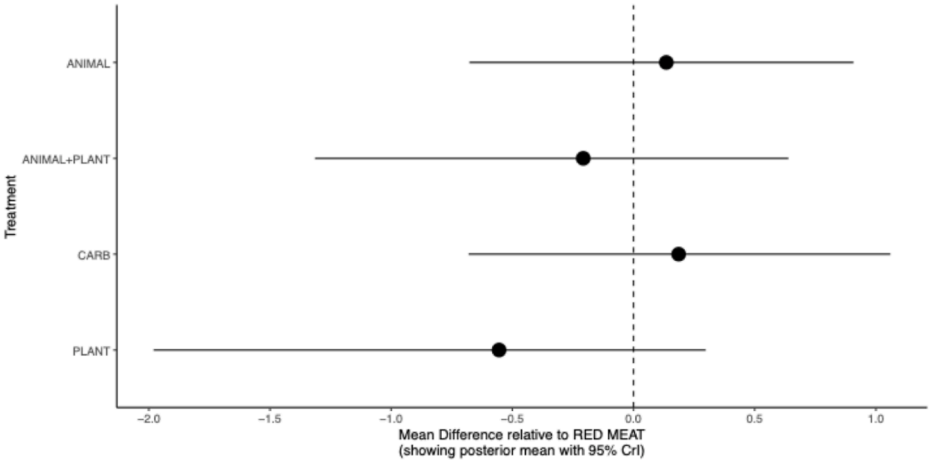

Fig. 8. Forest plot showing changes in C-reactive protein (mg/L) between the red meat intervention and the different comparison diets. Each row represents a specific diet, while the numbered point represents the corresponding mean difference, and the horizontal lines indicate 95 % credible intervals (CrI). The model was calculated using a random effects model. Studies included in each comparison were: animal protein [7,44,46], animal + plant protein [7], plant protein [59,62], and carbohydrate-rich foods [64,67,69,70,72].

the observed reductions exceeded the MCID. Interventions including a combination of animal and plant protein showed a smaller, clinically relevant, increase in TG compared to interventions with red meat. However, the certainty of evidence was rated as low. The findings of this NMA indicate that it is crucial to consider the comparison diet when evaluating the relationship between red meat consumption and CVD risk factors. In exploratory meta-regression analyses, which must be interpreted with caution due to the limited number of studies per comparison arm, we observed that the effect of red meat consumption on cardiometabolic outcomes may be influenced by study- and population-level characteristics. For TC, several covariates moderated the results in the comparison with plant-based protein, including participants' BMI, intervention duration, risk of bias, food provision, and fat content in red meat (grams). Notably, higher fat content (only in absolute terms) and longer intervention duration were associated with smaller reductions in TC, while higher BMI, greater risk of bias, and *ad libitum* food provision were linked to greater reductions. For HDL-C, the presence of conflicts of interest was associated with larger reductions, whereas higher risk of bias was linked to attenuated effects. No significant moderators were identified for LDL-C. In the animal + plant protein versus red meat comparison, the effects on TG were moderated by multiple factors (i.e., mean age, BMI, duration, risk of bias, conflicts of interest, food provision, type of meat, and fat content in red meat). Among these, older age, higher BMI, use of non-lean red meat, and higher fat content (both in absolute and relative terms) were associated with greater reductions in TG, whereas longer duration, higher risk of bias, presence of conflicts of interest, and *ad libitum* food provision were linked to smaller effects. These findings highlight the complexity of interpreting nutritional intervention studies and reinforce the importance of accounting for contextual and methodological factors in future research.

Our findings align with previous meta-analyses of RCTs, which indicate that the cardiometabolic impact of red meat consumption depends on the food it replaces [4]. In nutrition, the health impact of a specific food can be significantly influenced by the dietary component with which it is compared [74]. Therefore, it is crucial to establish a suitable comparator when evaluating the impact of a particular dietary pattern or food on health outcomes [75]. In general, diets and food categories such as processed meat and refined grains are identified as detrimental to cardiometabolic health [76–78]. Consequently, they are unsuitable for comparison, as their use increases the probability of positive or neutral outcomes in the assessment of the effects of other dietary interventions, such as red meat consumption [79]. In the present meta-analysis, the observed effects were dependent upon the type of comparison diet employed. Specifically, plant protein consumption induced beneficial effects on TC and LDL-C compared to the consumption of red meat. The results of the lipid profile analysis are consistent with those of the previous meta-analysis [4]. However, in that meta-analysis, the studies included non-RCTs [12–14] and interventions, where red meat was consumed along with other foods, fortified foods or the type of meat, was not specified [80]. The studies included in our analysis only considered those where the consumption of red meat represented the sole distinguishing factor between the red meat group and the comparator group. This approach allows us to identify the observed effect of the red meat intervention as being specific to the consumption of red meat itself, rather than being potentially biased by the presence of other specific foods.

The reduction of red meat caused beneficial effects on TC and LDL-C only when it was replaced by plant protein. It has been pointed out that dietary patterns that prioritize the consumption of plant-based protein sources are associated with beneficial effects on atherogenic lipoproteins [81]. Although the differences in cholesterol levels may appear to be minor, they could potentially significantly impact health over an extended period. In this context, it is important to consider that a reduction in LDL-C of one mmol/L (18 mg/dl) has been associated with a decrease in the relative risk of atherosclerotic cardiovascular disease by 10 % in the first year and 20 % after three years [82]. This arises from the fact that CVD risk depends on the duration of exposure to LDL-C, which highlights the importance of maintaining optimal LDL-C levels from an early age [83].

Compared to plant-based protein sources, red meat consumption was associated with an increase in HDL-C levels. While these findings are noteworthy, the relationship between HDL-C and atherosclerosis is complex. Although HDL-C has traditionally been considered protective against cardiovascular risk, evidence from Mendelian randomization studies and clinical trials does not support a causal role [84,85]. Furthermore, results from cohort studies suggest that very high HDL-C levels may paradoxically be associated with increased mortality risk in individuals at cardiovascular risk [84,85]. Additionally, in the present study, these differences, although statistically significant, were not clinically relevant (MCID = 0.10).

In comparison to other animal protein sources, plant protein sources are characterized by a lower content of saturated fat, the absence of cholesterol and heme iron, and a higher proportion of monounsaturated and polyunsaturated fats, dietary fiber, polyphenols, and other bioactive compounds [86]. Modelling data shows a significant reduction in predicted coronary heart disease risk when 5 % of total dietary energy from saturated fat is replaced with monounsaturated fatty acids (15 % lower risk), polyunsaturated fatty acids (25 % lower risk) or carbohydrates from whole grains (9 % lower risk) [87]. Therefore, the observed favorable effects of plant protein consumption in comparison to meat may be attributed to a combination of the potential anti-atherogenic properties of unsaturated fatty acids present in plant-based foods and the avoidance of saturated fat intake. Moreover, plant-based foods contain a range of bioactive compounds that are strongly correlated with a reduced risk of CVD, including dietary fiber and polyphenols [88–91].

In this study, the replacement of red meat with animal and plant protein in dietary interventions has shown increased TG levels. Given the heterogeneity of the foods included in this experimental group across the different studies, it is challenging to attribute the observed effects to a single food. However, the nutritional characteristics of the interventions may provide a potential explanation for the observed results. In one of the included studies, the experimental group that consumed red meat showed a reduction in energy intake and a greater reduction in body weight than the control group [44]. It has been demonstrated that changes in body weight are a major factor influencing TG levels [92]. Consequently, the observed effects may be attributable to alterations in body composition rather than changes in dietary composition. In other included studies, the group that consumed red meat demonstrated a reduced intake of saturated fatty acids and increased polyunsaturated fatty acids [7,64]. Substituting saturated fat acids with unsaturated fats, specifically polyunsaturated fats, has been associated with reduced TG levels [93,94]. Furthermore, this NMA revealed that carbohydrate consumption was associated with a significant increase in DBP values when compared to red meat intake. In this context, the studies included in the NMA primarily employed sources of refined carbohydrates [68,71,95]. In previous studies, a higher intake of refined grains was associated with increased DBP, even after adjusting for age, sex, BMI, metabolic equivalent, total energy intake, and other dietary factors [96]. Whilst the consumption of

whole grains appears to be associated with a lower risk of hypertension, the intake of refined versions of these foods is suggested to be detrimental to blood pressure management [97,98]. Contrary to what is reported with whole grains, the consumption of low-quality carbohydrates could lead to an increase in reactive oxygen species and a state of hyperinsulinemia, which would cause vascular resistance and a higher risk of hypertension [99].

The main strength of this study is its use of an NMA, which is a more precise method for comparing the effects of studies with multiple comparisons. This approach avoids the unit-of-analysis error that can occur with other methods [11]. Furthermore, only RCTs were included in which the difference between the experimental and control groups was determined by the consumption of unprocessed red meat versus the dietary source ingested by the comparison group. It is also important to consider the limitations of the present study. Firstly, there was a notable degree of inconsistency between the studies. Secondly, the differences between red meat and comparison diets were relatively minor in magnitude. Nevertheless, our findings have significant clinical and public health implications if applied to a population level. Thirdly, the CINeMA data indicated that a considerable number of comparisons were assigned a low or very low certainty rating, which limits the generalisability of the results. Fourthly, the present study examined the effects of individual foods in isolation, and the overall effect of the diet on lipid parameters may modify the effects of these foods. Finally, a limitation of this study is that not all participants had follow-up data available. To maintain comparability across analyses, we used final values for participants with missing follow-up data, which represents a limitation that may have affected the precision of our estimates.

5. Conclusions

The findings of the present NMA indicate that the effect of red meat on cardiovascular risk factors is conditional upon the food with which it is compared. Consumption of high-quality plant protein sources as a substitute for red meat was associated with more favorable changes in TC and LDL-C, with the effect on LDL-C being clinically relevant. This could explain the heterogeneity of results observed in previous studies. Interventions that combined animal and plant proteins resulted in a smaller increase in TG compared to those involving red meat, with low certainty of evidence.. This highlights the importance of considering the displacement effect in dietary recommendations, as the health impact of red meat may vary depending on the food it replaces. Future research should focus on long-term outcomes and explore the mechanisms underlying these differences, particularly regarding how various replacement foods influence cardiovascular health. These findings could inform more precise dietary guidelines aimed at reducing cardiovascular risk.

Author contribution

MLM, JFL-G, GB and AR designed research; MLM, GB and AR independently reviewed studies according to inclusion and exclusion criteria, extracted the data and performed the risk-of-bias assessment; JFL-G analyzed data; MLM, JFL-G, AR and AB wrote the paper. All authors read and approved the final manuscript.

Data availability

This systematic review does not include original data. Data are extracted from the literature and are publicly available. The dataset generated for the present analyses are available upon request to the corresponding author.

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This research received no external funding.

Conflict of Interest

All other authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.09.001.

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