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SYSTEMATIC REVIEW

Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular Risk Factors

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BACKGROUND: Findings among randomized controlled trials evaluating the effect of red meat on cardiovascular disease risk factors are inconsistent. We provide an updated meta-analysis of randomized controlled trials on red meat and cardiovascular risk factors and determine whether the relationship depends on the composition of the comparison diet, hypothesizing that plant sources would be relatively beneficial.

METHODS: We conducted a systematic PubMed search of randomized controlled trials published up until July 2017 comparing diets with red meat with diets that replaced red meat with a variety of foods. We stratified comparison diets into high-quality plant protein sources (legumes, soy, nuts); chicken/poultry/fish; fish only; poultry only; mixed animal protein sources (including dairy); carbohydrates (low-quality refined grains and simple sugars, such as white bread, pasta, rice, cookies/biscuits); or usual diet. We performed random-effects meta-analyses comparing differences in changes of blood lipids, apolipoproteins, and blood pressure for all studies combined and stratified by specific comparison diets.

RESULTS: Thirty-six studies totaling 1803 participants were included. There were no significant differences between red meat and all comparison diets combined for changes in blood concentrations of total, low-density lipoprotein, or high-density lipoprotein cholesterol, apolipoproteins A1 and B, or blood pressure. Relative to the comparison diets combined, red meat resulted in lesser decreases in triglycerides (weighted mean difference [WMD], 0.065 mmol/L; 95% CI, 0.000–0.129; *P* for heterogeneity <0.01). When analyzed by specific comparison diets, relative to high-quality plant protein sources, red meat yielded lesser decreases in total cholesterol (WMD, 0.264 mmol/L; 95% CI, 0.144–0.383; *P*<0.001) and low-density lipoprotein (WMD, 0.198 mmol/L; 95% CI, 0.065–0.330; *P*=0.003). In comparison with fish, red meat yielded greater decreases in low-density lipoprotein (WMD, –0.173 mmol/L; 95% CI, –0.260 to –0.086; *P*<0.001) and high-density lipoprotein (WMD, –0.065 mmol/L; 95% CI, –0.109 to –0.020; *P*=0.004). In comparison with carbohydrates, red meat yielded greater decreases in triglycerides (WMD, –0.181 mmol/L; 95% CI, –0.349 to –0.013).

CONCLUSIONS: Inconsistencies regarding the effects of red meat on cardiovascular disease risk factors are attributable, in part, to the composition of the comparison diet. Substituting red meat with high-quality plant protein sources, but not with fish or low-quality carbohydrates, leads to more favorable changes in blood lipids and lipoproteins.

Key Words: apolipoproteins ■ blood pressure ■ diet ■ lipids ■ meat ■ red meat

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Clinical Perspective

What Is New?

- High-quality plant protein sources (legumes, soy, nuts, and other plant protein sources) resulted in more favorable changes in total and low-density lipoprotein cholesterol in comparison with red meat intake in the first meta-analysis of randomized controlled trials examining the effects of red meat on changes in cardiovascular disease risk factors stratified by the specific food(s) used in the comparison diet.

What Are the Clinical Implications?

- Our findings emphasize the health-promoting effects of high-quality plant protein foods in comparison with red meat and provide evidence for public health messages and clinical advice to favorably impact lipid profiles in the general population.

Meat is a common source of protein and fat in many diets worldwide.[1] However, evidence from epidemiological studies suggests that higher consumption of red meat and processed meat is associated with a higher risk of developing type 2 diabetes mellitus,[2,3] cardiovascular disease (CVD),[4] and certain cancers.[5,6] Nevertheless, findings from randomized controlled trials (RCTs) assessing the effect of red meat intake on CVD risk factors are inconsistent.[7,8]

A recent meta-analysis of 24 RCTs assessing the effects of red meat intake on CVD risk factors concluded that ≥0.5 serving/d of red meat did not influence blood lipids, lipoproteins, or blood pressure in comparison with <0.5 serving/d.[8] This analysis combined estimates from all non-red meat comparison interventions that varied considerably in diet quality and composition, which may differentially affect CVD risk factors. Specification of an explicit comparison is the cornerstone of nutritional substitution analysis, which recognizes that adding or subtracting any calorie-bearing food source is compensated by a similar caloric substitution, assuming body weight is maintained. Analyses that do not specify a comparison implicitly compare the food(s) under study with the mixture of all other calorie-bearing foods in the diet, making interpretations and dietary recommendations difficult. For example, high-quality plant protein sources generally have higher proportions of polyunsaturated fatty acids and fiber and no cholesterol in comparison with red meat. Thus, we might expect plant protein sources to reduce blood concentrations of total and low-density lipoprotein cholesterol (LDL-C) in comparison with red meat.[9,10]

The purposes of this study were (1) to conduct a systematic review and meta-analysis of RCTs examining the effects of red meat consumption on blood lipids, lipoproteins, apolipoproteins, and blood pressure; and (2) to assess whether the observed effects differ depending on the food(s) consumed in the comparison diet. We hypothesized that the relative effect of red meat on CVD risk factors would vary by the comparison diet consumed, with a relative benefit from consuming high-quality plant protein sources.

METHODS

The data, analytical methods, and study materials will be available to other researchers for purposes of reproducing the results or replicating the procedure from the corresponding author on reasonable request.

Search Strategy

We have identified eligible studies in PubMed through database inception up to July 2017. We limited our search to PubMed because all studies included in a previous meta-analysis on red meat and blood lipids[8] that searched multiple databases were indexed in PubMed.

We used the following search terms to search the PubMed database: ("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]) with filters (1) humans, (2) aged ≥18 years, and (3) English. The PICOS (Population, Intervention, Comparator, Outcome, Study Design) criteria used to define our research question are listed in Table I in the online-only Data Supplement.

Selection Criteria

Inclusion criteria were the following: (1) participants aged ≥18 years and not pregnant, (2) intervention and comparison diets that prescribed differing amounts of red meat, (3) reporting ≥1 cardiovascular risk factor as a dependent variable (ie, total blood cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], triglycerides, apolipoproteins [A1 and B], or blood pressure), and (4) use of a RCT study design. Studies were included if the intervention lasted ≥2 weeks.

Data Extraction

A team of 6 investigators (M.G.-F., A.S., S.A.B., M.J., E.E., and M.J.S.) independently reviewed the abstracts of articles returned from our initial search (n=366) and determined their eligibility for inclusion based on the aforementioned selection criteria. We reviewed the full-length articles for studies deemed potentially eligible. Discrepancies in eligibility decisions were discussed at each stage of the process until the investigators reached a joint consensus. When discussing studies throughout this meta-analysis, we are referring to the entirety of each publication. Some studies included more than 1 intervention or comparison diet. Such interventions are presented separately and treated as independent point estimates in the analyses. We excluded 267 articles from the initial search because of incompatibility with the PICOS/inclusion criteria (Figure 1). We contacted corresponding authors for

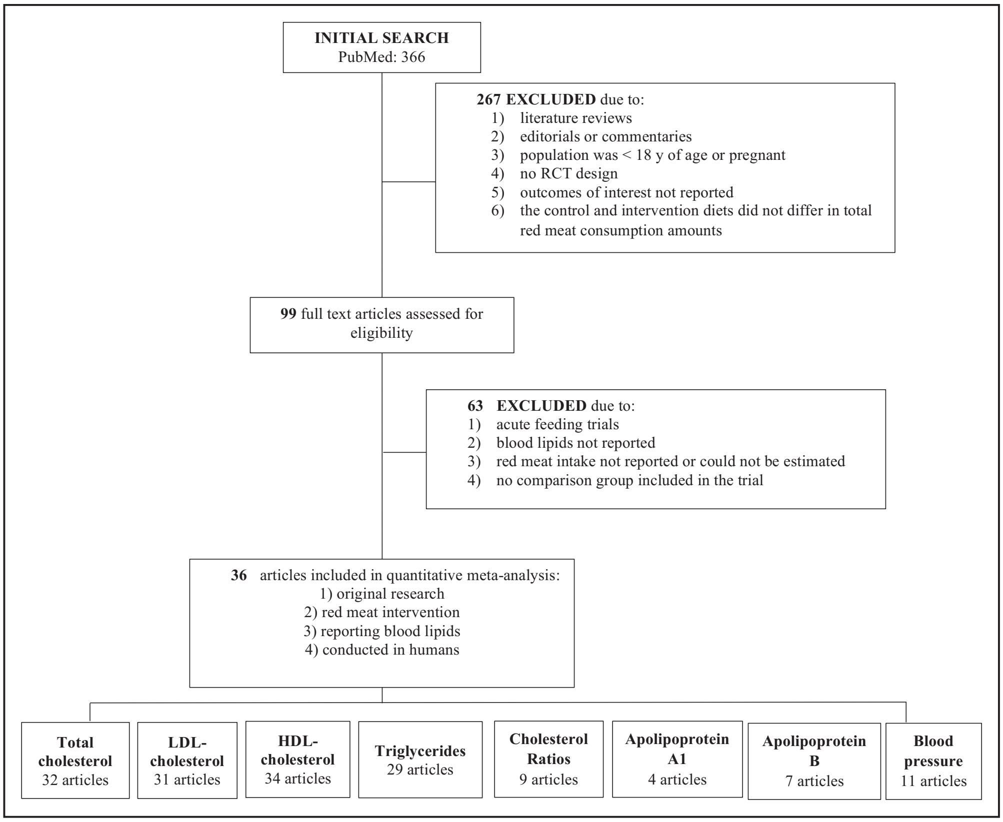

Figure 1. Flow chart depicting article selection process and final articles according to outcome of interest.
HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; and RCT, randomized controlled trial.

clarification on published and unpublished data as needed. The full texts of 99 articles were screened for eligibility; 62 were excluded because of interest were not reported (eg, red meat amount could not be estimated from the dietary data), or the intervention was <2 weeks. Thirty-six articles were included in this quantitative meta-analysis. The present meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[11]

We extracted the following data from these studies: (1) author names, (2) publication year, (3) population size and characteristics, (4) intervention duration, (5) protein source consumed in the comparison diet, (6) the amount of total red meat, (7) intervention type, (8) nutritional composition, (9) assessment of dietary compliance, (10) study quality (National Heart, Lung, and Blood Institute [NHLBI] Quality Assessment of Controlled Intervention Studies score ranging from 0 to 28 points), (11) funding source(s), and (12) pre- and postintervention values and changes in total cholesterol, LDL-C, HDL-C, triglycerides, apolipoproteins, cholesterol ratios, and blood pressure for red meat intervention and comparison diets.

Definitions of Red and Processed Meat

In accordance with a previous meta-analysis on this topic,[8] we used the 2015 Dietary Guidelines for Americans definition of red meat (or "meat"), "all forms of beef, pork, lamb, veal, goat, and nonbird game (eg, venison, bison, elk)," and processed meat, "preserved by smoking, curing, salting, and/or the addition of chemical preservatives."[12] Meat preserved only by refrigeration or freezing only was considered unprocessed meat.[13] Because all available meat available for purchase is processed to some extent (eg, slaughtering and packaging), we use the term minimally processed. Lean red meat is defined as <10 g total fat, <5 g saturated fat, and <95 mg cholesterol per 100 g.[14] In accordance with the American Heart Association's serving size specifications for cooked meat (2–3 ounces), we considered one serving of red meat to be equivalent to 2.5 ounces (70 g).

Calculations, Bias Assessment, and Statistical Analyses

Our primary aim was to assess the difference in pre- to post-intervention changes in blood lipids by comparing the red meat intervention with the comparison diet. Thus, the effect calculated for each study is the red meat change (post minus pre) minus the comparison group change (post minus pre). Secondary outcomes of interest included apolipoproteins, cholesterol ratios, and blood pressure.

We obtained or calculated the amount of red meat consumed by participants in each intervention diet from the dietary results available in the published journal article or via communications with study authors. We converted total cholesterol, LDL-C, HDL-C, and triglycerides to mmol/L (cholesterol conversion, mg/dL divided by 38.67; triglycerides conversion, mg/dL divided by 88.57). We used mg/dL for apolipoproteins A1 and B to be consistent with the majority of published studies. We extracted pre- and postintervention means, SDs, change values, and SD of the change values from the studies when available. We calculated unreported values from information provided in the study or raw data obtained from the authors. We calculated change value SDs using a correlation factor representative of the change value SDs that was available from the other published studies. We calculated the correlation factors in the intervention group and the control group for each of the prespecified main outcomes (correlation factors: total cholesterol: intervention= 0.79, control= 0.72; LDL-C: intervention= 0.76, control= 0.69; HDL-C: intervention= 0.87, control= 0.67; and triglycerides= 0.67, control= 0.78).

Crossover studies were treated as parallel studies, such that each intervention phase of a crossover study was treated as an independent arm of a parallel study. We assessed changes from baseline to postintervention within each intervention phase, comparing differences in red meat intervention with comparison group phases.[15] Although this is a conservative approach, this method approximates a paired analysis in this specific body of literature, as shown previously.[8] As a sensitivity analysis, we have stratified the main results for parallel studies and crossover studies.

We evaluated risks of selection, performance, and detection biases by using the NHLBI assessment tool (https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/rct).[16]

We estimated heterogeneity among studies using the I^2 statistic. I^2 statistic >30% was considered as moderate heterogeneity (http://handbook.cochrane.org).[17] Heterogeneity was statistically significant at $P \leq 0.10$, a conservative standard for meta-analyses. Primary analyses were conducted using random-effects models to incorporate within and between study components of variance. Fixed-effect models were used secondarily to confirm and compare results. Results are reported as weighted mean differences (WMDs) and 95% CI. For each study, we assessed the difference in the effect (postintervention minus preintervention values) of the red meat versus the comparison group, and weighted the difference by the inverse of their variance, a measure of the amount of information conveyed by each study, to get an overall WMD.

We used SAS version 9.4 (SAS Institute) to perform a 2-factor nested repeated-measures ANOVA to assess pre- and post-intervention changes in blood lipids and blood pressure adjusted for the length of intervention and sample size. These results are reported as adjusted least-squares means and their standard error.

Studies in figures and tables are organized in descending order by year of publication.

We examined potential sources of heterogeneity by conducting stratified analyses by the following comparison diet subcategories: high-quality plant protein sources (legumes, soy, nuts, and other plant protein sources, n=8); carbohydrates (refined carbohydrates including bread, rice, pasta, and high-sugar food, n=2 and whole grains, n=1); fish (including fatty fish and seafood, n=10); poultry (mainly chicken and turkey, n=6); poultry and fish combined (n=8); mixed animal-source proteins (fish, poultry, and dairy, n=4); and usual diet (n=2). See Table 1 for detailed information regarding the interventions. We also conducted stratified analyses by (1) intervention duration (<6 versus ≥6 weeks); (2) study design (crossover versus parallel); (3) quality score from the NHLBI assessment tool (<20 versus ≥20 points); (4) intervention adherence (yes/no by using question 9 of the quality score, "Was there high adherence to the intervention protocols for each treatment group?"); (5) lean versus nonlean red meat; (6) participants who were normolipidemic versus hyperlipidemic; (7) funding source (red meat industry versus other funding sources); and (8) dietary saturated fat levels (higher in meat intervention, higher in the comparison diet, or not different between red meat and the comparison diet).

We assessed publication bias by visually inspecting funnel plots to detect skewed (nonsymmetrical) distribution of standard errors around the study-level effect estimates, and the Egger and Begg tests, using a significance of $P<0.05$ to indicate significant asymmetry.[54,55]

We analyzed the change values using STATA/IC 14 (StataCorp) and Open Meta-Analyst (http://www.cebm.brown.edu/openmeta/).[56] We calculated the overall effect size using the metaan function in STATA (red meat intervention change value minus comparison diet change value).

Finally, we estimated the dose-response effect of red meat consumption using the dosresmeta package in R (version 3.1.1; R Development Core Team, 2011; http://cran.r-project.org).

RESULTS

Study Characteristics

The study characteristics of the 36 RCTs, representing 1803 participants, are described in Table 1. Of the 36 studies, 20 used a crossover design. Sample sizes ranged from 8 to 191 participants, and mean ages ranged from 22 to 70 years. Twenty-six studies were restricted to normolipidemic participants, whereas 11 included only participants with hypercholesterolemia. Intervention durations ranged from 2 to 36 weeks with a mean duration of 8.5 weeks. The amount of red meat consumed ranged from 46.5 to 500 g/d in the red meat interventions and 0 to 266 g/d in the comparison diets. Minimally-processed red meat was consumed in 24 studies, processed red meat was consumed in 5 studies, and the extent of red meat processing was not reported in 8 studies (see Table 1 for more detailed information).

Most articles included descriptions of methods for assessing or verifying participant compliance. Researchers provided food to participants in 32 studies. The most common methods for evaluating compliance were interviews, questionnaires, and diet records. Some studies used biomarkers, such as urinary 3-methyl histidine, urinary electrolyte excretion, or 24-hour nitrogen output. Dietary records or food-frequency questionnaires were used in all but 3 studies.[29,40,48] The number of participants who withdrew during the interventions was reported in all but 9 studies.[18–20,29,32,34,35,40,53] Twenty-four studies were categorized as high-quality (NHLBI quality score ≥20).

Table 1. Study Characteristics of Randomized Controlled Trials Included in a Meta-Analysis Assessing the Effects of Red Meat Consumption on Cardiovascular Disease Risk Factors

Study	No. of Participants	Participant Characteristics; Mean Age or Age Range; % Women	BMI (kg/m²) or Body Weight (kg)	Study Design; Intervention Duration (wk)	Red Meat Intervention: Total Red Meat in g/d; Type of Red Meat	Red Meat Intervention: Description	Comparison Diet: Total Red Meat Servings (g/d); Comparison Protein Source	Comparison Diet: Description	Quality Score*
O'Brien 1980[18]	29	Healthy, normolipidemic men; 42; 0%	NR	4 phase crossover; 6	170 g/d; minimally processed red meat (beef, pork, lamb)	Diet 1: Habitual diet + red meat, no fish or poultry + 3 eggs/d Diet 2: Habitual diet + red meat, no fish or poultry, no eggs, restriction of cholesterol intake lower 300 mg/d	Diet 1: 0 g/d; fish or poultry Diet 2: 0 g/d; fish or poultry	Diet 1: Habitual diet, 170 g/d of fish or poultry instead of red meat + 3 eggs/d Diet 2: Habitual diet, 170 g/d of fish or poultry instead of red meat, no eggs, restriction of cholesterol intake lower 300 mg/d	18
Flynn 1981[19]	129	Healthy, normolipidemic; 23–70; 43%	NR	2 phase crossover; 2	141 g/d; minimally processed raw beef	Habitual diet + red meat, 1 fresh egg daily, protein sources provided	0 g/d; poultry, fish	Habitual diet, 142 g/d poultry, fish, turkey or fish - but no other meat type, 1 fresh egg daily, protein sources provided	15
Flynn 1982[20]	76	Healthy, normolipidemic; 32–63; 38%	Female: 61 kg Male: 71 kg	2 phase crossover; 12	141 g/d; minimally processed raw beef or pork	Habitual diet + red meat, 1 egg/d in all groups, protein sources provided	0 g/d; fish or poultry	Habitual diet, 141 g/d of fish or poultry, 1 egg/d in all groups, protein sources provided	18
Wiebe 1984[21]	8	Healthy young normolipidemic men; 21; 0%	66.3 kg	2 phase crossover; 3	250 g/d; minimally processed beef patties	55% of protein in diet from beef, food provided	0 g/d; legumes and other plant protein	All protein in diet plant-based (except includes 45 g/d beef tallow margarine), protein sources: sunflower seeds, kidney beans, garbanzo beans, peas, peanut butter	19
Sinclair 1987[22]	13	Healthy, weight-stable, normolipidemic; 31; 54%	21.2 kg/m²	4 phase crossover (nonspecified assignment method); 2	500 g/d; minimally processed kangaroo	Low-fat diet (<7% total energy intake) with kangaroo meat as main protein source (other meat and fish excluded), protein sources provided	0 g/d; fatty fish or plant protein	Low-fat diet (<7% total energy intake) with either: (1) tropical fish (TF) 500 g/d, (2) southern fish (SF): 500 g/d, rich in docosahexaenoic acid, other meat and fish excluded, or (3) a vegetarian diet (veg) containing no 20- and 22-carbon PUFA; protein source provided	18
Prescott 1988[23]	50	Healthy, normolipidemic; 18–60; 60%	Meat group: 72.2 kg; nonmeat group: 68.1 kg	2 arm parallel; 12	57.5 g/d; supplement product mixture of processed and unprocessed red meat (beef, beef sausage, lamb, pork)	Habitual diet + mixture meat protein supplement, 2 meals/d and protein sources provided	0 g/d; legumes, eggs, and plant protein	Habitual diet + mixture nonmeat protein supplement (supplement includes egg, soya, brown rice, almonds, haricot beans), protein sources provided	22
Wolmarans 1991[24]	28	Healthy; men: 36; women: 30; 57%	<30 kg/m²	2 phase crossover; 6	Men: ≈300 g/d; women: 225 g/d; raw minimally processed beef, mutton	Replace all fish from habitual diet with red meat, prepackaged meat rations given to volunteers weekly, asked to keep weight constant	0 g/d; fatty fish	Replace all red meat from habitual diet with fish, men: 228 g fatty fish and women: 216 g fatty fish, asked to keep weight constant, prepackaged fish rations given weekly	18

(*Continued*)

Table 1. Continued

Study	No. of Participants	Participant Characteristics; Mean Age or Age Range; % Women	BMI (kg/m²) or Body Weight (kg)	Study Design; Intervention Duration (wk)	Red Meat Intervention: Total Red Meat in g/d; Type of Red Meat	Red Meat Intervention: Description	Comparison Diet: Total Red Meat Servings (g/d); Comparison Protein Source	Comparison Diet: Description	Quality Score*
Scott 1994[25]	38	Healthy, hypercholesterolemic; 20–55; 0%	NR	2 arm parallel; 5	85 g/1000 kcal; lean beef (only entrée), minimally processed strip loin steak	Habitual diet + red meat, protein source provided	0 g/d; chicken	Habitual diet, no red meat, 85 g of chicken per 1000 kcal (only entrée), protein source provided	25
Gascon 1995[26]	14	Healthy, nonsmoking, young, active, normolipidemic women; 22; 100%	22 kg/m² 58.7 kg	2 phase crossover; 4	230 g/d; minimally processed lean beef, pork, veal	≈70% protein from lean beef, pork, veal, eggs and egg substitutes, and partially skimmed milk and milk products; no alcohol; 7-day rotating menu meeting energy needs, some food provided	0 g/d; lean white fish	≈70% protein from lean white fish (cod, sole, pollack, and haddock with <1% fat); calcium (500 mg) and vitamin D (125 IU) supplement; no alcohol; 7-day menu meeting energy needs, some food provided	21
Davidson 1999[27]	191	Mild to moderate hypercholesterolemia; INT: 57; Comparison: 55; INT: 46% Comparison: 42%	INT: 27.6 Comparison: 27.1 kg/m²	2 arm parallel; 36	135 g/d; minimally processed lean beef veal or pork	National Cholesterol Education Program step 1 diet + red meat, at least 80% of meat as lean beef. Lamb included in other 20%, instructed to maintain baseline weight, no food provided	22.2 g/d; poultry or fish	National Cholesterol Education Program step 1 diet + red meat, at least 80% of meat as lean poultry or fish. Lamb included in other 20%, instructed to maintain baseline weight, no food provided	19
Wolmarans 1999[28]	39	Hypercholesterolemic; men: 35; women: 32; 49%	Men: 25.1 Women: 23.6 kg/m²	2 phase crossover; 6	120 g/d; minimally processed lean beef or lean mutton	Prudent diet + lean red meat: lean beef 5 times/wk, lean mutton 2 times/wk, max 2 eggs/wk, no food provided	0 g/d; lean chicken or fish	Prudent diet + skinless chicken and fish: skinless chicken 5 times/wk, hake 1 time/wk, pilchards or tuna 1 time/wk, max 2 eggs/wk, no food provided	18
Horrocks 1999[29]	40	NR; NR; 100%	NR	2 arm parallel (nonspecified assignment method); 4	200 g/d; DHA-enriched pork	NR	0 g/d; DHA-enriched chicken	NR	16
Ashton 2000[30]	42	Healthy men with no symptoms or prior diagnosis of CHD; 35–65; 0%	26.2 kg/m²	2 phase crossover; 4	150 g/d; minimally processed lean red meat	Habitual diet + red meat, 15 g PUFA margarine, no soy products, fats were provided	NR; tofu	The tofu diet was designed to replace 90–100% of the animal protein with 290 g of tofu, recommendations to consume 5 g butter, 5 g lard, and 8 mL olive oil, tofu, and fats provided	22
Beauchesne-Rondeau 2003[31]	17	Hypercholesterolemic men; 50; 0%	26.5 kg/m² 81.4 kg	3 phase crossover; 4	380 g/d; minimally processed lean ground beef, exterior round, sirloin tip	American Heart Association diet + red meat, 2 meals/d provided	0 g/d; chicken/turkey or lean fish	(1) Chicken diet : Skinless chicken and ground turkey (405 g for a 2811 kcal/d diet). (2) Lean fish diet : Fish such as pollack, cod, sole, and haddock with <1% fat (495 g for a 2811 kcal/d diet), 2 meals/d provided	19

(*Continued*)

Table 1. Continued

Study	No. of Participants	Participant Characteristics; Mean Age or Age Range; % Women	BMI (kg/m²) or Body Weight (kg)	Study Design; Intervention Duration (wk)	Red Meat Intervention: Total Red Meat in g/d; Type of Red Meat	Red Meat Intervention: Description	Comparison Diet: Total Red Meat Servings (g/d); Comparison Protein Source	Comparison Diet: Description	Quality Score*
Melanson 2003[32]	61	Overweight, normolipidemic women; 43; 100%	31.9 kg/m² 87.3 kg	2 arm parallel; 12	72 g/d; minimally processed lean sirloin beef	Hypocaloric (meal plans provided) beef diet + walking program, no food provided	NR; lean chicken	Hypocaloric (meal plans provided) chicken diet + walking program, red meat amount not reported but chicken is the primary protein source, no food provided	20
Grieger 2014[33]	80	Healthy, aging; 70; 51%	26.4 kg/m²	2 arm parallel; 8	68 g/d; cooked, raw, and prepared beef, lamb, pork, ham, and veal	Usual diet + 8 servings/fortnight of red meat, protein source and other food provided	NR; fatty fish	8 servings/fortnight of raw, canned, and marinated mixed fish, in addition to usual diet, which may include red meat	22
Haub 2005[34]	21	Healthy, normolipidemic men; 65; 0%	28.2 kg/m² 89.2 kg	2 arm parallel; 12	248 g/d; minimally processed red meat (cube steak, ground beef, beef tips)	Habitual diet and exercise training (3 d/wk), 0.6 g protein per kg/d from beef, protein sources provided	NR; plant protein	Habitual diet and exercise training (3 d/wk), 0.6 g protein per kg/d from plant-based protein foods (breakfast patties, grillers, "chick" patties and veggie dogs), protein sources provided	21
Mamo 2005[35]	20	Dyslipidemic, hypertriglyceridemic, overweight; INT mean: 55; Comparison mean: 41; 40%	31.7 kg/m²	2 arm parallel; 6	496 g/d; minimally processed lean beef or veal, pork or lamb	25% of total energy intake derived from lean beef, veal and lamb; isocalorically matched to habitual energy intake, 35% energy from carbohydrate, 30% energy from fat, red meat provided	174.5 g/d; lean beef, pork, or veal	14% of total energy intake derived from protein (assume 7% lean beef, veal lamb); isocalorically matched to habitual energy intake, 53% energy from carbohydrate, 30% energy from fat; estimate 174.5 g/d lean beef, pork, or veal, red meat provided	14
de Mello 2006[36]	17	Patients with type 2 diabetes mellitus with macroalbuminuria; 50; 18%	26.2 kg/m²	3 phase crossover; 4	141 g/d; beef	Usual diet + red meat (0.5–0.8 g per kg body/d), no food provided	0 g/d; chicken, dairy, plant protein	(1) Low-protein diet (veg): Protein content was 0.5–0.8g per kg in the form of vegetable and dairy protein only (11.6% of calories from protein). (2) Chicken diet: Replace all meat in the usual diet with dark chicken meat (skinless leg quarter, 173 g/d).	20
Hodgson 2006[37]	60	Hypertensive; comparison: 60; INT: 57; 37%	Comparison: 27.9 Meat: 27.5 kg/m²	2 arm parallel; 8	215 g/d; minimally processed lean red meat	Protein diet: Partially replace energy intake from carbohydrate with protein from lean red meat, protein source provided	NR; plant protein	Usual diet: variable protein source that did not exclude red meat, no food provided	23
Liao 2007[38]	30	Obese, but otherwise healthy adults; 20–60; 80%	Soy group: 29.6 Traditional: 30 kg/m²	2 arm parallel; 8	≈170 g/d; red meat type NR	Traditional low-calorie diet: 2/3 of protein from animal foods, ≈1–2 servings/d of red meat, no food provided	0 g/d; soy protein	Soy low-calorie diet: Soy was the only source of protein (45 g/d of soy protein), some food provided	18

(*Continued*)

Table 1. Continued

Study	No. of Participants	Participant Characteristics; Mean Age or Age Range; % Women	BMI (kg/m²) or Body Weight (kg)	Study Design; Intervention Duration (wk)	Red Meat Intervention: Total Red Meat in g/d; Type of Red Meat	Red Meat Intervention: Description	Comparison Diet: Total Red Meat Servings (g/d); Comparison Protein Source	Comparison Diet: Description	Quality Score*
Mahon 2007[39]	54	Postmenopausal women, hyperlipidemic, prediabetic, normo-insulinemic; 58; 100%	29.6 kg/m²	4 arm parallel; 9	115 g/d, minimally processed cooked beef tenderloin	1250 kcal/d weight loss diet, 1000 kcal/d lacto-ovo vegetarian basal diet plus 250 kcal/d beef, 5-day fixed menu rotation, protein source provided	0 g/d; Chicken or carbohydrates	(1) Chicken diet: 1250 kcal/d weight loss diet, 1000 kcal/d lacto-ovo- vegetarian basal diet plus 250 kcal/d chicken breast and butter, day fixed menu rotation, protein source provided (2) Carbohydrate diet (carb): 1250 kcal/d weight loss diet, 1000 kcal/d lacto-ovo- vegetarian basal diet plus 250 kcal/d shortbread cookies and sugar-coated chocolate, 5-day fixed menu rotation, protein source provided	17
Ouellet 2008[40]	18	White, overweight or obese participants with insulin resistance; Men: 58 and women: 55; 48%	Men: 30.9 and women: 33.8 kg/m²	2 phase crossover; 8	200 g/d; minimally processed lean ground beef, beef cubes, lean ground veal, pork tenderloin, pork shoulder cubes, chop trimmed of fat, and lean ham	National Cholesterol Education Program – ATP III, American Diabetes Association and Dietary Reference Intakes recommendations. BPVEM diet containing lean beef, pork, veal, eggs, milk, and milk products, diets only differing in protein source, no food provided	0 g/d; cod	National Cholesterol Education Program – ATP III, American Diabetes Association and Dietary Reference Intakes recommendations, instead of red meat, no food provided	18
Nowson 2009[41]	95	Normal-hypertensive postmenopausal women; 59; 100%	29.6 kg/m²	2 arm parallel; 14	86 g/d; raw minimally processed lean beef, veal, lamb or combination (meat cooked before consumption)	Vitality Diet (VD): habitual diet + red meat and low salt: red meat (6 servings/wk), low-sodium bread, no-added salt beans, salt-free margarine, and low-sodium stock powder, restrictions on cheese consumption and cereal (4 servings/d max), and encouraged to consume at least 3 servings/d low-fat milk and dairy products, protein source provided	<28 g/d; raw minimally processed lean beef, veal, lamb or combination (meat cooked before consumption)	Reference Healthy Diet (RHD): high grain, dairy and salt: provided with regular-salt margarine, regular-salt baked beans, and canned tuna, to be consumed with normal diet with encouragement to consume at least 4 servings/d breads and cereals and 3 servings/d low-fat milk and dairy products, food provided	20
Navas-Carretero 2009[42]	25	Young iron-deficient women with normal lipid, glucose and insulin concentrations; 18–30; 100%	22.1 kg/m²	2 phase crossover; 8	112.5 g/d; red meat type NR	Usual diet + red meat (112.5 g/d –reported red meat + poultry together, estimated actual intake based on assigned intake of 5 portions/wk), no food provided	22.3 g/d; fatty fish	Oily fish diet: Usual diet + 105 g/d oily fish (salmon, water-packed tuna, sardines in olive oil, lean fish), no food provided	20

(*Continued*)

Table 1. Continued

Study	No. of Participants	Participant Characteristics; Mean Age or Age Range; % Women	BMI (kg/m²) or Body Weight (kg)	Study Design; Intervention Duration (wk)	Red Meat Intervention: Total Red Meat in g/d; Type of Red Meat	Red Meat Intervention: Description	Comparison Diet: Total Red Meat Servings (g/d); Comparison Protein Source	Comparison Diet: Description	Quality Score*
Lindqvist 2009[43]	35	Overweight, normolipidemic, men; 48; 0%	28.3 kg/m²	2 phase crossover; 6	46.5 g/d; pork, browned pork fillets	Habitual diet + red meat, protein source provided and meals provided (5 d/wk)	NR; herring	Habitual diet, 150 g of raw herring 5 d/wk, protein source provided (fish cooked before consumption)	23
Zhang 2010[44]	92	Adult men with hypercholesterolemia; 35–70; 0%	Meat: 26.9; typical fish diet: 26.3; oily fish: 26.7 kg/m²	3 arm parallel; 8	114.8 g/d; minimally processed beef and pork	Habitual diet + red meat (lunch provided 5 d/wk)	NR; fish and fatty fish	(1) Typical fish diet (FD): Lunch of hairtail, carp, grass carp (71.4 g/d) (2) Oily fish diet (OF): Lunch (5 d/wk) of Atlantic farmed salmon fillet (71.4 g/d). No red meat in the lunches but habitual diet for dinner	20
Zhang 2012[45]	126	Middle-aged and elderly women with hypertriglyceridemia; 35–70; 100%	INT: 26.0 kg/m² Comparison: 27.7 kg/m²	4 arm parallel; 8	114.8 g/d; minimally processed beef and pork	Habitual diet + red meat (lunch provided 5 d/wk)	NR; herring and chicken	Habitual diet, (lunch provided), herring: 57.4 g/d, chicken: 57.4 g/d, no red meat in the lunches but habitual diet for dinner	24
Roussell 2012[46]	36	Healthy, hypercholesterolemia (elevated LDL); 50; 58%	25.7 kg/m²	4 phase crossover; 5	113 g/d or 153 g/d; minimally processed lean beef	2 diets (all meals provided): (1) BOLD (Beef in an Optimal Lean Diet) (28% total fat, 6% saturated fatty acids, 19% protein), 113 g/d of beef. (2) BOLD diet + (28% total fat, 6% saturated fatty acids, 27% protein) 153 g/d of beef, lean beef minimally processed	20 g/d or 28 g/d; poultry, pork, fish	2 diets (all meals provided): (1) Healthy American Diet (HAD): Poultry/Pork/Fish, lean beef minimally processed (20 g/d), full-fat cheese, dairy, butter, tuna. (2) Dietary Approached to Stop Hypertension (DASH): Poultry/Pork/Fish lean beef (28g/d), low-fat cheese, yogurt	20
Murphy 2012[47]	144	Overweight/obese who consume pork less than once a week; 48; NR	32 kg/m²	2 arm parallel; 24	Men: 150 g/d and women 107.14 g/d; lean steak, stir fry, diced, mince and sausage	Habitual diet + red meat (7 servings of 150 g/wk for men and 5 servings for women), protein source provided	<100 g/wk; no substitution protein	Habitual diet, <100 g/wk of pork, no substitution protein	24
Foerster 2014[48]	20	Healthy; 40; 50%	24.4 kg/m²	2 phase crossover; 3	200 g/d; pork cutlet, beef steak, and other red meat	Habitual diet + red meat, minimal amounts of dietary fiber, protein sources provided	<30 g/d; whole-grain products	Habitual diet and low red meat intake (<30 g/d), high amounts of whole grain products	19
Hosseinpour-Niazi 2014[49]	40	Type 2 diabetes mellitus, serum glucose concentrations and medication stable; 52; 77%	INT: 27.7 Comparison: 27.8 kg/m²	2 phase crossover; 8	343 g/d; red meat type NR	Follow Therapeutic Life Change (TLC) diet without legumes, 50%–60% carbohydrate, 15% protein, and 25%–35% of energy from fat; no food provided	266 g/d; legumes and plant protein	Follow TLC diet same as intervention but replace 2 servings of red meat with legumes 3 d/wk; other protein sources: lentils, chickpeas, beans, peas	20

(*Continued*)

Table 1. Continued

Study	No. of Participants	Participant Characteristics; Mean Age or Age Range; % Women	BMI (kg/m²) or Body Weight (kg)	Study Design; Intervention Duration (wk)	Red Meat Intervention: Total Red Meat in g/d; Type of Red Meat	Red Meat Intervention: Description	Comparison Diet: Total Red Meat Servings (g/d); Comparison Protein Source	Comparison Diet: Description	Quality Score*
Aadland 2015[50]	20	Healthy; 51; 65%	25.6 kg/m²; 75.7 kg	2 phase crossover; 4	130 g/d; minimally processed beef sirloin and pork	Norwegian diet + meat diet (containing lean beef, pork, chicken, turkey, eggs, and milk products); supplemented with cod liver oil containing EPA and DHA; also includes margarine, food provided	0 g/d; lean seafood	Norwegian diet + lean-seafood diet (stock fish, pollack, cod), food provided	21
Sayer 2015[51]	19	Obese with systolic blood pressure in the prehypertensive range; 61; 68%	30.9 kg/m²	2 phase crossover; 6	121 g/d; minimally processed pork and beef	DASH style diet with pork (DASH-P) providing 55% of dietary protein, plus 2 weekly servings of lean beef, with targeted macronutrient ranges (18% protein, 27% fat, 55% carb), and a prescribed 7-day cycle menu, protein source provided	10.7 g/d; chicken and fish	DASH style diet with chicken and fish (DASH-CF) providing 55% of dietary protein plus 2 weekly servings of lean beef, with targeted macronutrient ranges (18% protein, 27% fat, 55% carb), and a prescribed 7-day cycle menu, protein source provided	20
Hill 2015[52]	62	Overweight and obese adults with metabolic syndrome; 30–60; 55%	M-DASH: 34.7; BOLD: 34.6; BOLD+: 35.1 kg/m²	3 arm parallel; 24	139 g/d and 196 g/d; select grade top round, ribeye, chuck shoulder pot roast, and 95% lean ground beef	BOLD: A modified DASH diet rich in animal protein (red meat = 139 g/d). BOLD+: Same as BOLD, but with higher protein content (red meat = 196.2 g/d), food provided	11.7 g/d; dairy, chicken, fish	M-DASH: Modified DASH diet rich in plant protein (plant protein from grains, nuts/seeds, pulses, and soy + dairy/chicken/fish protein), food provided	20
Thorning 2015[53]	14	Postmenopausal, healthy women; 59; 100%	28.8 kg/m²	3 phase crossover; 2	253 g/d; high-fat processed and unprocessed pork and beef	Macronutrient-matched nondairy, high-meat comparison, isocaloric weight maintenance	87 g/d and 194 g/d; high-fat processed and unprocessed pork and beef	(1) Cheese diet: High cheese intervention (96–120 g/d); isocaloric weight maintenance; cheese (2) Carbohydrate diet (carb): Nondairy, low-fat, high-carbohydrate comparison, isocaloric weight maintenance; carbohydrate food (fruit, white bread, pasta and rice, marmalade, cakes, sweetened biscuits and chocolate); food provided	22

Values are means; SDs or ranges are in parentheses. When the red meat amount is not mentioned as raw, is it assumed to be cooked amount. BMI indicates body mass index; BOLD, Beef in an Optimal Lean Diet; BP, blood pressure; BPVEM, beef, pork, veal, eggs, and milk products; CHD, coronary heart disease; DHA, docosahexaenoic acid; E, total energy; EPA, eicosapentaenoic; INT: intervention; LDL, low density lipoprotein; max, maximum; NR, not reported; and PUFA, polyunsaturated fatty acids.

*Quality score from National Heart, Lung and Blood Institute (Quality Assessment of Controlled Intervention Studies): Score ranging from 0 to 28 points.

Effects of Red Meat Relative to All Comparison Diets Combined

Studies in figures and tables are organized in descending order by year of publication, within the larger categories of comparison diets. Means, SDs, and mean differences for total cholesterol, LDL-C, HDL-C, and triglycerides in red meat interventions and comparison diets are presented in Tables II through V in the online-only Data Supplement.

In random-effects analyses of all studies (n=36), no significant differential effects of red meat versus all comparison diets combined were observed in total cholesterol (n=32), LDL-C (n=31), HDL-C (n=34), total:HDL-C (n=7), HDL-C:LDL-C (n=4), very-low-density lipoprotein cholesterol (n=5), apolipoprotein A1 (n=4), apolipoprotein B (n=7), or blood pressure (n=11) (see Figures 2 and 3 and Figures I through IV in the online-only Data Supplement). For all studies combined, relative to the comparison diets, red meat yielded lesser decreases in triglycerides (WMD, 0.065 mmol/L; 95% CI, 0.000–0.129; *P* for heterogeneity <0.01) (Figure 2B).

With interventions in which only lean red meat was consumed, relative to all comparison diets, red meat yielded greater decreases in total cholesterol (WMD, –0.05 mmol/L; 95% CI, –0.12 to –0.02; *P*=0.04) and LDL-C (WMD, –0.08 mmol/L; 95% CI, –0.15 to –0.02; *P*=0.03), but lesser decreases in triglycerides (WMD, 0.10 mmol/L; 95% CI, 0.02–0.18; *P*=0.04). We observed a trend for red meat to yield greater decreases in total cholesterol and LDL-C when saturated fat intake in the comparison diet was higher than in the red meat group (≥5% difference). No significant differential effects of red meat were observed for total cholesterol or LDL-C when dietary saturated fat intake in the red meat group was higher or similar to that in the comparison diet. In addition, no significant differential effects were observed when the studies were analyzed according to funding source (red meat industry versus other) or according to the study design (crossover versus parallel) (Table VI in the online-only Data Supplement). As shown by the ANOVA time-effect results, we observed overall decreases from pre- to post-intervention in total cholesterol, LDL-C, HDL-C, and triglycerides in both red meat and comparison diets (Figures V and VI in the online-only Data Supplement).

The dose-response meta-analyses showed no significant effects of red meat intake (evaluated as continuous

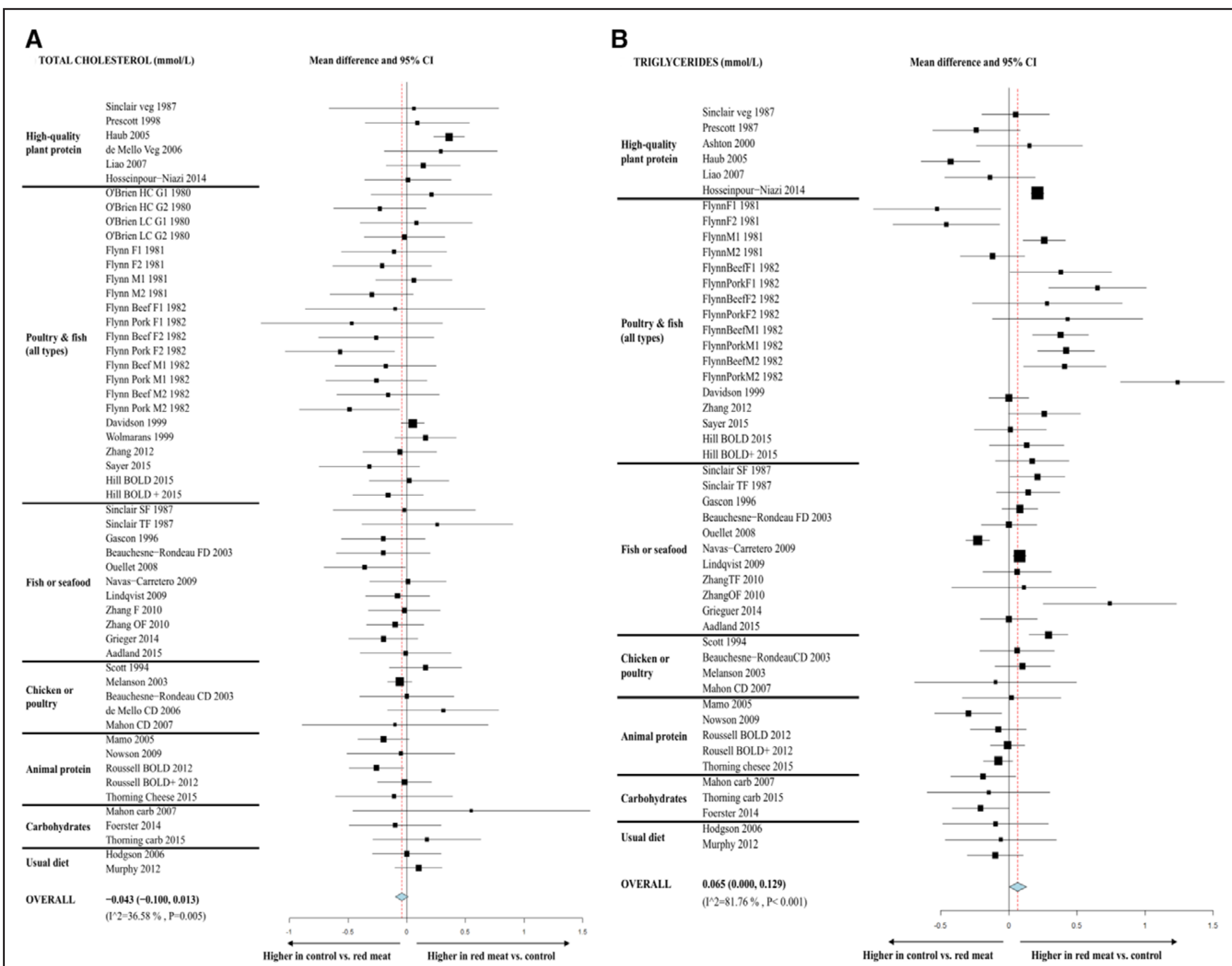

Figure 2. Changes in total cholesterol and triglyceride concentrations comparing red meat interventions and all comparison diet combined.
Random effects model meta-analysis for changes in total cholesterol (**A**) and triglyceride concentrations (**B**) from randomized controlled trials comparing red meat interventions and all comparison diets combined. Data are shown in descending order by year of publication and categorically by comparison diet type. HC G1 indicates first group consuming high-cholesterol diet; HC G2, second group consuming high-cholesterol diet; LC G1, first group consuming low-cholesterol diet; LC G2, second group consuming low-cholesterol diet; F1, first female group; F2, second female group; M1, first male group; M2, second male group; SF, southern fish; TF, tropical fish; F, fish; OF, oily fish; CD, chicken diet; carb, carbohydrates; and veg, vegetarian comparison. Detailed information of the mean changes in each group and differences between groups are presented in the online-only Data Supplement. Conversion factor: Total cholesterol from mmol/L to mg/dL: 38.67; and triglycerides: mg/dL: 88.57.

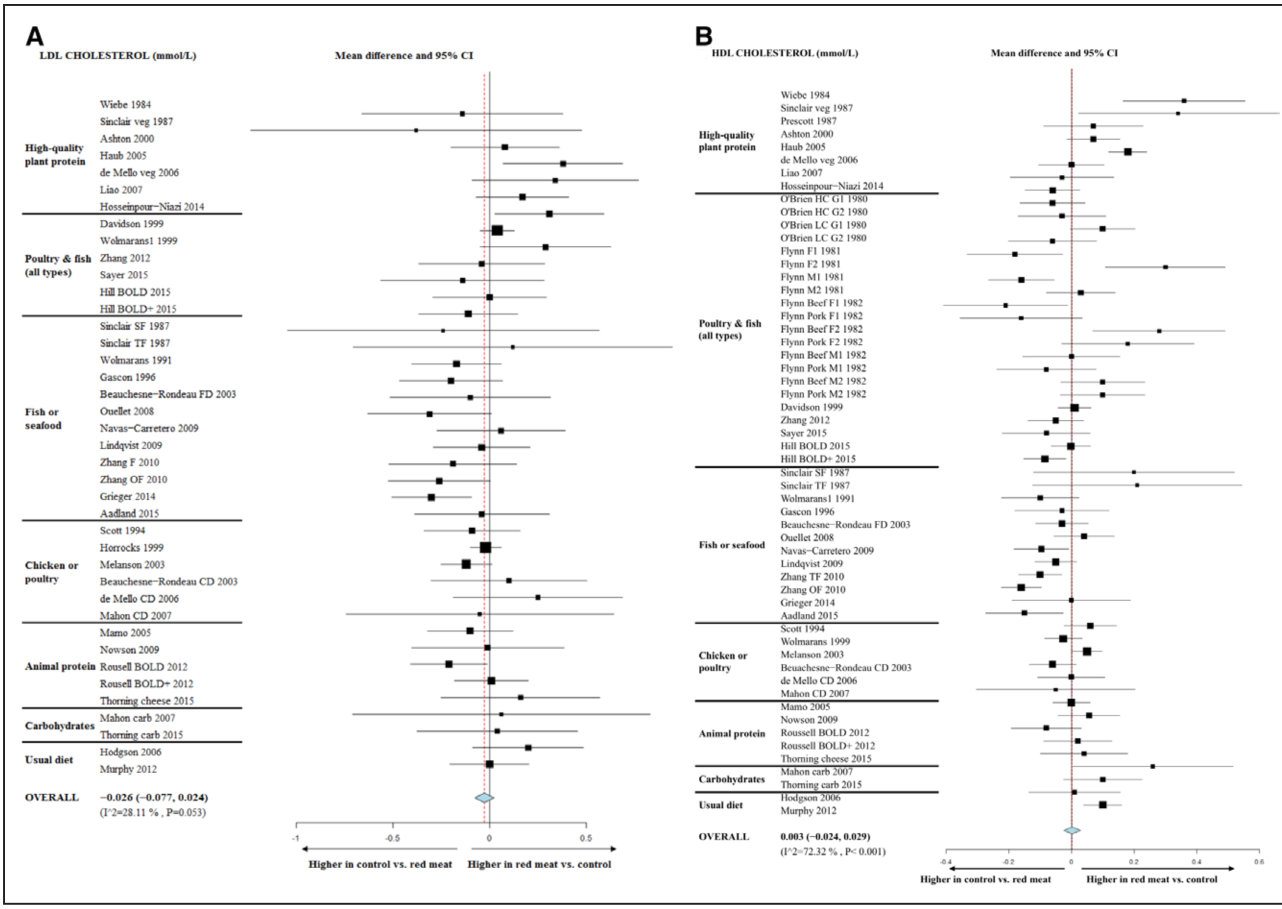

Figure 3. Changes in LDL and HDL cholesterol and triglyceride concentrations comparing red meat interventions and all comparison diet combined.
Random-effects model meta-analysis for changes in LDL (**A**) and HDL cholesterol concentrations (**B**) from randomized controlled trials comparing red meat interventions and all comparison diets combined. Data are shown in descending order by year of publication and categorically by comparison diet type. HC G1 indicates first group consuming high-cholesterol diet; HC G2, second group consuming high-cholesterol diet; LC G1, first group consuming low-cholesterol diet; LC G2, second group consuming low-cholesterol diet; F1, first female group; F2, second female group; M1, first male group; M2, second male group; SF, southern fish; TF, tropical fish; F, fish; OF, oily fish; CD, chicken diet; carb, carbohydrates; and veg, vegetarian diet. Detailed information of the mean changes in each diet and differences between diets are presented in the online-only Data Supplement. Conversion factor: LDL and HDL cholesterol from mmol/L to mg/dL: 38.67. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

in g/d) on blood lipids or apolipoproteins within the studied intake range of 0 to 500 g/d (total cholesterol *P*=0.73, LDL-C *P*=0.49, HDL-C *P*=0.57, and triglycerides *P*=0.05).

Effects of Red Meat Relative to Specific Comparison Diets

Random-effects summary statistics and forest plots stratified by comparison diets are presented in Figure 4 and Figures VII through X in the online-only Data Supplement, respectively. Compared with high-quality plant protein sources, red meat yielded lesser decreases in total cholesterol (WMD, 0.264 mmol/L; 95% CI, 0.144–0.383; *P*<0.001) and LDL-C (WMD, 0.198 mmol/L; 95% CI, 0.065–0.330; *P*=0.003). Relative to fish-only comparison diets, red meat resulted in greater decreases in total cholesterol (WMD, –0.109 mmol/L; 95% CI, –0.211 to –0.007; *P*<0.036), LDL-C (WMD, –0.173 mmol/L; 95% CI, –0.260 to –0.086; *P*<0.001), and HDL-C (WMD, –0.065 mmol/L; 95% CI, –0.109 to –0.020; *P*=0.004). In comparison with chicken or poultry diets, red meat showed no significant differential effects on lipid variables. When considering poultry and fish together as the comparison, red meat yielded greater decreases in total cholesterol (WMD, –0.092 mmol/L; 95% CI, –0.177 to –0.008; *P*=0.032) but lesser decreases in triglyceride concentrations (WMD, 0.224 mmol/L; 95% CI, 0.077–0.371; *P*=0.003). In comparison with carbohydrates, red meat yielded lesser decreases in HDL-C (WMD, 0.139 mmol/L; 95% CI, 0.004–0.275; *P*=0.043) as it did when usual diet was the comparison (WMD, 0.081 mmol/L; 95% CI, 0.008–0.153; *P*=0.030). Also, in comparison with carbohydrates, red meat yielded greater decreases in triglyceride concentrations (WMD, –0–181 mmol/L; 95% CI, –0.349 to –0.013; *P*=0.035) as it did in comparison with combined animal protein sources (WMD, –0.093 mol/L; 95% CI, –0.176 to –0.011, *P*=0.027). Sensitivity analyses using a fixed-effect inverse variance approach yielded consistent results.

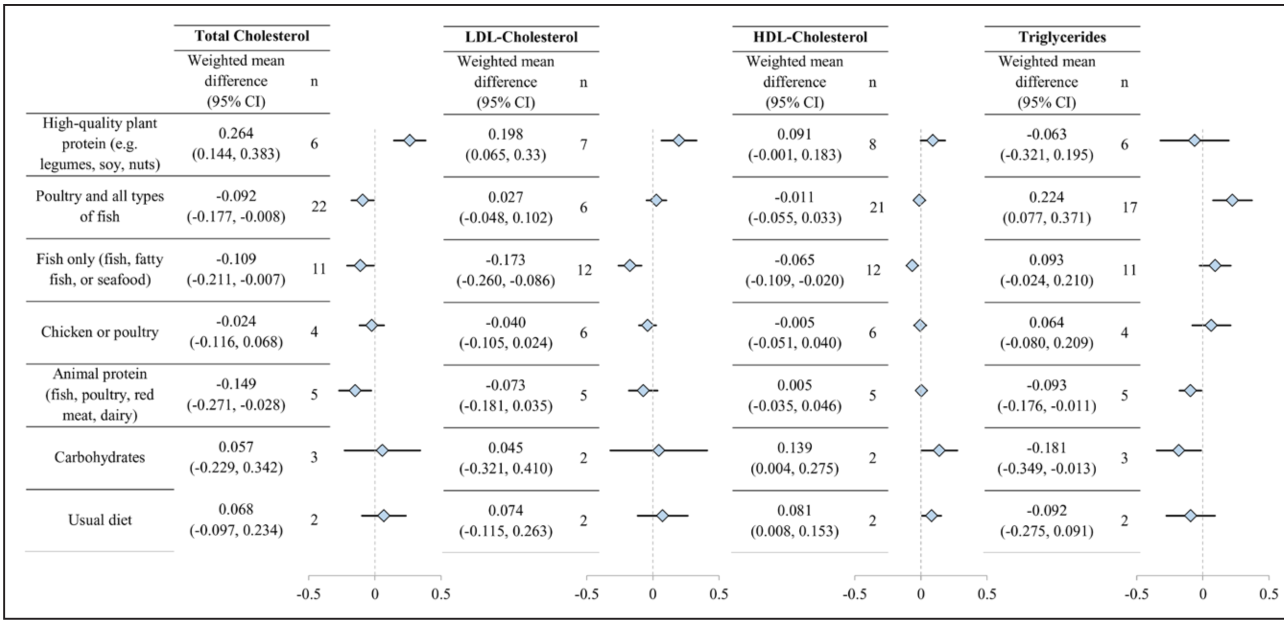

Figure 4. Results from random-effects meta-analysis assessing the relative effects of red meat intake on changes in total, LDL, HDL cholesterol, and triglycerides concentrations (mmol/L) from randomized controlled trials stratified by type of comparison diet.
Positive values indicate lesser changes in blood lipid concentrations with the red meat intervention in comparison with the comparison diet. Changes pre- to postintervention stratified by comparison diet using repeated-measures ANOVA are presented in Figures V and VI in the online-only Data Supplement. n indicates the number of intervention comparisons. Conversion factor: total, LDL, and HDL cholesterol from mmol/L to mg/dL: 38.67; and triglycerides: mg/dL: 88.57. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

Publication Bias

The Egger and Begg tests did not indicate the presence of publication bias (*P*>0.05 for all outcomes). The funnel plots showed agreement with the statistical test because they lacked apparent asymmetry.

DISCUSSION

In the present meta-analysis including 36 RCTs, relative to all comparison diets combined, red meat consumption had no differential effects on total cholesterol, LDL-C, HDL-C, apolipoproteins A1 and B, or blood pressure, but yielded lesser decreases in triglyceride concentrations. In analyses stratified by type of comparison diet, substituting red meat with high-quality plant foods (ie, soy, nuts, and legumes) led to more favorable changes in total cholesterol and LDL-C concentrations. Our results suggest improvements in some lipid parameters when red meat was consumed versus combined animal protein, usual diet, or carbohydrates; and mixed effects in comparison with fish or poultry. Our findings underscore the importance of considering the comparison diet interventions as a determinant of the relative effects of red meat on CVD risk factors.

Results in Relation to Previous Literature

Previous meta-analyses[7,8] have reported no differential effects of red meat intake on CVD risk factors relative to combined comparison diets. These meta-analyses were limited to a restrictive red meat intake cutoff (<0.5 or ≥0.5 servings per day), did not stratify by the type of comparison diet,[8] or were limited to studies where participants consumed only minimally processed beef.[7] In one meta-analysis,[7] the only red meat protein analyzed was beef, and it was compared only with poultry and fish combined. Moreover, heterogeneity was high in most of the analyses. While our results are consistent with these findings, the current meta-analysis included a broader variety and differing amounts of red meats, which allowed for the inclusion of 13 additional RCTs. One potential explanation for the lack of significance in these analyses, including ours in which all comparison diets were analyzed together, is that many of the trials followed diets that differed in protein source but both interventions adhered to nutritional recommendations.[57] Furthermore, most studies matched macronutrient distribution between the red meat and comparison diets. This often required the addition of saturated fat and cholesterol-rich foods (such as butter) to the comparison diet to match the higher concentration of saturated fat and cholesterol in red meat. In addition, usual diets tend to be high in refined carbohydrates, and most studies have found that both refined carbohydrates and saturated fat have detrimental effects on cardiovascular health.[58] Our findings are consistent with a recent meta-analysis of prospective cohort studies including 432 179 adults, with a median follow-up of 25 years and 40 181 deaths. This study found that the risk of all-cause mortality was 18% (95% CI, 8%–29%) higher when carbohydrates were replaced by animal-

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derived fat or protein but was lowered by 18% (95% CI, 22%–13%) when carbohydrate was replaced by plant-based fat or protein.[59]

In our meta-analysis, we observed differential effects of red meat on blood lipids depending on the comparison diets, thereby confirming the importance of the substitution sources when analyzing the effects of a macronutrient or food on health. For instance, we found fish-only comparison diets to be potentially beneficial for HDL-C in comparison with red meat, although it appeared that red meat intake yielded lower LDL-C relative to fish intake. The potentially beneficial effects of red meat consumption versus fish on total cholesterol and LDL-C observed in our analyses may primarily reflect studies in which participants consumed lean, unprocessed meat. Indeed, lean red meat, but not nonlean red meat, yielded favorable changes in total cholesterol and LDL-C relative to the combined comparison diets.

As hypothesized, based on previous studies of fatty acids[10] and epidemiological studies of plant-based dietary patterns,[60] improvements in several blood lipid parameters were observed when healthy sources of plant protein were compared with red meat. Plant-based foods are increasingly recognized for their potential in preventing chronic diseases, and several previous meta-analyses of RCTs have investigated their effects on CVD risk factors, including blood lipids.[61–68] In a brief review of previously published meta-analyses of RCTs (Table 2),[61–68] we found that tree nuts, especially walnuts, improved total cholesterol and LDL-C relative to a range of comparison diets. Soy-containing foods or soy protein improved all lipid and lipoprotein parameters, and legumes reduced LDL-C when measured against comparison diets. These meta-analyses included a variety of comparison diets (detailed in Table 2 footnote). In further analyses, we considered the impact of replacing a single serving (85 g) of lean beef (200 kcal, or 10% of a 2000 kcal diet) by isocaloric equivalent amounts of peanuts, mixed nuts, and soybeans on blood lipids based on fatty acid profiles derived from the US Department of Agriculture National Nutrient Database.[69] Using established equations,[10] we calculated expected reductions in LDL-C (mmol/L) of 0.053 (peanuts), 0.060 (mixed nuts), and 0.062 (soybeans), and also favorable changes in total cholesterol, HDL-C, and triglycerides. These calculations, which did not consider differences in fiber, phytochemicals, or dietary cholesterol, are consistent with our meta-analyses and previous meta-analyses documenting improved lipid profiles when red meat is replaced by high-quality plant sources of protein. Taken together, these results suggest important potential cardiovascular benefits from replacing red meat with nuts, soy, and other healthy plant foods, which is consistent with previous prospective analyses of major protein sources and plant-based dietary indices in relation to the risk of CVD and mortality.[59,60,70,71]

Table 2. Summary of Published Meta-Analyses on Plant Foods and Blood Lipids (Intervention Plant Foods Versus Comparison Diets)

Intervention Food/ Food Group	Total Cholesterol, mmol/L	No. of Studies	LDL Cholesterol, mmol/L	No. of Studies	HDL Cholesterol, mmol/L	No. of Studies	Triglycerides, mmol/L	No. of Studies
Tree nuts	−0.09 (−0.11 to −0.08)*[61]	38	−0.11 (−0.13 to −0.09)*[61]	38	0.00 (−0.02 to 0.02)[61]	38	−0.02 (−0.04 to 0.00)[61]	37
							−0.06 (−0.09 to −0.03)*[62]	44
Walnuts	−0.18 (−0.24 to −0.12)*[63]	23	−0.14 (−0.20 to −0.08)*[63]	23	0.002 (−0.02 to 0.02)[63]	24	−0.05 (−0.10 to −0.005)[63]	23
Almonds	−0.18 (−0.34 to −0.02)*[64]	5	−0.15 (−0.29 to 0.00)[64]	4	−0.05 (−0.10 to 0.01)[64]	4	−0.04 (−0.20 to 0.11)[64]	5
Soy protein or products	−0.22 (−0.14 to −0.29)*[65]	28	−0.23 (−0.16 to −0.31)*[65]	29	0.07 (0.00 to 0.14)[65]	29	−0.09 (0.00 to −0.16)[65]	26
			−0.23 (−0.28 to −0.18)[66]	31	0.04 (0.01 to 0.07)*[66]	29	−0.17 (−0.25 to 0.08)[66]	27
Dietary pulses	−0.14 (−0.22 to −0.06)*[67]	35	−0.13 (−0.19 to −0.06)*[67]	35	0.04 (0.02 to 0.06)*[67]	35	−0.06 (−0.09 to −0.02)*[67]	35
			−0.17 (−0.25 to −0.09)*[68]	22				

Results from this table are from previously published meta-analyses: Del Gobbo (2015),[61] Blanco Mejia (2014),[62] Guasch-Ferré (2018),[63] Phung (2009),[64] Harland (2008),[65] Anderson (2011),[66] Tokede (2015),[67] and Ha (2014)[68] Results indicated as mmol/L. Positive values indicate greater increases in blood lipid concentrations in the plant food intervention in comparison with the comparison group. The LDL estimate from Anderson (2011)[66] reflects meta-analysis of studies using parallel designs. The estimate for crossover studies was −0.16 (−0.22 to −0.11), n=28.* HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

*Statistically significant. Comparison diets varied within meta-analyses. For nuts, control diets included usual/habitual, National Cholesterol Education Program, low-fat diet, and Mediterranean. Other studies examined the effect of substituting nuts for specific foods, such as cheese, pretzels, whole wheat muffins, olive oil, meat, etc. For the soy and legume studies, all comparison diets were specified as either nonsoy or nonlegume/pulse. Some comparison diets included specific protein sources (eg, chicken soup, chicken, milk, casein, whey, red meat) or carbohydrate source (eg, oat, oat bran, wheat, corn flakes, white bread, white flour, carrots, maltodextrin, whole wheat), whereas others prescribed a specific diet type.

Potential Mechanisms

Several possible mechanisms may explain the greater improvements in blood lipids for high-quality plant protein sources in comparison with red meat interventions. In comparison with red meat, plant protein sources contain less saturated fat and no cholesterol and more monounsaturated and polyunsaturated fat, fiber, antioxidants, polyphenols, and other bioactive compounds.[72] Various soluble fibers reduce total and LDL-C by similar amounts. For example, 3 g soluble fiber from oats can decrease total cholesterol and LDL-C by ≈0.13 mmol/L.[9] However, saturated fat and cholesterol increase total and LDL-C concentrations in numerous controlled feeding studies.[10] The saturated, polyunsaturated, and monounsaturated fatty acid composition per 100 g are 3.5 g/11.9 g/30.9 g in almonds, 0.7 g/2.7 g/1.1 g in soybeans, and 11.8 g/0.7 g/8.4 g in raw beef. Dietary iron and heme iron, which are found primarily in red meat, have also been associated with myocardial infarction and coronary heart disease.[73] Excess heme iron may impose oxidative injury, which is associated with several cardiovascular risk factors, including dyslipidemia, insulin resistance, and inflammation, and may contribute to the development of atherosclerosis.[74] Meat is also high in phosphatidylcholine, choline, carnitine, and trimethylamine-*N*-oxide. These dietary precursors of trimethylamine-*N*-oxide generated by intestinal microbes in mice and humans[75] have been associated with higher CVD risk.[76] Although the studies included in our meta-analysis mostly examined minimally processed lean red meats, high sodium and nitrate/nitrite concentrations used for the preservation of processed meats may increase CVD risk via increased blood pressure[77] and endothelial dysfunction, respectively.[78,79]

Strengths and Limitations

Our analysis reflects the most inclusive assessment of the effects of red meat consumption on CVD risk factors conducted to date. Strengths of the present study include the use of results derived from a systematic search process conducted by several investigators. In particular, the inclusion of studies using RCTs allowed us to draw causal conclusions with minimal bias. Also, the total number of participants included in the present meta-analysis was relatively large. Limitations of the present study also warrant consideration. First, most of the individual studies were small, which decreased our power to detect statistically significant effects within intervention subcategories. Second, the magnitude of the differences between red meat and comparison diets is small. Nonetheless, our findings have important clinical and public health implications if translated to a population level. Third, dietary intervention trials often suffer from low compliance, which could minimize consumption differences between comparison diets, biasing results toward the null.[80] Fourth, for practical reasons, none of the studies used a double-blinded design. Fifth, we only examined individual foods in relation to each other, and it is possible that the total effect of the diet on lipid parameters modifies the effects of these foods. Sixth, we cannot directly extrapolate CVD risk from intermediate biomarkers such as lipids, apolipoproteins, and blood pressure. In addition, significant heterogeneity was present in some analyses, which may have affected the findings; however, heterogeneity was reduced when the analyses were stratified by comparison group diet.

Future Directions

Future interventions should consider appropriate comparison foods when examining the effects of red meat intake, or any particular food, on cardiovascular risk factors and should prioritize the use of RCTs to identify food sources that promote optimal health and prevent chronic disease. In particular, there is a need to determine the relative effects of different plant protein sources and red meats with different processing methods and saturated fat content on CVD and other chronic disease risk factors. As described in the 2015 Dietary Guidelines Advisory Committee Report, plant-based dietary patterns, specifically healthy vegetarian and Mediterranean-style diets, are of particular importance and should be recommended for their health benefits and to promote environmental sustainability.[12] The majority of studies were conducted in European and American populations, warranting future studies to replicate these findings in non-European populations.

CONCLUSIONS

In conclusion, previously noted inconsistencies regarding the effects of red meat on CVD risk factors may be attributable, in part, to the composition of the comparison diet. Findings from the present systematic review and meta-analysis showed that total red meat intake did not differentially influence blood lipids and apolipoproteins, with the exception of triglycerides, when all comparison diets were analyzed together. In comparison with red meat, consumption of high-quality plant protein sources (ie, soy, nuts, and legumes) leads to more favorable changes in blood concentrations of total cholesterol and LDL-C. Future interventions should consider appropriate comparison foods when examining the effects of red meat intake on cardiovascular risk factors.

ARTICLE INFORMATION

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.118.035225.

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Drs Guasch-Ferré, Satija, Hu, Willett, and Stampfer designed research. Drs Guasch-Ferré, Satija, and Blondin, M. Janiszewski, E. Emlen, and Drs O'Connor, Campbell, and Stampfer conducted the research; Drs Guasch-Ferré, Satija, and Blondin, M. Janiszewski, E. Emlen, and Dr Stampfer performed the systematic review; Drs Guasch-Ferré, Satija, Blondin, and O'Connor analyzed the data; and Drs Guasch-Ferré, Satija, Blondin, Willett, and Stampfer drafted the manuscript. All the authors made critical revisions to the manuscript for important intellectual content; Drs Guasch-Ferré, Willett, and Stampfer had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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