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REVIEW

Meat consumption and risk of ischemic heart disease: A systematic review and meta-analysis

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ABSTRACT

There is uncertainty regarding the association between unprocessed red and processed meat consumption and the risk of ischemic heart disease (IHD), and little is known regarding the association with poultry intake. The aim of this systematic review and meta-analysis was to quantitatively assess the associations of unprocessed red, processed meat, and poultry intake and risk of IHD in published prospective studies. We systematically searched CAB Abstract, MEDLINE, EMBASE, Web of Science, bioRxiv and medRxiv, and reference lists of selected studies and previous systematic reviews up to June 4, 2021. All prospective cohort studies that assessed associations between 1(+) meat types and IHD risk (incidence and/or death) were selected. The meta-analysis was conducted using fixed-effects models. Thirteen published articles were included ($n_{total} = 1,427,989$; $n_{cases} = 32,630$). Higher consumption of unprocessed red meat was associated with a 9% (relative risk (RR) per 50 g/day higher intake, 1.09; 95% confidence intervals (CI), 1.06 to 1.12; $n_{studies} = 12$) and processed meat intake with an 18% higher risk of IHD (1.18; 95% CI, 1.12 to 1.25; $n_{studies} = 10$). There was no association with poultry intake ($n_{studies} = 10$). This study provides substantial evidence that unprocessed red and processed meat, though not poultry, might be risk factors for IHD.

Introduction

Ischemic heart disease (IHD) is a major cause of morbidity and the single leading cause of mortality globally, responsible for over nine million deaths in 2016 (GBD 2016 Causes of Death Collaborators 2017). High meat consumption has been hypothesized to increase the risk of IHD because of its high content of saturated fat and, for processed meat, of sodium; there is substantial evidence that high intakes of saturated fat raise low-density lipoprotein cholesterol (LDLc), and that high sodium consumption raises blood pressure, both well-established risk factors for IHD (Clarke et al. 1997; Rosendorff et al. 2015).

Results from previous meta-analyses on unprocessed red meat and IHD were based on few studies, with two early meta-analyses finding no association for incident IHD (fatal or non-fatal) (Micha, Wallace, and Mozaffarian 2010) or fatal IHD (Abete et al. 2014) and two more recent meta-analyses reporting a positive association for incident IHD (fatal and non-fatal) (Bechthold et al. 2019; Zeraatkar et al. 2019). Likewise, the evidence for processed meat has yielded

mixed results with most (Micha, Wallace, and Mozaffarian 2010; Bechthold et al. 2019; Zeraatkar et al. 2019), but not all (Abete et al. 2014) studies reporting a positive association with incident IHD (fatal and/or non-fatal). Several recent very large studies of meat intake and IHD risk, in a total of over 1 million adults, have not been included in previous meta-analyses, therefore an updated analysis of this topic is timely (Key et al. 2019; Papier et al. 2021; Al-Shaar et al. 2020; Iqbal et al. 2021; Møller et al. 2021; Saito et al. 2020).

To provide a more comprehensive and up to date assessment of the association between meat intake and IHD, we conducted a systematic review and meta-analysis of the prospective evidence on unprocessed red meat, processed meat, and poultry intake.

Material and methods

This review was registered on December 18, 2019 in the International Prospective Register of Systematic Reviews

(PROSPERO) database (identifier CRD42019162753). We followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) protocols throughout the design, implementation, analysis, and reporting (Stroup et al. 2000).

Search strategy

The search terms included beef (including hamburger), lamb, veal, goat, pork, horse meat, mutton, venison, boar, hare, rabbit, game, sausage, ham, bacon, pastrami, deli/luncheon meat, nuggets, chicken, turkey, geese, and duck; IHD, coronary heart disease or coronary artery disease (includes angina pectoris, myocardial infarction (MI) [fatal and/or non-fatal]; see Methods, supplementary material). The databases searched were CAB Abstracts [OvidSP] (1973 onwards), Embase [OvidSP] (1974 onwards), Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 onwards), Science Citation Index Conference Proceedings Citation Index – Science [Web of Science Core Collection, Thomson Reuters](1945 onwards), and the preprint servers medRxiv (2019 onwards) and bioRxiv (2013 onwards). We additionally retrieved articles from the reference lists of included articles, systematic reviews and meta-analyses (additional details see Methods, supplementary material). The literature search was conducted by one librarian (NR) and two authors (AK, KP) until June 4th, 2021 (an update was added upon reviewers' request). No language restrictions were applied.

Study selection

Two authors (AK, KP) reviewed the titles and abstracts of all articles using Rayyan (Ouzzani et al. 2016) and included studies that met the following criteria: 1) prospective cohort design, 2) peer-reviewed (except if uploaded on preprint servers), 3) available in full-text, and 4) assessed the relationship between 1(+) meat types and IHD. The meat types included were unprocessed red meat, processed meat, and poultry. Where no composite unprocessed red meat estimate was given, estimates for single meat type (e.g. beef) were used if these were distinctively separate from processed meat. If more than one unprocessed red meat type was provided (e.g. pork and beef), both were used in separate analyses. Processed meat was defined as a composite by studies without restrictions to the definition. Poultry included either only unprocessed poultry or poultry including processed poultry, whichever was reported. We excluded prospective studies based on broader dietary patterns (e.g. vegetarian diets, data-derived dietary patterns, dietary indices) if they did not report single meat item results and studies that investigated total meat or other meat types only. Where two or more studies were based on the same cohort, we included the study with the largest number of cases (Figure S1 and Table S1, supplementary material). Any disagreement was resolved through discussion.

Data extraction

Three authors (AK, KP, NS) extracted the study information independently. Where multiple outcomes were reported within one study, we used the outcome that provided the largest case numbers; where separate estimates were available for men and women, we pooled these in the meta-analyses; where multivariable models were reported with and without additional adjustment for potential mediators (the predefined protocol mediators included: cholesterol and, or blood pressure), the multivariable model with the most extensive adjustment but without those mediating variables was selected. If the only multivariable model available included cholesterol and, or blood pressure, this was selected rather than crude or minimally adjusted models (i.e. the models that did not include the essential confounding factors outlined in the quality assessment scale outlined below).
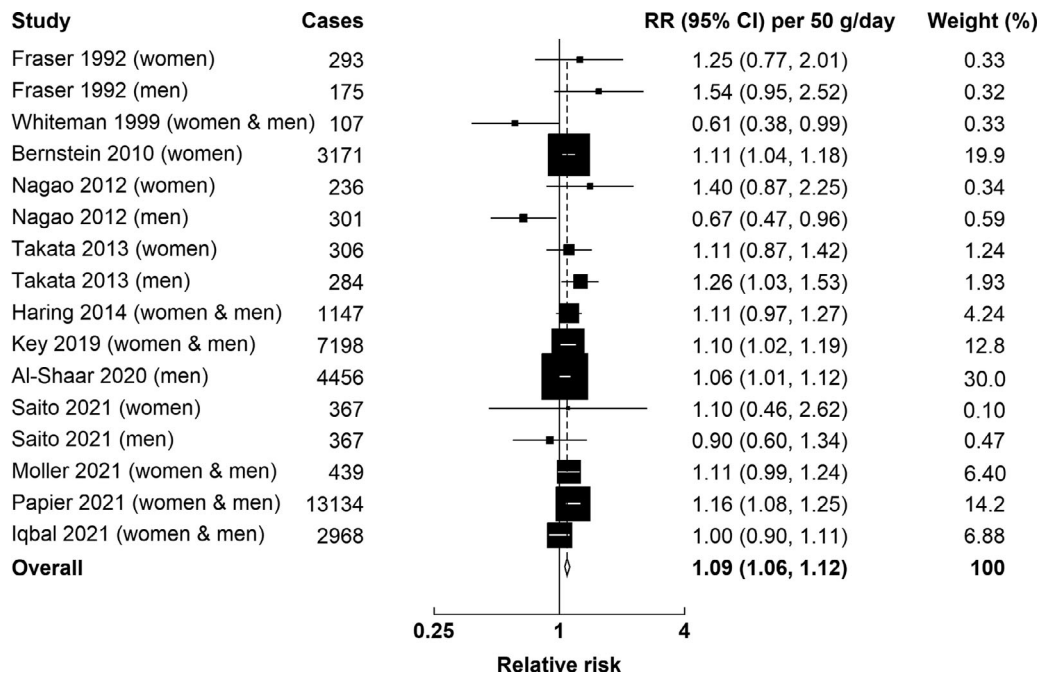
Bias

Three authors (AK, KP, NS) assessed the risk of bias using an adapted Newcastle-Ottawa Quality Assessment Scale for cohort studies by assigning one point each for 1) study representativeness (only counting population based-cohorts), 2) using a validated tool of dietary assessment, 3) adjusting for at least age, sex, smoking, physical activity and some measure of socioeconomic status (e.g. income, occupation, education), 4) ascertaining or verifying outcome information using record linkage, and 5) having over two years of total follow-up to reduce the risk of reverse causality. Studies were considered high quality if they met at least 4 of the 5 criteria (Stang 2010).

Statistical analysis

We used fixed-effects models to calculate summary relative risks (RRs) and 95% confidence intervals (CIs) for dose-response meta-analyses using the METAN command in Stata (Harris et al. 2008). In this method, summary RRs (combined study-specific results) are calculated as weighted averages, with each weight proportional to the inverse of the variance of the study-specific log RR (Green et al. 2011).

Where studies provided RRs and 95% CIs per higher daily gram intakes these were used. For studies that only reported estimates for categorical exposures, we calculated study-specific slopes and 95% CIs from the natural logs of RRs and CIs across categories of meat intake to estimate RRs and CIs per unit change using the GLST command in Stata (Greenland and Longnecker 1992; Orsini, Bellocco, and Greenland 2006). This method requires that the distribution of cases and non-cases (or person-time) is known and that categorical variables have at least three categories. In studies that only reported total cases/controls (or person-years) we estimated the distribution of cases and non-cases (or person-time) by dividing the total numbers evenly across the categories.

We assigned the mean or median for each category of meat intake to the corresponding RRs where available.

Study	Cases		RR (95% CI) per 50 g/day	Weight (%)
Fraser 1992 (women)	293		1.25 (0.77, 2.01)	0.33
Fraser 1992 (men)	175		1.54 (0.95, 2.52)	0.32
Whiteman 1999 (women & men)	107		0.61 (0.38, 0.99)	0.33
Bernstein 2010 (women)	3171		1.11 (1.04, 1.18)	19.9
Nagao 2012 (women)	236		1.40 (0.87, 2.25)	0.34
Nagao 2012 (men)	301		0.67 (0.47, 0.96)	0.59
Takata 2013 (women)	306		1.11 (0.87, 1.42)	1.24
Takata 2013 (men)	284		1.26 (1.03, 1.53)	1.93
Haring 2014 (women & men)	1147		1.11 (0.97, 1.27)	4.24
Key 2019 (women & men)	7198		1.10 (1.02, 1.19)	12.8
Al-Shaar 2020 (men)	4456		1.06 (1.01, 1.12)	30.0
Saito 2021 (women)	367		1.10 (0.46, 2.62)	0.10
Saito 2021 (men)	367		0.90 (0.60, 1.34)	0.47
Moller 2021 (women & men)	439		1.11 (0.99, 1.24)	6.40
Papier 2021 (women & men)	13134		1.16 (1.08, 1.25)	14.2
Iqbal 2021 (women & men)	2968		1.00 (0.90, 1.11)	6.88
Overall			**1.09 (1.06, 1.12)**	**100**

0.25   1   4

Relative risk

Figure 1. Relative risk and 95% confidence intervals of ischemic heart disease for each 50 g/day increase in unprocessed red meat consumption ($I^2 = 41.3\%$, $Q = 25.6$, $p_{het} = 0.04$). Abbreviations: CI, confidence interval; RR, relative risk. RRs are represented by squares, with their 95% CIs as horizontal lines; the size of the squares is inversely proportional to the variance of the log RR. The diamond reflects the combined effect based on fixed effects analysis.

Where these were not reported, we calculated the midpoint for each category using the category intake range. For studies with an open-ended intake range, we assumed that the category width was the same as the adjacent category. If studies reported intakes by frequency, we assumed the following serving sizes: unprocessed red meat and poultry 85 g (Schwingshackl et al. 2017; Richman et al. 2011), processed meat 30 g (Larsson and Orsini 2014). We rescaled all intakes for the trend analysis to 50 g/day for each meat type.

We reran analyses by subgroups when more than one study was available: duration of follow-up, study location, sex, degree of adjustment, single versus repeated dietary assessment methods, and study quality. We planned to investigate associations by acute MI (ICD code I21) and fatal versus non-fatal MI, but there were insufficient data available.

To identify potential sources of heterogeneity and assess the robustness of the overall estimates, we conducted sensitivity analyses where we removed one study at a time and re-analyzed the rest. Upon reviewer request, we additionally conducted random-effects meta-analyses to assess the effect of additional adjustment for heterogeneity between the studies. To make use of all extracted data, we used fixed-effects meta-analyses to calculate summary RRs and 95% CIs for high versus low meat consumption based on the categories described in the individual studies. This sensitivity analysis included all studies that reported risks for two or more meat intake categories.

We assessed the statistical heterogeneity of studies using the Q test and the I^2 statistic (with a value of $I^2 > 50\%$ considered to represent potentially important heterogeneity) (Higgins and Thompson 2002). We assessed publication bias using Funnel plots and Egger's test. All analyses were conducted in STATA 16.1.

Results

The initial literature search (October 30, 2019) resulted in 2171 records of which 1099 records were included after a title and abstract screen (Figure S1, supplementary material). Of these, 38 were assessed in full text, of which seven were selected and screened for potentially eligible references (Table S1, supplementary material). A search of previous systematic reviews yielded two additional full texts. The search was updated on May 20, 2020 yielding one additional study, and on June 4, 2021 yielding 5 additional studies of which one was an updated analysis of a study from the original search including more cases (Al-Shaar et al. 2020; Ascherio et al. 1994) and one was a full text peer reviewed publication of a preprint included in the first updated search (Table S1, supplementary material) (Papier et al. 2020, 2021).

Study characteristics

A total of 13 cohort studies including 1,437,989 individuals and 32,630 cases were identified (Table 1). The studies were conducted in Asia (n = 3), the US (n = 4), Australia (n = 1), Europe (n = 4), and for one multi-country cohort in the Americas, Asia, Africa and Europe. Most studies included predominantly middle-aged or older adults at baseline. The maximum follow-up time ranged from 6–30 years. Meat intake categories varied, with unprocessed red meat intake in the lowest intake category ranging from 0–25 g/day and in the highest from 10–141 g/day; processed meat from 0–10 g/day to 9–78 g/day; and poultry from 0–12 g/day to 22–68 g/day (Table S2, supplementary material). All but one study used food frequency questionnaires (FFQs) to assess meat intake. Three studies used repeated FFQs (Bernstein

Table 1. Characteristics of included studies.

First author (publication year), country, cohort name	Sample size (% women), age at entry, max. FUP	Exposure (meat type)	Dietary assessment[a]	Outcome (cases)	Outcome assessment method	Adjustment factors	RR (95% CI), trends or high versus low
Fraser et al. (1992), USA, The Adventist health Study (ADHS)	n 26,473 (W 60), M 51.3 (SD 16.0) / W 53.2 (SD 16.6) years, 6 years FUP	RM[b]	semi-quantitative FFQ	IHD, fatal (n 463)	Ascertained from annual questionnaires verified with medical records, National Death Index, church records, California death certificates, autopsy reports and next to kin calls.	Age, sex, smoking, PA, relative weight, high BP, other diet[c].	$HR_{red\ meat}$ high vs. low, W:1.28 (0.76, 2.16), M: 1.74 (1.01, 3.01)
Whiteman et al. (1999), UK, OXCHECK	n 10,522 (W 53), 35–64 years, 9 years FUP	RM, PM, P[d]	simple FFQ	IHD, fatal (n 107)	Ascertained from death registers.	Age group, sex, smoking.	$RR_{red\ meat}$ high vs. low 0.55 (0.31, 0.99) $RR_{proc\ meat}$ high vs. low 1.28 (0.46, 3.54) $RR_{poultry}$ high vs. low, 0.95 (0.38, 2.38)
Burke et al. (2007), Australia, Study of indigenous Australians	n 514 (W 50), 15–88 years, 14 years FUP	PM	FFQ	IHD, fatal and non-fatal (n 130)	Ascertained from hospital and death records.	Age, sex, total chol, mean arterial pressure, WC.	$RR_{proc\ meat}$ high vs low 2.21 (1.05, 4.63)
Bernstein et al. (2010), USA, Nurses' Health study (NHS)	n 84,136 (W 100), 30–55 years, 26 years FUP	RM, PM, P	semi-quantitative FFQ (with repeat measurement)	IHD, fatal[e] (n 952) and MI, non-fatal (n 2,210)	Ascertained from self-report verified with medical report, letter or interview from hospital admissions, state vital records, National Death Index, next of kin or postal system, autopsy reports.	Age, time period, smoking, alcohol, PA, family hist MI, menopause, aspirin use, multivitamin use, BMI, total EI, other diet[c].	$HR_{red\ meat}$ per 85 g/d 1.19 (1.07, 1.32) $HR_{proc\ meat}$ per 30 g/d 1.20 (1.03, 1.40) $HR_{poultry}$ per 85 g/d 0.90 (0.75, 1.08)
Nagao et al. (2012), Japan, Japan Collaborative Cohort study (JACC)	n 51,683 (W 60), 40–79 years, 20 years FUP	RM, PM, P	semi-quantitative FFQ	IHD, fatal (n 537)	Ascertained from death records.	Age, edu, smoking, alcohol, PA, hist HT or DM, perceived mental stress, BMI, total EI, other diet[c].	$HR_{red\ meat}$ Q5 vs. Q1, W:1.23 (0.82, 1.85), M: 0.70 (0.47, 1.04) $HR_{proc\ meat}$ Q5 vs. Q1, W: 0.98 (0.59, 1.62), M: 0.56 (0.36, 0.88) $HR_{poultry}$ Q5 vs. Q1, W: 1.06 (0.69, 1.62), M: 0.86 (0.60, 1.23)
Takata et al. (2013), China, Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS)	n 134,290 (W 54), W 40–70 / M 40–74 years, W 13/ M 8 years FUP	RM, P	semi-quantitative FFQ	IHD, fatal (n 590)	Ascertained from death registers and verified with home visits	Age, income, occupation, edu, smoking, alcohol (in M), PA, comorbidity index, total EI, other diet[c]	$HR_{red\ meat}$ Q5 vs. Q1, W:1.28 (0.84, 1.96), M: 1.54 (1.02, 2.32) $HR_{poultry}$ Q5 vs. Q1, W: 1.24 (0.82, 1.89), M: 0.95 (0.63, 1.41)
Haring et al. (2014), USA, The Atherosclerotic Risk in Community Study (ARIC)	n 12,066 (W 56), 45–64 years, 23 years FUP	RM, PM, P	semi-quantitative FFQ (with repeat measurement)	IHD, fatal and MI, definite/ probable non-fatal (n 1,147)	Ascertained from study visits, yearly telephone FUP calls, review of hospital discharge lists and	Age, sex, race, study center, edu, smoking, alcohol, PA, systolic BP, antihypertensive	$HR_{red\ meat}$ high vs. low 1.13 (0.89, 1.44) $HR_{proc\ meat}$ high vs. low 1.04 (0.85, 1.29)

Reference	Population	Meat types	Dietary assessment	Outcome	Ascertainment	Adjustments	Results (HR)
					medical charts, death certificates, next of kin interviews, and physician-completed questionnaires.	med, HDL chol, total chol, lipid lowering med, BMI, WHR, total EI, other diet.[c]	$HR_{poultry}$ high vs. low 0.79 (0.64, 0.98)
Key et al. (2019), Europe (10 countries) European Prospective Investigation into Cancer and Nutrition (EPIC)	n 409,885 (W 74), W 51.3 (SD 9.8) / M 52.7 (SD 10.3) years 18 years FUP	RM, PM, P[d]	semi-quantitative FFQ	IHD, fatal and MI, first non-fatal (n 7,198)	Ascertained from morbidity and hospital registries, self-report with confirmation with medical records; mortality registries; active FUP, next of kin info depending on study center.	Age, sex (strat.), study center (strat.), work, edu, smoking, alcohol, PA, hist DM, HT, or hyperlipidemia, BMI, total EI, other diet.[c]	$HR_{red\ meat}$ per 50 g/d 1.10 (1.02, 1.19) $HR_{proc.\ meat}$ per 100 g/d 1.14 (1.04, 1.24) $HR_{poultry}$ per 20 g/d W: 1.02 (0.91, 1.15), M: 0.98 (0.93, 1.04)
Al-Shaar et al. (2020), USA, Health Professional's FUP study (HPFS)	n 43,272 (W 0), 40–75 years, 30 years FUP	RM, PM	semi-quantitative FFQ (with repeat measurement)	IHD, fatal (n 1860) and non-fatal MI (n 4456)	Ascertained from coworkers, next of kin reports, National Death Index, autopsy and medical records.	Age, time, race/ethnicity, work, profession, living arrangement, marital status, smoking, alcohol, PA, family hist MI or stroke, multivitamin use, aspirin use, BMI, total EI, other diet.[g]	$HR_{red\ meat}$ per 85 g/d 1.11 (1.02, 1.21) $HR_{proc\ meat}$ per 30 g/d 1.15 (1.06, 1.25)
Saito et al. (2020), Japan, Japan Public Health Center-based Prospective Study (JPHC)	n 87507 (W54), 45–74, (average), 14 years FUP	RM[b,f], PM, P	semi-quantitative FFQ	IHD, fatal (n 600)	Ascertained from the residential registry and death certificates.	Age, center area, smoking, alcohol, PA, hist HT or DM, BMI, total EI, other diet.[c]	HR_{beef} Q4 vs. Q1, W:0.94 (0.60, 1.48), M: 0.89 (0.64, 1.23) HR_{pork} Q4 vs. Q1, W:1.03 (0.60, 1.79), M: 1.02 (0.69, 1.51) $HR_{proc\ meat}$ Q4 vs. Q1, W: 0.95 (0.61, 1.49), M: 0.84 (0.64, 1.23) $HR_{poultry}$ Q4 vs. Q1, W: 1.02 (0.66, 1.58), M: 1.09 (0.79, 1.50)
Møller et al. (2021), Denmark, National Survey on Diet and Physical Activity (DNSDP)	n 8007, (W 53),15–75, median 9.8 years FUP	RM, PM, P	7-day food diaries	IHD, fatal or non-fatal (n 439)	Ascertained from the National Patient Register and Register of Causes of Death	Age, sex, ethnicity, edu, smoking, PA, alcohol, hist DM, BMI and total EI.	$HR_{red\ meat}$ per 100 g/d 1.23 (0.99, 1.53) $HR_{proc\ meat}$ per 50 g/d 1.09 (0.93, 1.29) $HR_{poultry}$ per 100 g/d 0.92 (0.62, 1.37)
Papier et al. (2021), UK, UK Biobank (UKB)	n 435,337 (W 54), 37–73 years, mean 8.0 years FUP	RM, PM, P[d]	simple FFQ (with repeat measurement)	IHD, non-fatal and fatal (n 13,299)	Ascertained from NHS central registers, HES, Scottish Morbidity records, Patient Episode records.	Age, age group (strat.), sex (strat.), region (statr.), ethnicity, deprivation, edu, work, smoking, alcohol, PA, BMI, menopause, HRT, OCP use, parity, other diet.[c]	$HR_{red\ meat}$ per 50 g/d 1.16 (1.08, 1.25) $HR_{proc\ meat}$ per 20 g/d 1.09 (1.04, 1.15) $HR_{poultry}$ per 30 g/d 1.08 (1.02, 1.14)

Table 1. Continued.

First author (publication year), country, cohort name	Sample size (% women), age at entry, max. FUP	Exposure (meat type)	Dietary assessment[a]	Outcome (cases)	Outcome assessment method	Adjustment factors	RR (95% CI), trends or high versus low
Iqbal et al. (2021), 21 countries,[g] Prospective Urban and Rural Epidemiology (PURE) Study	n 134,297 (31640 for poultry) (W 58), 35–70 years, median 9.5 year FUP	RM, PM, P	semi-quantitative FFQ	MI, non-fatal (n 2968)	Ascertained from participants, family member reports and medical records (where available).	Age, sex, location, study center (random effect), edu, wealth index, smoking, PA, DM status, BP lowering med, total EI, other diet.[c]	$HR_{red\ meat}$ per 100 g/d 1.00 (0.97, 1.03) $HR_{proc\ meat}$ per 100 g/d 1.14 (0.98, 1.32) $HR_{poultry}$ per 100 g/d 1.04 (0.98, 1.08)

Abbreviations: BMI, body mass index; BP, blood pressure; chol, cholesterol; DM, Diabetes Mellitus; EI, energy intake; edu, education; FFQ, food frequency questionnaire; FUP, follow up; HDL, high-density lipoprotein; hist, history of; HRT, hormone replacement therapy; HT, hypertension; IHD, ischemic heart disease; MI, myocardial infarction; M, men; med, medication; OCP, oral contraceptive pill; P, poultry; PA, physical activity; PM, processed meat; PUFA, polyunsaturated fatty acids; RM, unprocessed red meat; SD, standard deviation; SF, saturated fat; strat, stratified; W, women; WC, waist circumference; WHR, waist-to-hip ratio.

[a]If not further specified no repeat measurement was used to correct for regression dilution bias or dietary change.[b]Beef only.

[c]Diet in detail for Fraser et al. 1992: nut intake and bread intake; Bernstein et al. 2010: cereal fiber intake and trans fat; Nagao et al. 2012: rice, fish, soy, vegetable, and fruit intake; Takata et al. 2013:vegetable, fruit, fish intake, as well as poultry for unprocessed red meat intake and vice versa; Haring et al. 2014: carbohydrate intake, fiber intake, and magnesium intake; Key et al. 2019: fruit and vegetables intake, sugars, cereal fiber, for P: additionally adjusted for red and processed meat, white fish, fatty fish, milk, yogurt, cheese, egg intake; Al-Shaar et al. 2020: poultry (unprocessed), fish, egg, high fat dairy, low fat dairy, nuts, legumes, soy, whole grains, fruit, vegetables, coffee, and glycemic index; Saito et al. 2020: fruit intake, vegetables, fish, dairy, egg, sodium and total fat as well as poultry and processed meat intake for unprocessed red meat intake and vice versa; Papier et al. 2021: fruit and vegetable, cereal fiber intake, oily fish intake, and non-oily fish intake; and Iqbal et al. 2021: fruits, vegetables, dairy, poultry, fish, refined grains, processed foods, legumes, total fiber, as well as poultry for unprocessed red meat intake and vice versa.

[d]Excluding processed poultry.

[e]Any sudden death within 1 hour of the onset of symptoms in women with no other plausible cause of death also considered fatal IHD.

[f]Pork only.

[g]Bangladesh, India, Pakistan, Tanzania, and Zimbabwe. Middle-income countries included Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, occupied Palestine territory, Philippines, Poland, South Africa, and Turkey, Canada, Saudi Arabia, Sweden, and the United Arab Emirates.

Table 2. Subgroup analyses of associations of meat intake and ischemic heart disease per 50 g/day.

Study characteristics	Unprocessed red meat[a]			Processed meat			Poultry		
	N_{est}	RR (95% CI)	P_{het}	N_{est}	RR (95% CI)	P_{het}	N_{est}	RR (95% CI)	P_{het}
Main analysis	16	1.09 (1.06, 1.12)		12	1.18 (1.12, 1.25)		14	1.02 (0.97, 1.07)	
Sex									
Women	5	1.11 (1.05, 1.18)		3	1.33 (1.04, 1.71)		5	0.96 (0.87, 1.06)	
Men	5	1.07 (1.02, 1.12)	0.26	3	1.23 (1.07, 1.41)	0.58	4	0.96 (0.84, 1.09)	0.91
Adjustment[b]									
Adequate	10	1.09 (1.06, 1.12)		8	1.17 (1.11, 1.24)		10	1.04 (0.99, 1.11)	
Inadequate	6	1.10 (1.04, 1.17)	0.78	4	1.31 (1.02, 1.68)	0.40	4	0.94 (0.85, 1.05)	0.09
Study quality[c]									
High	12	1.09 (1.06, 1.12)		9	1.17 (1.10, 1.24)		11	1.03 (0.97, 1.10)	
Low	4	1.11 (1.04, 1.17)	0.65	3	1.40 (1.11, 1.76)	0.13	3	0.99 (0.91, 1.08)	0.47
Use of repeated measurement									
Yes	4	1.10 (1.06, 1.14)		4	1.25 (1.15, 1.36)		3	1.02 (0.96, 1.09)	
No	12	1.08 (1.03, 1.13)	0.50	8	1.13 (1.04, 1.22)	0.08	11	1.02 (0.93, 1.11)	0.95
Follow-up time									
<=10 years	12	1.08 (1.05, 1.11)		10	1.17 (1.09, 1.24)		12	0.97 (0.91, 1.03)	
10+ years	4	1.15 (1.07, 1.24)	0.10	2	1.24 (1.10, 1.41)	0.38	2	1.13 (1.03, 1.24)	0.01
Region									
Asia	6	1.09 (0.96, 1.24)		4	0.33 (0.14, 0.80)		6	1.09 (0.82, 1.45)	
USA	5	1.09 (1.05, 1.13)		3	1.25 (1.12, 1.40)		2	0.92 (0.85, 1.01)	
Europe	5	1.10 (1.05, 1.15)	0.93	5	1.16 (1.09, 1.24)	0.01	6	1.07 (1.00, 1.14)	0.03

Abbreviations: CI, confidence interval; RR, relative risk; N/A, not available; N_{est}, number of estimates
[a]Estimates included those for beef only, using pork for Saito et al. (2020) given in Table S5, supplementary material.
[b]Adequate adjustment defined as adjusting for at least age, sex, smoking, physical activity and some measure of socioeconomic status (e.g. income, occupation, education).
[c]Study quality was considered high where at least 4 of the 5 criteria (representativeness (1), validated dietary assessment (2), appropriate adjustment (3), outcome assessment or validated using record linkage (4), and follow-up greater than two years (5)) were met.

et al. 2010; Haring et al. 2014; Al-Shaar et al. 2020), and one study used two or more 24 h recall questionnaires during follow-up to correct for regression dilution bias and diet change (Papier et al. 2021). A multi-country European study used a single 24 h recall conducted either on the day of recruitment or later (mean of 1.4 years between the two dates) to calibrate intakes across the different countries (Key et al. 2019; Slimani et al. 2002).

Seven studies investigated both fatal and non-fatal IHD including MI (Al-Shaar et al. 2020; Bernstein et al. 2010; Burke et al. 2007; Haring et al. 2014; Key et al. 2019; Møller et al. 2021; Papier et al. 2021), one study was restricted to non-fatal MI (Iqbal et al. 2021), and five were restricted to fatal IHD (Saito et al. 2020; Fraser et al. 1992; Nagao et al. 2012; Takata et al. 2013; Whiteman et al. 1999). Six studies presented trend results in their study findings (Bernstein et al. 2010; Al-Shaar et al. 2020; Iqbal et al. 2021; Møller et al. 2021; Papier et al. 2021; Key et al. 2019) and for six studies trends could be estimated with the available estimates (Fraser et al. 1992; Haring et al. 2014; Nagao et al. 2012; Takata et al. 2013; Whiteman et al. 1999; Saito et al. 2020).

Overall, six studies graded 5 points on the Quality Assessment Scale, three graded 4 points, and four 3 points. Ten studies were representative, ten used a validated dietary assessment tool, eight met the minimum adjustment level, and all studies used record linkage to ascertain or validate IHD cases and followed participants up for more than two years (Table S3, supplementary material).

Unprocessed red meat intake and IHD

The summary RR of IHD for each 50 g/day intake of unprocessed red meat consumption was 1.09 (95% CI, 1.06 to 1.12), based on 16 estimates from 12 studies (Figure 1). There was medium heterogeneity ($I^2 = 41.3\%$, $Q = 25.6$, $p = .04$ for heterogeneity). Results did not differ by subgroup, were robust to the exclusion of any one study (Table 2; Table S4, supplementary material), and were unchanged but with wider confidence intervals when using a random effects analysis (RR 1.09, 95%-CI 1.04, 1.14). The summary RR was 1.12 when comparing the highest versus lowest categories of unprocessed red meat (95% CI 1.07 to 1.17), based on 16 estimates from 12 studies (Figure S2, supplementary material).

Pooled associations were the same when estimates of pork were included instead of beef for Saito et al. (2020) (RR per 50 g/day 1.09, 95%-CI 1.06, 1.12, $I^2 = 41.0\%$, $Q = 25.4$, $p = .05$ for heterogeneity; RR high vs. low 1.12, 95%-CI 1.07, 1.17; Table S5, supplementary material).

Processed meat intake and IHD

The summary RR of IHD for each 50 g/day intake of processed meat was 1.18 (95% CI 1.12 to 1.25), based on 12 estimates from ten studies (Figure 2). There was medium heterogeneity ($I^2 = 37.7\%$, $Q = 17.6$, $p = .09$ for heterogeneity). Subgroup analyses showed that the association was restricted to studies from the USA and Europe; in pooled analyses of two studies conducted in Asia there was evidence of an inverse association ($p = .010$ for heterogeneity; Table 2). Main analyses were robust to the exclusion of any one study (Table S4, supplementary material), and were unchanged but with wider confidence intervals when using a random effects analysis (RR 1.19, 95%-CI 1.08, 1.30). The summary RR was 1.11 when comparing the highest versus lowest categories of processed meat (95% CI 1.06 to 1.16),
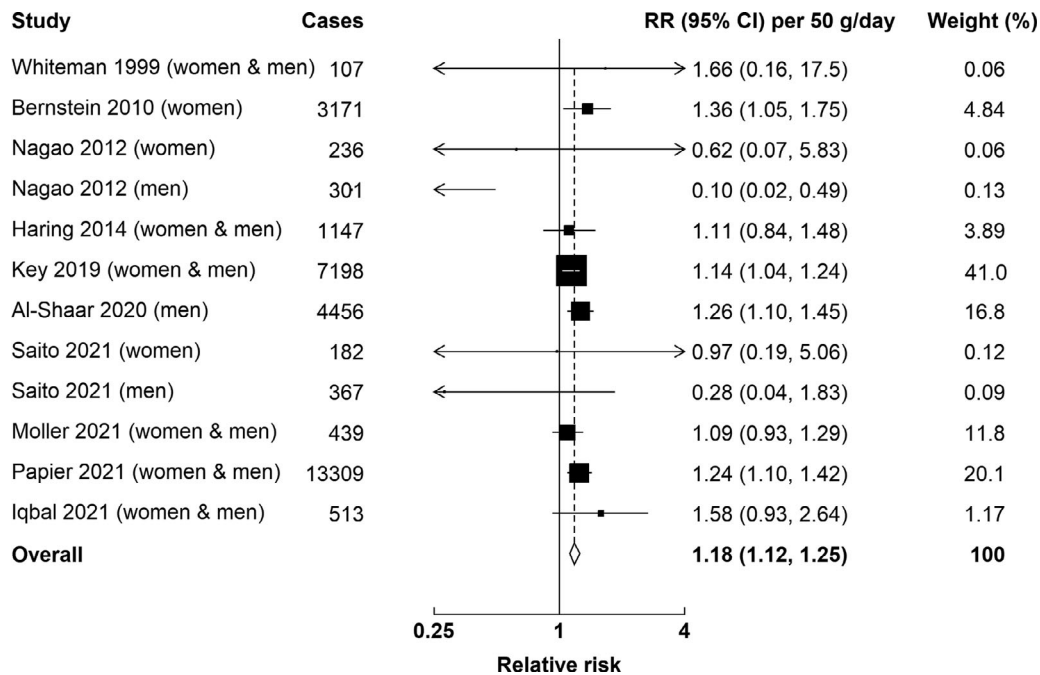
Figure 2. Relative risk and 95% confidence intervals of ischemic heart disease for each 50 g/day increase in processed meat consumption ($I^2 = 37.7\%$, Q = 17.6, phet = 0.09). Abbreviations: CI, confidence interval; RR, relative risk. RRs are represented by squares, with their 95% CIs as horizontal lines; the size of the squares is inversely proportional to the variance of the log RR. The diamond reflects the combined effect based on fixed effects analysis.
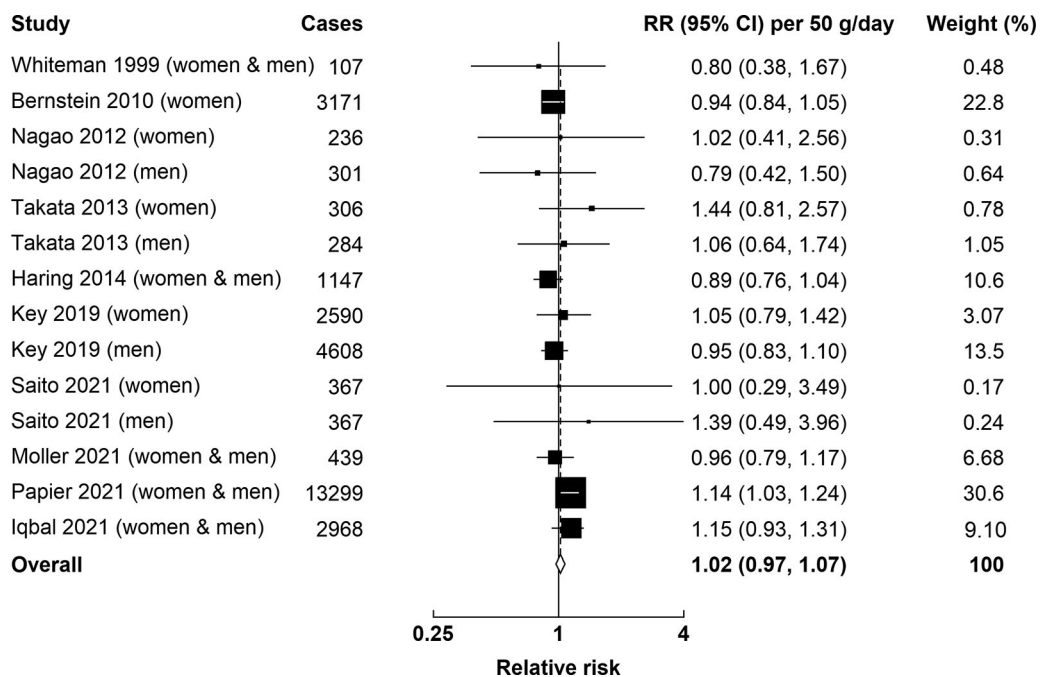
Figure 3. Relative risk and 95% confidence intervals of ischemic heart disease for each 50 g/day increase in poultry consumption ($I^2 = 20.0\%$, Q = 16.2, phet = 0.24). Abbreviations: CI, confidence interval; RR, relative risk. RRs are represented by squares, with their 95% CIs as horizontal lines; the size of the squares is inversely proportional to the variance of the log RR. The diamond reflects the combined effect based on fixed effects analysis.

based on 13 estimates from 11 studies (Figure S3, supplementary material).

Poultry intake and IHD

The summary RR of IHD for each 50 g/day intake of poultry was 1.02 (95% CI 0.97 to 1.07), based on 14 estimates from ten studies (Figure 3). There was low heterogeneity (I^2 = 20.0%, Q = 16.2, p = .24 for heterogeneity). The results in

subgroups were unchanged, except for two studies with >10 years of follow-up (p = .008 for heterogeneity) and analyses in European studies only where modest positive associations were observed (p = .030 for heterogeneity, Table 2). Main analyses were robust to the exclusion of any one study (Table S4, supplementary material) and unchanged when using a random effects analysis (RR 1.01, 95%-CI 0.95, 1.08). There was no evidence of an association when comparing highest versus lowest categories of poultry

intake (RR 1.03; 95% CI 0.99 to 1.07), based on 13 estimates from ten studies (Figure S4, supplementary material).

Publication bias

There was no evidence of publication bias for associations between unprocessed red meat intake (incremental Egger's p = .70; n = 16; high vs. low Egger's p = .62, n = 16 including beef estimates for Saito et al. 2020; incremental Egger's p = .67; n = 16; high vs. low Egger's p = .80, n = 16 including pork estimates for Saito et al. 2020), processed meat intake (incremental Egger's p = .28, n = 12; high vs. low Egger's p = .51, n = 13), and poultry intake and IHD risk (incremental Egger's p =.88, n = 14; high vs. low Egger's p =.35, n = 13), and the funnel plots did not suggest asymmetry (Figures S5–S10, supplementary material).

Discussion

In this meta-analysis of prospective studies including over 1.4 million adults, a 50 g/day higher consumption of unprocessed red meat and processed meat was associated with 9% and 18% higher IHD risks, respectively; there was no evidence for an association of IHD risk with poultry consumption.

Our findings for unprocessed red (including 34,949 cases from 12 studies) and processed meat (including 31,426 from 10 studies) are in the same direction as recent meta-analyses that considered both incident and fatal IHD (Bechthold et al. (2019) included 6,659 cases for unprocessed red meat and 7,038 cases for processed meat from five studies; Zeraatkar et al. (2019) included 2,350 cases from one study for both meat types). We did not identify any previous meta-analysis for poultry intake.

The positive association of unprocessed red meat and processed meat intake and IHD risk might be explained by one or more of several different mechanisms. A prominent hypothesized mechanism is saturated fat intake, which has been shown to increase LDLc, a causal risk factor for IHD (Mensink 2016; Holmes et al. 2015; Clarke et al. 1997; Bergeron et al. 2019). Unprocessed red and processed meat contain higher amounts of saturated fat per gram than poultry, which could explain the absence of an association with poultry intake (McCance and Widdowson 2014). Another mechanism that might be specific to red meat intake is trimethylamine-N-oxide (TMAO), which might contribute to an increased risk of IHD by promoting atherosclerosis (Wang et al. 2019; Heianza et al. 2020; Tang et al. 2013); red meat intake can lead increased circulating TMAO derived from intestinal microbiota metabolism of dietary L-carnitine (Wang et al. 2019; Koeth et al. 2013). All processed meat has high sodium content (Micha, Michas, and Mozaffarian 2012), which likely increases the risk of high blood pressure (He and MacGregor 2002), a causal risk factor for IHD (Rosendorff et al. 2015). There is also some evidence that suggests that red and processed meat consumption is positively associated with higher levels of inflammatory biomarkers due to their high heme content (Azadbakht and Esmaillzadeh 2009). However the specific causal mechanisms linking red and processed meat with IHD remain unclear (C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) 2011).

Strengths

This systematic review and meta-analysis of prospective cohort studies includes the largest number of IHD cases to date, including over four times the number of IHD cases than any previous meta-analysis investigating associations for unprocessed red and processed meat. We investigated associations for IHD with unprocessed red meat, processed meat, and poultry intakes separately, which had not been done for poultry in previous reviews. Selecting only prospective cohort studies minimized the risk of recall bias; associations remained robust when restricting to studies with 10+ years of follow-up. Moreover, all 13 studies assessed or validated IHD via record linkage and we only considered studies that considered IHD separately and not in combination with other outcomes. Furthermore, we conducted sensitivity analyses excluding one study at a time to assess the robustness of the main results and high versus low meta-analyses to include all available research.

Limitations

A limitation of this systematic review and meta-analysis is that there were differences in the outcome definitions used in the individual included studies. For instance five of the studies only assessed fatal IHD (Takata et al. 2013; Fraser et al. 1992; Nagao et al. 2012; Whiteman et al. 1999; Saito et al. 2020). Therefore, it is possible that the lack of inclusion of incident cases in these studies affected the estimates. However, this meta-analysis included the two largest studies of meat and IHD risk, which both considered incident and fatal IHD (Key et al. 2019; Papier et al. 2021). We were unable to investigate associations by MI (acute, fatal, non-fatal) as planned, since there were no available data.

Most of the included studies used FFQs to assess dietary intake, which are subject to both random and systematic error, and can reduce the power to detect associations (Freedman et al. 2011; Kipnis et al. 2003). Similarly, most studies only used one measurement of diet, which can lead to regression dilution bias and the underestimation of the association (Clarke et al. 1999). Another potential limitation is the inconsistency of meat classifications between the studies. For instance, some studies included processed chicken in their processed meat definition (Key et al. 2019; Papier et al. 2021; Møller et al. 2021; Iqbal et al. 2021), some did not (Bernstein et al. 2010; Saito et al. 2020), and many did not clearly specify their definition criteria (Burke et al. 2007; Whiteman et al. 1999; Takata et al. 2013; Nagao et al. 2012; Haring et al. 2014). Considering the different biological pathways suggested, this could have affected the study estimates. We included one American study that only included beef for the unprocessed red meat estimate (Fraser et al. 1992), but the National Health and Nutrition Examination

Survey 1999–2000 showed that 74% of unprocessed red meat consumed in the US was beef (Zeng et al. 2019). We also included one Japanese study that reported unprocessed red meat as beef and pork, separately. We included beef in the main analyses, to be comparable with the other study, but also reran analyses with pork to assess any differences due to the higher consumption of pork in the cohort (Saito et al. 2020).

The comparability of studies might be affected by differences in statistical adjustment and assessment of confounding factors. Specifically, some studies did not adjust for socioeconomic status, which has been found to be associated with both diet quality (Darmon and Drewnowski 2015) and IHD risk (Gupta and Yusuf 2019). Likewise, higher consumption of meat is often associated with higher energy intake and other dietary components (Vergnaud et al. 2010), which may confound its association with IHD. Not all of the studies adjusted for energy intake or other dietary factors, increasing the potential for residual confounding. Some studies also included adjustment for additional factors that might lie on the pathway between meat intake and IHD risk, such as plasma cholesterol, and blood pressure. As a result, it is possible that some study estimates were over adjusted; studies that adjusted for potential mediators tended to show smaller or statistically insignificant RRs (Fraser et al. 1992; Haring et al. 2014; Key et al. 2019). Additionally, we were unable to investigate the effects of confounding by matching the levels of adjustment between studies because this information was mostly not provided. It is also possible that for the studies that only reported categorical exposures and did not report the distribution of cases and non-cases, we may have under-estimated the study specific slopes by assuming that cases and non-cases were evenly distributed across the categories; since this is unlikely to be the case. However, findings from the high versus low analyses were similar suggesting that this is unlikely to have had substantial impacts on the total estimates.

A broader consideration is that any effect of meat on risk of IHD is likely to be affected by the composition of the total dietary intake of an individual. For example, if meat can raise risk because the saturated fat it contains raises LDLc (Clarke et al. 1997), the IHD risk for an individual would be expected to be determined by the saturated fat content of all the meats consumed, which varies considerably, and by the saturated fat content of the rest of an individual's diet; it is possible that some people with a relatively high intake of saturated fat from meat may have a low intake of saturated fats from other foods, and vice versa; exploring this was beyond the scope of the current analysis, but our findings should be interpreted in the light of current guidelines for healthy diets (e.g. Eatwell in the UK) which emphasize the need to limit total intakes of dietary components such as saturated fat and salt (Public Heath England 2018).

Finally, the generalizability of our findings to non-white European populations is unclear. Seven studies and the majority of participants included in this meta-analysis were of white European ancestry. Of the remaining six studies, one included a small proportion of adults from African American descent (Haring et al. 2014), one was conducted in Australian Aborigines (Burke et al. 2007), three were conducted in East Asian adults (Nagao et al. 2012; Takata et al. 2013; Saito et al. 2020), and one study was conducted across several continents (including a diverse cohort) (Iqbal et al. 2021). In our subgroup analyses, we observed different associations for processed meat and IHD risk when restricted to East Asian cohorts. It is possible that these apparent differences relate to the lower amounts of processed meat consumed by these populations; the g/day intake of processed meat was lower than that reported in most of the other cohorts. Comparatively our increments are relatively large and therefore extrapolate beyond the range of intakes for most participants in the study, thus magnifying more modest associations; this compromise is a limitation of this type of meta-analysis of diet in disparate populations. Additionally, it is possible that the difference might relate to the different types of processed meats being consumed between the study cohorts and how they were classified. Larger case numbers and additional studies in non-white European cohort studies could help clarify if associations are generalizable.

In conclusion, this large meta-analysis of meat intake and IHD risk shows that unprocessed red and processed meat might be risk factors for IHD. This supports public health recommendations to reduce the consumption of unprocessed red and processed meat intake for the prevention of IHD.

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Disclosure statement

All authors declare that there are no conflicts of interest.

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