Inquiry into the Definitions of meat and other animal products

Senate Standing Committees on Rural and Regional Affairs and Transport

Australian Sustainable Animal Protein Production (ASAPP) Submission

August 2021

Main Submission Author(s):

Prof. Paul Wood

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Supplementary Evidence

The following article and reference papers are provided to supplement specific questions and statements made within the hearing, additional to the original references of the ASAPP submission. Of core concern is the supplanting of solid peer reviewed science by ideology, and in particular denigration and misrepresentation of natural whole foods such meat and dairy. This misinformation is widely disseminated in social media and in advertising including label claims and associated images. Of very serious concern is the attacks on scientists who seek to publish high quality work that doesn't align with some ideological positions of anti-animal sourced foods activist groups.

HEALTH

Scientists cast doubt on ‘dangerous’ implications of red meat health risks data in Global Burden of Disease study

By Kevin White | 12 November 2021 | **4 min read**

The data has been widely used to support lower red meat consumption

A group of international scientists have questioned the “reliability” of data linking meat consumption to a dramatic increase in deaths, which has been referenced in major policy documents – including Henry Dimbleby’s National Food Strategy.

The scientists, led by professor Alice Stanton of the Royal College of Surgeons in Ireland, cast doubt on apparently compelling data in the most recent Global Burden of Disease study, published biannually in scientific journal The Lancet since 1990, which has been seized upon in the development of public policy advising on lower red meat consumption.

Data in the influential GBD’s most recent 2019 edition, published in October 2020 and supported by a Lancet publication in 2021, claimed global human deaths from eating red meat had risen from just 25,000 in the GBD 2017 data to 896,000 in 2019, a 36-fold (3,484%) increase in the threat to human health from eating meat in two years.

At the same time, the GBD study recorded the dietary risk of food high in salt fell by 40%.

The data was subsequently cited in the NFS’s evidence document as justification – alongside the meat sector’s impact on the environment – for a reduction in the consumption of meat.

It has also been referred to in publications by the UN Food System Summit, and the EU’s Farm To Fork Strategy, with a “clear message that eating red meat is bad for human health, regardless of your age, gender or health”, said professor Stanton.

But after a “forensic examination” of the data and its assumptions by the group – which also includes globally-recognised meat expert professor Frederic Leroy of Vrije Universiteit in Brussels –it was then compared to a collection of global meta-analyses looking at the relationship between eating red meat and human ill health and deaths. The scientists concluded they could “find no relationship” between the meta-analyses and the GBD data.

In correspondence to The Lancet, seen by The Grocer, they warned it would be “highly inappropriate and imprudent for these estimates to be utilised in any national or international policy documents, nor in any regulatory or legislative decisions”.

However, repeated requests for The Lancet to peer review the data and to publish the evidence behind it were either declined or ignored, with further requests to the GBD team at the University of Washington to publish its evidence also refused.

The group then approached rival scientific journal The Annals of Internal Medicine in a bid to publish its findings.

In a letter from its editor-in-chief, seen by The Grocer, she agreed the group’s concerns were “valid”, with the journal’s statistical editors noting “there are many more problems” with the GBD’s analytical approach. However, it declined to publish its evidence as it would be “inappropriate”.

Professor Stanton told The Grocer she was “very concerned” that without publishing any supporting evidence, the GBD analysis now suggested eating meat had become significantly more dangerous to human health.

“Since the GBD is regarded as the top source of global health metric worldwide, it’s of huge importance there is public trust in its estimates, and that they are published on a peer-reviewed basis,” she added.

“This hasn’t happened in its 2019 analysis. This data would require a change in public health practice and advice on what the public should eat if it was to be believed,” she added.

“What would happen to child and maternal nutrition, iron deficiency and anaemia rates worldwide, if [the data] was obeyed? There are huge dangers to human health if we don’t objectively look at the available evidence.”

ASAPP Comment:

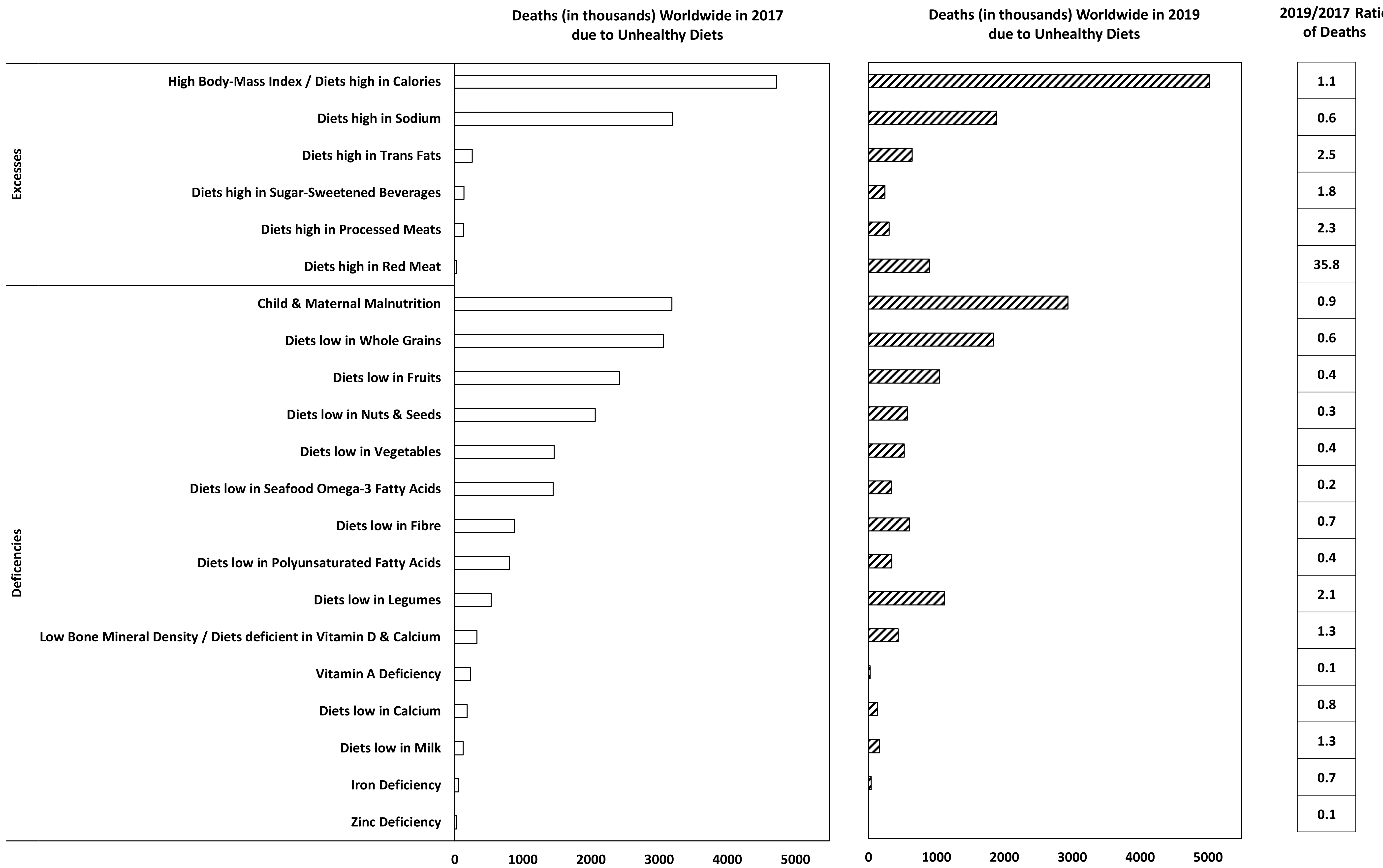
This Paper is currently under review for publication by the Lancet. We would be happy to provide it as soon as it's allowed under academic publication protocols.

Major issues include the failure to follow PRISMA and GATHER academic rules regarding sources and data analysis detail and the apparent claims that are contrary to all major published studies (as summarised in the graphs below).

This has highly significant relevance to global dietary guidelines and is currently being reviewed by USDA. The GBD is a major reference for government policy and also extensively used in many of the anti-meat publications such as food in the Anthropocene.

Figure 1

A


Deaths (in thousands) Worldwide in 2017 due to Unhealthy Diets
Deaths (in thousands) Worldwide in 2019 due to Unhealthy Diets
2019/2017 Ratio of Deaths
Excesses
Deficencies
High Body-Mass Index / Diets high in Calories
Diets high in Sodium
Diets high in Trans Fats
Diets high in Sugar-Sweetened Beverages
Diets high in Processed Meats
Diets high in Red Meat
Child & Maternal Malnutrition
Diets low in Whole Grains
Diets low in Fruits
Diets low in Nuts & Seeds
Diets low in Vegetables
Diets low in Seafood Omega-3 Fatty Acids
Diets low in Fibre
Diets low in Polyunsaturated Fatty Acids
Diets low in Legumes
Low Bone Mineral Density / Diets deficient in Vitamin D & Calcium
Vitamin A Deficiency
Diets low in Calcium
Diets low in Milk
Iron Deficiency
Zinc Deficiency
0
1000
2000
3000
4000
5000
1.1
0.6
2.5
1.8
2.3
35.8
0.9
0.6
0.4
0.3
0.4
0.2
0.7
0.4
2.1
1.3
0.1
0.8
1.3
0.7
0.1

B

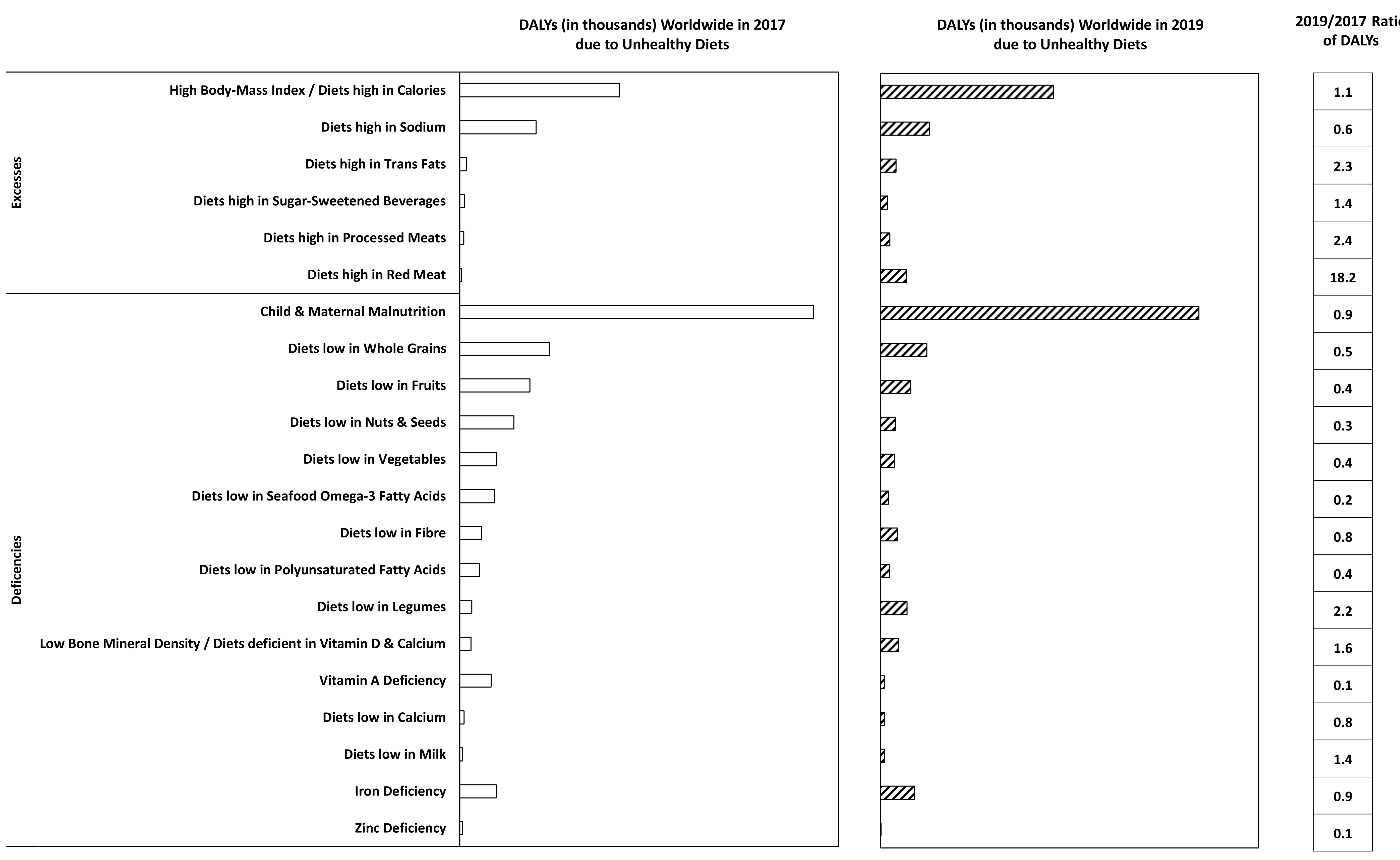

DALYs (in thousands) Worldwide in 2017 due to Unhealthy Diets
DALYs (in thousands) Worldwide in 2019 due to Unhealthy Diets
2019/2017 Ratio of DALYs
Excesses
Deficencies
High Body-Mass Index / Diets high in Calories
Diets high in Sodium
Diets high in Trans Fats
Diets high in Sugar-Sweetened Beverages
Diets high in Processed Meats
Diets high in Red Meat
Child & Maternal Malnutrition
Diets low in Whole Grains
Diets low in Fruits
Diets low in Nuts & Seeds
Diets low in Vegetables
Diets low in Seafood Omega-3 Fatty Acids
Diets low in Fibre
Diets low in Polyunsaturated Fatty Acids
Diets low in Legumes
Low Bone Mineral Density / Diets deficient in Vitamin D & Calcium
Vitamin A Deficiency
Diets low in Calcium
Diets low in Milk
Iron Deficiency
Zinc Deficiency
0
100000
200000
300000
1.1
0.6
2.3
1.4
2.4
18.2
0.9
0.5
0.4
0.3
0.4
0.2
0.8
0.4
2.2
1.6
0.1
0.8
1.4
0.9
0.1

Figure 2

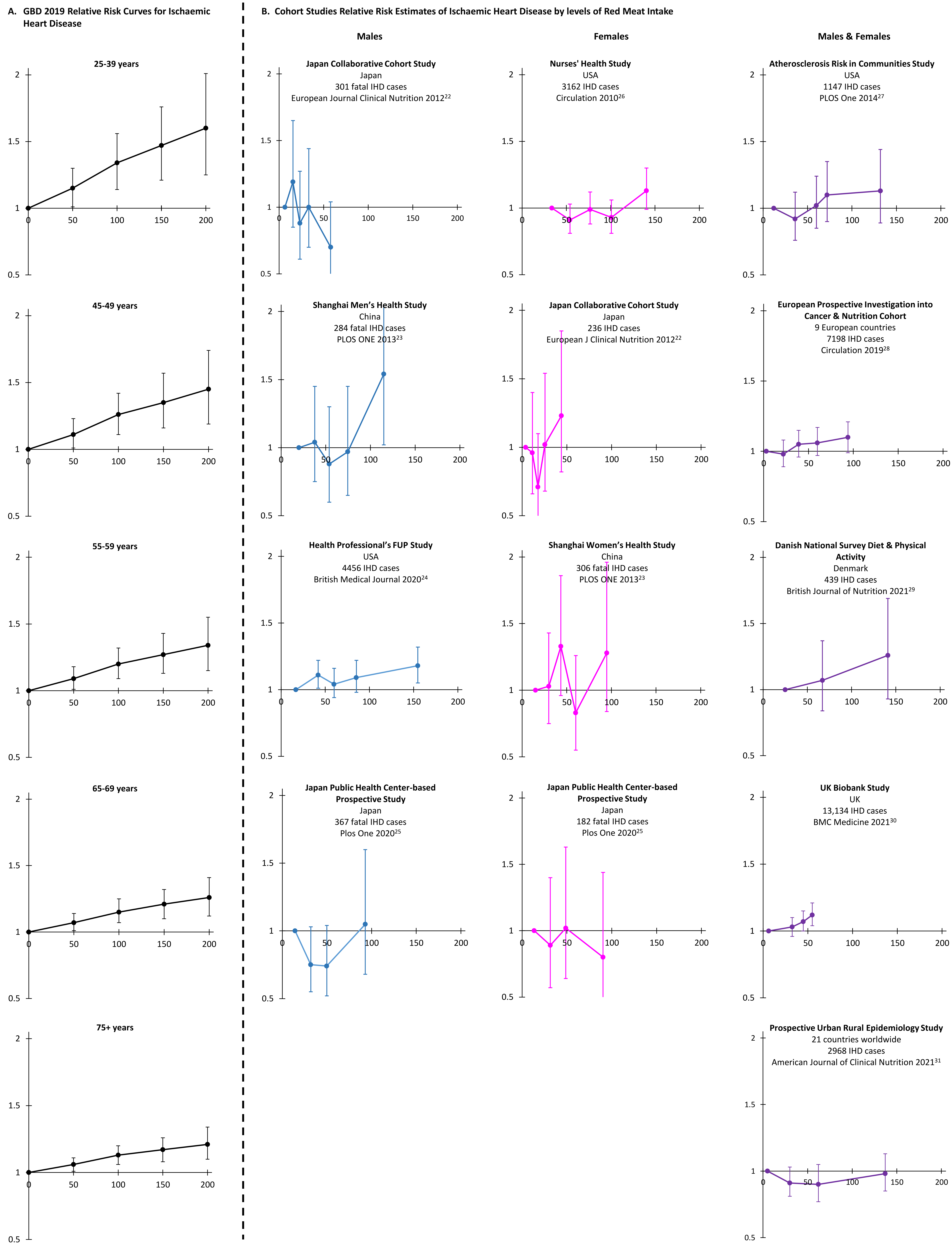

A. GBD 2019 Relative Risk Curves for Ischaemic Heart Disease
25-39 years
45-49 years
55-59 years
65-69 years
75+ years
B. Cohort Studies Relative Risk Estimates of Ischaemic Heart Disease by levels of Red Meat Intake
Males
Females
Males & Females
Japan Collaborative Cohort Study
Japan
301 fatal IHD cases
European Journal Clinical Nutrition 2012[22]
Nurses' Health Study
USA
3162 IHD cases
Circulation 2010[26]
Atherosclerosis Risk in Communities Study
USA
1147 IHD cases
PLOS One 2014[27]
Shanghai Men's Health Study
China
284 fatal IHD cases
PLOS ONE 2013[23]
Japan Collaborative Cohort Study
Japan
236 IHD cases
European J Clinical Nutrition 2012[22]
European Prospective Investigation into Cancer & Nutrition Cohort
9 European countries
7198 IHD cases
Circulation 2019[28]
Health Professional's FUP Study
USA
4456 IHD cases
British Medical Journal 2020[24]
Shanghai Women's Health Study
China
306 fatal IHD cases
PLOS ONE 2013[23]
Danish National Survey Diet & Physical Activity
Denmark
439 IHD cases
British Journal of Nutrition 2021[29]
Japan Public Health Center-based Prospective Study
Japan
367 fatal IHD cases
Plos One 2020[25]
Japan Public Health Center-based Prospective Study
Japan
182 fatal IHD cases
Plos One 2020[25]
UK Biobank Study
UK
13,134 IHD cases
BMC Medicine 2021[30]
Prospective Urban Rural Epidemiology Study
21 countries worldwide
2968 IHD cases
American Journal of Clinical Nutrition 2021[31]

Figure 3

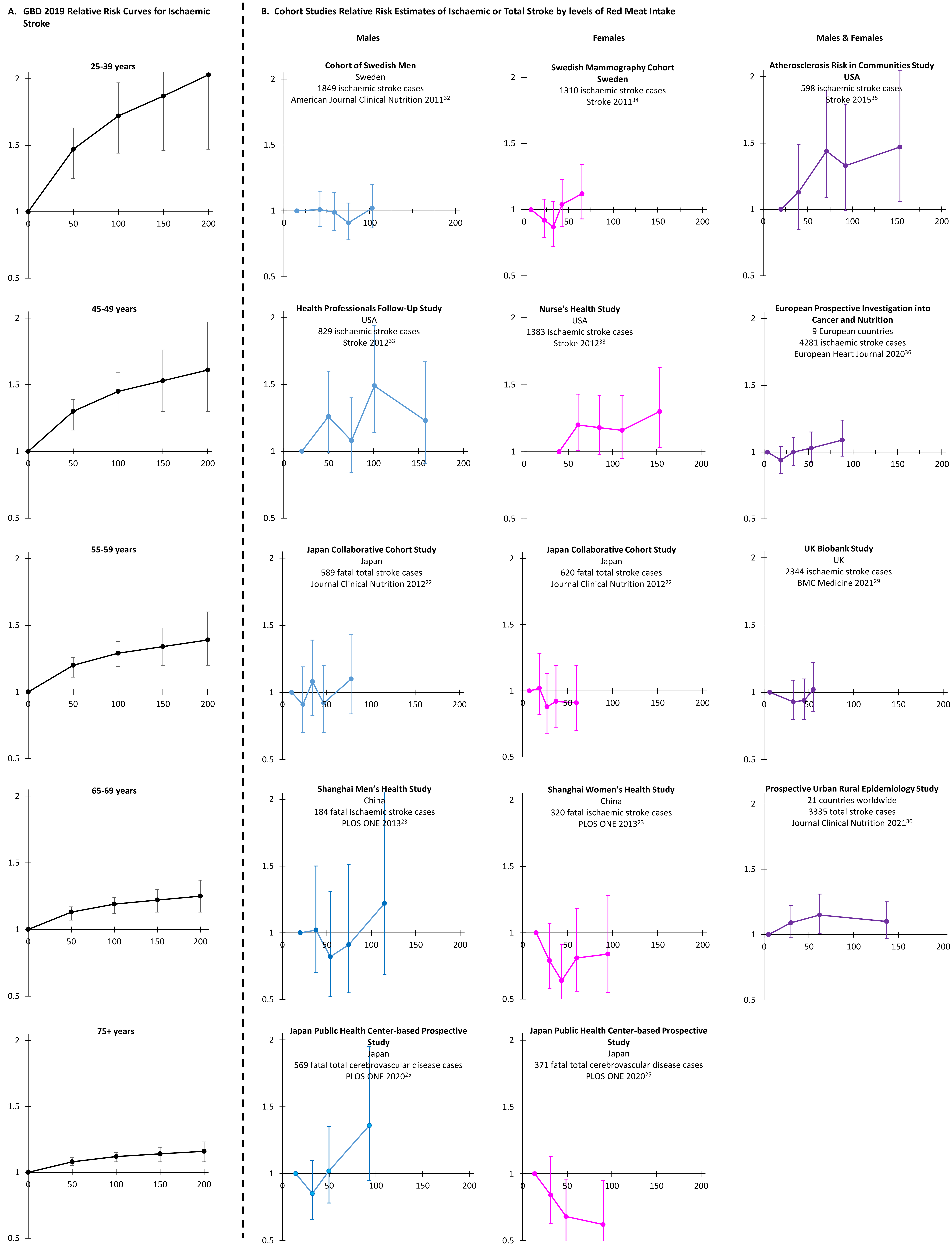
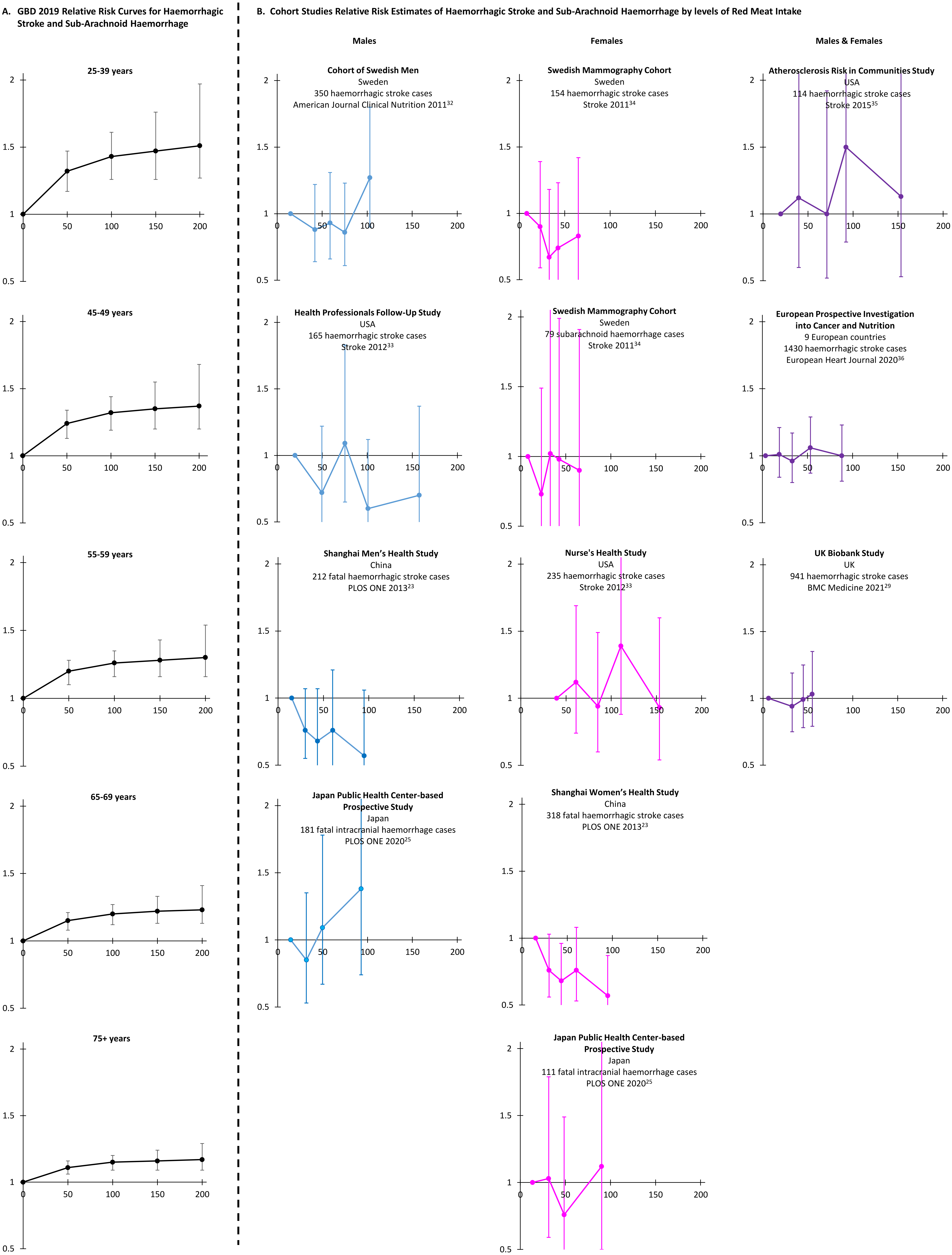

A. GBD 2019 Relative Risk Curves for Ischaemic Stroke
B. Cohort Studies Relative Risk Estimates of Ischaemic or Total Stroke by levels of Red Meat Intake
Males
Females
Males & Females
25-39 years
45-49 years
55-59 years
65-69 years
75+ years
Cohort of Swedish Men
Sweden
1849 ischaemic stroke cases
American Journal Clinical Nutrition 2011[32]
Swedish Mammography Cohort
Sweden
1310 ischaemic stroke cases
Stroke 2011[34]
Atherosclerosis Risk in Communities Study
USA
598 ischaemic stroke cases
Stroke 2015[35]
Health Professionals Follow-Up Study
USA
829 ischaemic stroke cases
Stroke 2012[33]
Nurse's Health Study
USA
1383 ischaemic stroke cases
Stroke 2012[33]
European Prospective Investigation into Cancer and Nutrition
9 European countries
4281 ischaemic stroke cases
European Heart Journal 2020[36]
Japan Collaborative Cohort Study
Japan
589 fatal total stroke cases
Journal Clinical Nutrition 2012[22]
Japan Collaborative Cohort Study
Japan
620 fatal total stroke cases
Journal Clinical Nutrition 2012[22]
UK Biobank Study
UK
2344 ischaemic stroke cases
BMC Medicine 2021[29]
Shanghai Men's Health Study
China
184 fatal ischaemic stroke cases
PLOS ONE 2013[23]
Shanghai Women's Health Study
China
320 fatal ischaemic stroke cases
PLOS ONE 2013[23]
Prospective Urban Rural Epidemiology Study
21 countries worldwide
3335 total stroke cases
Journal Clinical Nutrition 2021[30]
Japan Public Health Center-based Prospective Study
Japan
569 fatal total cerebrovascular disease cases
PLOS ONE 2020[25]
Japan Public Health Center-based Prospective Study
Japan
371 fatal total cerebrovascular disease cases
PLOS ONE 2020[25]

Figure 4


A. GBD 2019 Relative Risk Curves for Haemorrhagic Stroke and Sub-Arachnoid Haemorrhage
B. Cohort Studies Relative Risk Estimates of Haemorrhagic Stroke and Sub-Arachnoid Haemorrhage by levels of Red Meat Intake
Males
Females
Males & Females
25-39 years
45-49 years
55-59 years
65-69 years
75+ years
Cohort of Swedish Men
Sweden
350 haemorrhagic stroke cases
American Journal Clinical Nutrition 2011[32]
Swedish Mammography Cohort
Sweden
154 haemorrhagic stroke cases
Stroke 2011[34]
Atherosclerosis Risk in Communities Study
USA
114 haemorrhagic stroke cases
Stroke 2015[35]
Health Professionals Follow-Up Study
USA
165 haemorrhagic stroke cases
Stroke 2012[33]
Swedish Mammography Cohort
Sweden
79 subarachnoid haemorrhage cases
Stroke 2011[34]
European Prospective Investigation into Cancer and Nutrition
9 European countries
1430 haemorrhagic stroke cases
European Heart Journal 2020[36]
Shanghai Men's Health Study
China
212 fatal haemorrhagic stroke cases
PLOS ONE 2013[23]
Nurse's Health Study
USA
235 haemorrhagic stroke cases
Stroke 2012[33]
UK Biobank Study
UK
941 haemorrhagic stroke cases
BMC Medicine 2021[29]
Japan Public Health Center-based Prospective Study
Japan
181 fatal intracranial haemorrhage cases
PLOS ONE 2020[25]
Shanghai Women's Health Study
China
318 fatal haemorrhagic stroke cases
PLOS ONE 2013[23]
Japan Public Health Center-based Prospective Study
Japan
111 fatal intracranial haemorrhage cases
PLOS ONE 2020[25]

Annals of Internal Medicine REVIEW

Red and Processed Meat Consumption and Risk for All-Cause Mortality and Cardiometabolic Outcomes

A Systematic Review and Meta-analysis of Cohort Studies

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Background: Dietary guidelines generally recommend limiting intake of red and processed meat. However, the quality of evidence implicating red and processed meat in adverse health outcomes remains unclear.

Purpose: To evaluate the association between red and processed meat consumption and all-cause mortality, cardiometabolic outcomes, quality of life, and satisfaction with diet among adults.

Data Sources: EMBASE (Elsevier), Cochrane Central Register of Controlled Trials (Wiley), Web of Science (Clarivate Analytics), CINAHL (EBSCO), and ProQuest from inception until July 2018 and MEDLINE from inception until April 2019, without language restrictions, as well as bibliographies of relevant articles.

Study Selection: Cohort studies with at least 1000 participants that reported an association between unprocessed red or processed meat intake and outcomes of interest.

Data Extraction: Teams of 2 reviewers independently extracted data and assessed risk of bias. One investigator assessed certainty of evidence, and the senior investigator confirmed the assessments.

Data Synthesis: Of 61 articles reporting on 55 cohorts with more than 4 million participants, none addressed quality of life or satisfaction with diet. Low-certainty evidence was found that a reduction in unprocessed red meat intake of 3 servings per week is associated with a very small reduction in risk for cardiovascular mortality, stroke, myocardial infarction (MI), and type 2 diabetes. Likewise, low-certainty evidence was found that a reduction in processed meat intake of 3 servings per week is associated with a very small decrease in risk for all-cause mortality, cardiovascular mortality, stroke, MI, and type 2 diabetes.

Limitation: Inadequate adjustment for known confounders, residual confounding due to observational design, and recall bias associated with dietary measurement.

Conclusion: The magnitude of association between red and processed meat consumption and all-cause mortality and adverse cardiometabolic outcomes is very small, and the evidence is of low certainty.

Primary Funding Source: None. (PROSPERO: CRD42017074074)

Ann Intern Med. doi:10.7326/M19-0655 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 1 October 2019.

Growing evidence shows an increased risk for cardiometabolic disease associated with the consumption of red and processed meat. Although previous systematic reviews reported positive associations between red meat intake and all-cause mortality (1), cardiovascular mortality (2), and stroke (3) and between processed meat consumption and all-cause mortality (1, 4), cardiovascular mortality (2), stroke (3), coronary heart disease (5), and type 2 diabetes (5), results have not been consistent. One review did not find an association between unprocessed red meat and all-cause mortality (4), and another found no association with cardiovascular disease (5). Although Aune and colleagues (6) reported a relationship between red meat intake and type 2 diabetes, Micha and colleagues (5) did not detect this association in a review published 1 year later.

Methodological limitations in previous reviews included failure to address risk of bias of primary studies (for example, references 3 and 6), lack of evaluation of certainty of evidence (for example, references 2 to 6), and failure to consider the magnitude of observed effect (for example, references 2 to 6). These limitations may have affected the credibility of recommendations issued by governments and authoritative organizations regarding red and processed meats.

As part of NutriRECS (Nutritional Recommendations and accessible Evidence summaries Composed of Systematic reviews), a new initiative to establish trustworthy dietary recommendations that meet internationally accepted standards for guideline development, we developed guidelines addressing red and processed meat consumption (7). To inform these recommendations, we conducted 5 systematic reviews of the evidence (8–11). Here, we present results from a systematic review of cohort studies addressing the association between red and processed meat consumption and all-cause mortality, cardiometabolic outcomes, quality of life, and satisfaction with diet among adults.

See also:

Related articles
Editorial comment

Web-Only
Supplement

METHODS

We registered a protocol for this review at PROSPERO (CRD42017074074) in August 2017.

Data Sources and Search Strategy

An experienced research librarian developed the search strategy, which was used across all supporting reviews except the one addressing public values and preferences (Supplement 1, available at Annals.org). We searched MEDLINE, EMBASE (Elsevier), Cochrane Central Register of Controlled Trials (Wiley), Web of Science (Clarivate Analytics), CINAHL (EBSCO), and ProQuest from inception. We also reviewed reference lists of relevant systematic reviews. The final search of all databases included references up to July 2018, except for the MEDLINE search, which included references up to April 2019.

Study Selection

We included cohort studies in any language that enrolled at least 1000 adults, compared participants consuming different amounts of unprocessed red meat or processed meat, and reported on 1 or more of our outcomes of interest. Red meat and processed meat were defined, respectively, as mammalian meat and white or red meat preserved by smoking, curing, salting, or adding chemical compounds (for example, hot dogs, charcuterie, sausage, ham, and deli meats) (12). We also included studies comparing vegetarians with nonvegetarians for sensitivity analyses. Our outcomes of interest were determined in consultation with our guideline panel—which comprised members of the public, clinicians, epidemiologists, and methodologists—and include all-cause mortality, cardiovascular mortality (or fatal coronary heart disease or fatal myocardial infarction [MI]), cardiovascular disease (or coronary heart disease), stroke, MI, type 2 diabetes, anemia, quality of life, and satisfaction with diet. For studies reporting on ischemic and hemorrhagic stroke separately, we included results only for ischemic stroke in our meta-analyses (13).

Cohorts in which more than 20% of the sample was younger than 18 years, had a noncardiometabolic disease (such as cancer), or was pregnant at baseline were excluded. We also excluded studies in which diet was assessed before adulthood, participants were asked to recall their diet before adulthood, or dietary assessments were completed by proxies, as well as studies that reported on specific components of red meat (such as iron or fat) or specific types of red meat (such as lamb). However, we did include studies reporting on beef–pork combinations because beef and pork account for most red meat intake in most Western populations (14, 15). If we encountered more than 1 eligible article on the same exposure and cohort and addressing the same outcome, we included results only from the study with the longest follow-up. If the follow-up was the same, we chose the study with the most participants.

Pairs of reviewers completed calibration exercises, after which they performed screening independently and in duplicate, with disagreements resolved by discussion or through third-party adjudication by an expert research methodologist. Screening was done in 2 stages: First, the reviewers assessed titles and abstracts; then, for those deemed potentially eligible, they evaluated the full-text articles.

Data Extraction and Quality Assessment

Using standardized, pilot-tested forms, reviewers completed calibration exercises and worked in pairs to independently extract the following information from eligible studies: cohort characteristics (such as cohort name and country), participant characteristics (including age and proportion who were female), diet characteristics (such as frequency and quantity of consumption of unprocessed red meat or processed meat), and outcomes (including absolute and relative effect measures for outcomes of interest and measures of variability). Disagreements between pairs of extractors were resolved through discussion or by third-party adjudication by an expert research methodologist.

Reviewers, working independently and in duplicate, assessed each study's risk of bias by using the CLARITY (Clinical Advances Through Research and Information Translation) risk-of-bias instrument for cohort studies, omitting an item related to co-interventions that was not relevant to our review (16). Disagreements were resolved through discussion or by third-party adjudication. Research methodologists and nutrition researchers were consulted to confirm the appropriateness of the CLARITY instrument and to advise us regarding criteria for evaluating each of its items. The instrument and detailed guidance are presented in Supplement Table 1 (available at Annals.org). Studies rated as high risk of bias on 2 or more of the 7 domains were considered to have a high overall risk of bias. This threshold, although somewhat arbitrary, represents a compromise between excessive stringency and leniency.

Data Synthesis and Analysis

We conducted separate analyses for unprocessed red meat, processed meat, and mixed unprocessed red and processed meat. If an article reported on red meat and did not specify whether it was processed or unprocessed, we assumed that it included both unprocessed and processed red meat. We included such studies in the analysis of mixed unprocessed red and processed meat because most processed meat is typically consumed as red meat (17, 18).

For our primary analyses, we conducted a random-effects dose–response meta-analysis using methods proposed by Greenland and Longnecker (19) and Orsini and colleagues (20). These methods require knowledge of the distribution of events and number of participants or person-years and mean or median quantity of intake across categories of exposure. When results from studies were analyzed across quantiles of intake but person-years or number of participants was not reported within each quantile, we estimated these values by using figures reported for the total population and dividing the total person-years or total number of participants by the number of quantiles. For studies reporting effect estimates stratified by participant characteristics (such as sex), we meta-analyzed across subgroups by using the fixed-effects model. For studies that treated the exposure as a continuous predictor in a logistic regression and did not present categorical analyses, we calculated a regression coefficient based on the relative effect reported and meta-analyzed these regression coefficients with effects from other studies obtained via the estimation method described by Greenland and Longnecker (19). These studies were excluded from the nonlinear analyses. For analyses including 5 or more studies, we tested for nonlinearity by using restricted cubic splines with knots at 10%, 50%, and 90% and a Wald-type test. For analyses in which we observed statistically significant nonlinear associations, we present results from the nonlinear model.

For studies reporting the intake of red meat or processed meat as a range of values, we assigned the midpoint of upper and lower boundaries in each category as the average intake. If the highest or lowest category was open ended, we assumed that the open-ended interval was the same size as the adjacent interval. For studies reporting exposure as number of servings, we assumed that each serving of unprocessed red meat was equal to 120 g; processed meat, 50 g; and mixed unprocessed red and processed meat, 100 g. These serving sizes were selected for comparability with those used in other systematic reviews, as well as to reflect serving sizes used by the U.S. Department of Agriculture and United Kingdom Food Agency (1–3, 21–25). We report results corresponding to the effects of a reduction in unprocessed red or processed meat intake of 3 servings per week.

We used the dosresmeta package in R, version 3.5.1 (R Foundation for Statistical Computing), for our dose–response meta-analyses (26). Further details about these meta-analyses, including sample code, are presented in Supplement 2 (available at Annals.org).

As a secondary analysis, we used the Hartung–Knapp–Sidik–Jonkman approach to calculate pooled relative effects, comparing the lowest category of exposure in each study with the highest one (27, 28). We also present results using a random-effects meta-analysis with the restricted maximum likelihood estimator. In these analyses, we also included studies comparing vegetarians with nonvegetarians. For studies that treated the exposure as a continuous predictor in logistic regression models and did not present categorical analyses, we converted relative effect estimates from the logistic regression model to correspond to a difference in intake of 1 serving per day—which was the difference observed most often between lowest and highest categories of consumption across studies—and used them in our meta-analyses. We used the metafor package in R (version 3.5.1) for these secondary analyses (29).

Because all outcomes of interest were rare (<10% event rate) within included studies for all analyses, we assumed that odds ratios and hazard ratios were similar to estimates of relative risk. We quantified heterogeneity using the I^2 statistic and interpreted the magnitude of heterogeneity according to guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* (0% to 40%, low; 30% to 60%, moderate; 50% to 90%, substantial; 75% to 100%, considerable) (30). We also visually inspected forest plots for consistency, given that I^2 statistics may be artificially inflated when effect estimates from primary studies are very precise—as was the case in many of our analyses (31). For all meta-analyses with at least 10 studies, we used the Egger test to look for small study effects (32).

We conducted a priori specified meta-regressions to test for differences among studies at higher versus lower risk of bias. For analyses with a statistically significant subgroup effect based on risk of bias, we present results only for studies at lower risk of bias. We had also planned to conduct subgroup analyses on the effects of red versus white processed meat and the effects of red meat consumption in iron-deficient populations, as well as a sensitivity analysis on the robustness of results to incomplete outcome data (33). However, we could not complete these additional analyses because of insufficient information reported in the primary studies.

Certainty of Evidence

One investigator assessed certainty of evidence by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for each outcome, and the senior investigator confirmed the assessments (34). According to GRADE, observational studies start at low certainty and may be downgraded for risk of bias, inconsistency, indirectness, imprecision, or publication bias and may be upgraded for large effect, if suspected biases work against the observed direction of effect, or for dose–response gradient. To calculate absolute effects presented in summary-of-findings tables, we used population risks from the Emerging Risk Factors Collaboration to calculate risk differences associated with a reduction in red meat intake of 3 servings per week (35). The Emerging Risk Factors Collaboration is a consortium of 102 international cohorts, primarily from North America and western Europe, including mostly middle-aged to older adults who are omnivores.

Role of the Funding Source

This review received no external funding or other support.

RESULTS

Study Selection

Supplement Figure 1 (available at Annals.org) presents study selection details. A total of 62 articles including 56 cohorts proved eligible. One article did not provide sufficient quantitative information for meta-analysis (36). The quantitative analysis included 61 reports of 55 cohorts (4.2 million participants). Thirty-one cohort studies (2.2 million participants) were eligible for inclusion in the dose–response meta-analyses.

Study Characteristics

We found 20 articles (30 cohorts) addressing all-cause mortality; 18 (28 cohorts), cardiovascular mortality; 9 (7 cohorts), cardiovascular disease; 6 (7 cohorts),

Table 1. Summary of Findings for Unprocessed Red Meat Intake (Reduction of 3 Servings per Week) and Risk for Cardiometabolic Outcomes

Outcome	Studies, *n*	Participants, *n*	Follow-up, *y*	RR (95% CI)	Population Risk per 1000 Persons Over 10.8 y*	Risk Difference per 1000 Persons (95% CI)	GRADE Certainty of Evidence	Plain-Language Summary
All-cause mortality	8	893 436	9–28	0.93 (0.87–1.00)	113	−8 (0 to −15)	Very low due to observational design, imprecision†‡	We are uncertain of the effects of unprocessed red meat on all-cause mortality.
Cardiovascular mortality	7	874 896	9–28	0.90 (0.88–0.91)	41	−4 (−5 to −4)	Very low due to observational design, risk of bias§	We are uncertain of the effects of unprocessed red meat on cardiovascular mortality.
Cardiovascular disease	3	191 803	8–26	0.95 (0.85–1.06)	76	−3 (−11 to 5)	Very low due to observational design, imprecision‖	We are uncertain of the effects of unprocessed red meat on cardiovascular disease.
Stroke (fatal and nonfatal)	6	254 742	12–26	0.94 (0.90–0.98)	19	−1 (0 to −2)	Low due to observational design	Reduction in unprocessed red meat may have little or no effect on stroke.
Fatal stroke	3	671 259	Median, 5.5–15.6	0.94 (0.89–0.99)	1	0	Very low due to observational design, risk of bias¶	We are uncertain of the effects of unprocessed red meat on fatal stroke.
MI (fatal and nonfatal)	1	55 171	Median, 13.6	0.93 (0.87–0.99)	36	−3 (0 to −5)	Very low due to observational design, risk of bias**	We are uncertain of the effects of unprocessed red meat on MI.
Type 2 diabetes††	6	293 869	5–28	0.90 (0.88–0.92)	56	−6 (−7 to −4)	Low due to observational design	Reduction in unprocessed red meat may result in a very small decrease in type 2 diabetes.

GRADE = Grading of Recommendations Assessment, Development and Evaluation; MI = myocardial infarction; RR = relative risk.
* Based on the Emerging Risk Factors Collaboration, which comprises 102 cohorts including 698 782 participants, with a median follow-up of 10.8 y (5th/95th percentile: 2.8–25.6 y). Numbers of events accrued are 78 853, 28 964, 52 765, 13 113, 768, 24 848, and 38 851 for all-cause mortality, cardiovascular mortality, cardiovascular disease, fatal and nonfatal stroke, fatal stroke, fatal and nonfatal MI, and type 2 diabetes, respectively.
† CI around absolute effect includes both appreciable benefit and no appreciable benefit.
‡ I^2 = 96.0%; *P* for Q test < 0.001. However, the evidence was not downgraded for inconsistency because overlap exists between CIs of most studies.
§ Four of 7 studies are at high risk of bias due to lack of periodic repeated measurement of diet and inadequate adjustment for confounders.
‖ CI around absolute effect includes both appreciable benefit and harm.
¶ Two of 3 studies are at high risk of bias due to assessment of exposure only at baseline for more than 10 y of follow-up and inadequate adjustment for confounders.
** Study at high risk of bias due to assessment of diet only at baseline for >10 y of follow-up and inadequate adjustment for confounders.
†† We found a statistically significant difference between studies at high risk and those at low risk of bias. Here, we report results from studies at low risk.

fatal and nonfatal stroke; 8 (11 cohorts), fatal stroke; 1 (1 cohort), fatal and nonfatal MI; 1 (1 cohort), nonfatal MI; 24 (25 cohorts), type 2 diabetes; and 1 (1 cohort), anemia (Supplement Table 2, available at Annals.org). We found no publications reporting on nonfatal stroke, fatal MI, quality of life, or satisfaction with diet.

Eighteen cohorts were from North America (United States and Canada), 21 from Europe, 15 from Asia, and 1 from the Middle East. The number of participants in each cohort ranged from 1757 to 536 969. Participants ranged in age from 17 to 92 years, with most cohorts recruiting those aged 40 to 50 years. Follow-up ranged from 2 to 28 years. Authors of 8 articles disclosed intellectual, financial, or personal conflicts of interest. All studies were funded by governmental bodies, with some receiving additional support from not-for-profit organizations.

Risk of Bias

Supplement Tables 3 through 11 (available at Annals.org) present risk-of-bias assessments. The proportion of studies with high overall risk of bias varied on the basis of outcome: 10 of 31 studies for all-cause mortality, 17 of 22 for cardiovascular mortality, 3 of 8 for cardiovascular disease, 3 of 7 for fatal and nonfatal stroke, 10 of 13 for fatal stroke, 1 of 1 for fatal and nonfatal MI, 0 of 1 for nonfatal MI, 15 of 27 for type 2 diabetes, and 0 of 1 for anemia. The most common limitations in the studies were a lack of periodic repeated evaluation of dietary intake with a measure validated for red and processed meat and inadequate adjustment for potential confounders.

Reduction of 3 Servings per Week of Unprocessed Red Meat

Table 1 presents results of the possible effect of a reduction in unprocessed red meat intake of 3 servings per week. Details are presented in Supplement Table 12 (available at Annals.org). Results showed a very small apparent effect on cardiovascular mortality, fatal and nonfatal stroke, fatal stroke, fatal and nonfatal MI, and type 2 diabetes, but not all-cause mortality or cardiovascular disease. We found evidence of a subgroup difference between studies at higher and those at lower risk of bias for type 2 diabetes ($P < 0.001$), so we present results from studies with a lower risk of bias. We did not find evidence of publication bias for type 2 diabetes.

The certainty of evidence was downgraded from low to very low for all-cause mortality and cardiovascular disease because CIs around absolute effect estimates included appreciable benefit as well as no effect or appreciable harm. The certainty of evidence for cardiovascular mortality, fatal stroke, and fatal and nonfatal MI was downgraded to very low because of the lack of periodic repeated measurement of diet and inadequate adjustment for potential confounders in the primary studies.

Reduction of 3 Servings per Week of Processed Meat

Table 2 presents results of the possible effect of a reduction in processed meat intake of 3 servings per week. Details are presented in Supplement Table 13 (available at Annals.org). Results show a very small apparent effect on all-cause mortality, cardiovascular mortality, fatal and nonfatal stroke, fatal stroke, fatal and nonfatal MI, and type 2 diabetes, but not cardiovascular disease. We found evidence of a nonlinear association between processed meat intake and type 2 diabetes ($P < 0.001$), with a decrease from 3 to 0 servings per week associated with a very small reduced risk for type 2 diabetes (Figure). We found no evidence of publication bias for type 2 diabetes.

The certainty of evidence was downgraded to very low for cardiovascular mortality, fatal stroke, fatal and nonfatal MI, and type 2 diabetes because of a lack of periodic repeated measurement of diet and inadequate adjustment for potential confounders in the primary studies, as well as for type 2 diabetes because of substantial statistical heterogeneity.

Reduction of 3 Servings per Week of Mixed Unprocessed Red and Processed Meat

Supplement Table 14 (available at Annals.org) presents results of the possible effect of a reduction in intake of mixed unprocessed red and processed meat of 3 servings per week. Details are presented in Supplement Table 15 (available at Annals.org). Results show a small to very small apparent effect on all-cause mortality, cardiovascular mortality, cardiovascular disease, fatal and nonfatal stroke, fatal stroke, fatal and nonfatal MI, and type 2 diabetes, but not on nonfatal MI or anemia. We found evidence of a subgroup difference between studies at higher and those at lower risk of bias for all-cause mortality ($P = 0.002$) and type 2 diabetes ($P = 0.027$), so we present results only from studies at lower risk of bias. We found evidence of a nonlinear association between intake of mixed unprocessed red and processed meat and all-cause mortality ($P = 0.037$), with a reduction from 3 to 0 servings per week associated with a small decrease in risk (Supplement Figure 2, available at Annals.org). We found no evidence of publication bias for type 2 diabetes.

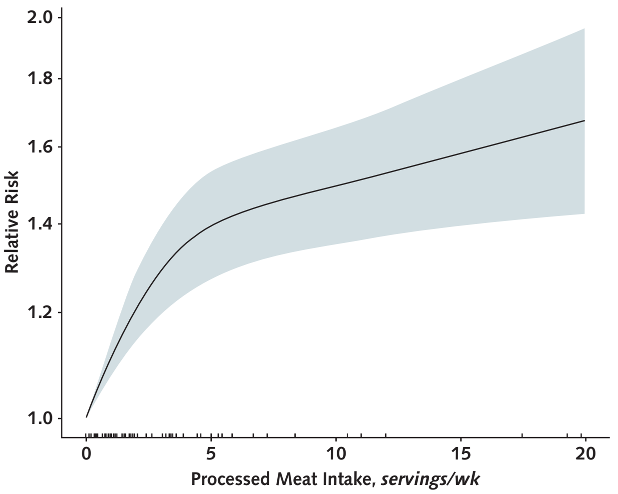
The certainty of evidence was downgraded to very low for cardiovascular mortality, fatal stroke, and fatal and nonfatal MI because of a lack of periodic repeated

Table 2. Summary of Findings for Processed Red Meat Intake (Reduction of 3 Servings per Week) and Risk for Cardiometabolic Outcomes

Outcome	Studies, *n*	Participants, *n*	Follow-up, *y*	RR (95% CI)	Population Risk per 1000 Persons Over 10.8 y*	Risk Difference per 1000 Persons (95% CI)	GRADE Certainty of Evidence	Plain-Language Summary
All-cause mortality	8	1 241 900	9–28	0.92 (0.87–0.96)	113	−9 (−15 to −5)	Low due to observational design†	Reduction in processed meat may result in a very small decrease in all-cause mortality.
Cardiovascular mortality	7	1 240 634	9–28	0.90 (0.84–0.97)	41	−4 (−7 to −1)	Very low due to observational design, risk of bias‡§	We are uncertain of the effects of processed meat on cardiovascular mortality.
Cardiovascular disease	3	200 421	8–26	0.97 (0.87–1.09)	76	−2 (−10 to 7)	Low due to observational design‖	Reduction in processed meat may have little or no effect on cardiovascular disease.
Stroke (fatal and nonfatal)	6	254 742	12–26	0.94 (0.90–0.98)	19	−1 (0 to −2)	Low due to observational design	Reduction in processed meat may have little or no effect on stroke.
Fatal stroke	2	571 378	15–16	0.95 (0.92–0.98)	1	0	Very low due to observational design, risk of bias¶	We are uncertain of the effects of processed meat on fatal stroke.
MI (fatal and nonfatal)	1	55 171	Median, 13.6	0.94 (0.91–0.98)	36	−2 (−3 to −1)	Very low due to observational design, risk of bias**	We are uncertain of the effects of processed meat on MI.
Type 2 diabetes	14	669 530	5–28	0.78 (0.72–0.84)††	56	−12 (−16 to −9)	Very low due to observational design, risk of bias, inconsistency‡‡§§	We are uncertain of the effects of processed meat on type 2 diabetes.

GRADE = Grading of Recommendations Assessment, Development and Evaluation; MI = myocardial infarction; RR = relative risk.
* Based on the Emerging Risk Factors Collaboration, which comprises 102 cohorts including 698 782 participants, with a median follow-up of 10.8 y (5th/95th percentile: 2.8–25.6 y). The numbers of events accrued are 78 853, 28 964, 52 765, 13 113, 768, 24 848, and 38 851 for all-cause mortality, cardiovascular mortality, cardiovascular disease, fatal and nonfatal stroke, fatal stroke, fatal and nonfatal MI, and type 2 diabetes, respectively.
† I^2 = 87.4%; *P* for *Q* test < 0.001. However, the evidence was not downgraded for inconsistency because overlap exists between CIs of most studies.
‡ Four of 7 studies at high risk of bias, primarily because of a lack of periodic repeated measurement of diet and inadequate adjustment for confounders.
§ I^2 = 84.9%; *P* for *Q* test < 0.001. However, the evidence was not downgraded for inconsistency because overlap exists between CIs of most studies.
‖ I^2 = 59.6%; *P* for *Q* test = 0.098. However, the evidence was not downgraded for inconsistency because overlap exists between CIs of studies.
¶ Two of 2 studies had high risk of bias due to lack of periodic repeated measurement of diet and inadequate adjustment for confounders.
** Study had high risk of bias due to measurement of diet only at baseline for >10 y of follow-up and inadequate adjustment for confounders.
†† Nonlinear relationship. Effect estimate presented represents reduction in intake from 3 to 0 servings per week.
‡‡ Nine of 14 studies had high risk of bias, primarily due to lack of periodic repeated measurement of diet and inadequate adjustment for confounders.
§§ I^2 = 54.5%; *P* for *Q* test < 0.001.

Figure. Nonlinear association between processed meat intake and type 2 diabetes.



The solid black line represents the point estimate, the shaded region represents the 95% CIs, and tick marks represent the positions of the study-specific estimates.

measurement of diet and inadequate adjustment for potential confounders in the primary studies.

Comparison of Extreme Categories of Intake

Results from meta-analyses comparing extreme categories of intake were generally consistent with the findings from our dose–response meta-analyses, although effect sizes typically were smaller than those from dose–response meta-analyses (Supplement Tables 16 to 18, available at Annals.org).

DISCUSSION

We found low- to very-low-certainty evidence that reducing unprocessed red meat intake by 3 servings per week is associated with a very small reduction in risk for cardiovascular mortality, stroke, MI, and type 2 diabetes. Likewise, we found low- to very-low-certainty evidence that a reduction in processed meat intake is associated with a small to very small reduction in risk for all-cause mortality, cardiovascular mortality, stroke, MI, and type 2 diabetes. The magnitude of apparent effect of processed meat consumption on adverse cardiometabolic outcomes was somewhat greater than that observed for unprocessed red meat.

According to the GRADE system, the certainty of evidence may be upgraded if evidence suggests a dose–response relationship between the exposure and the outcomes of interest. Although we found evidence for dose–response relationships, we did not upgrade the certainty of evidence because of the possibility that red and processed meat consumption may be correlated with other dietary components, which may then confound their relationship to health outcomes (37). Support for this concern comes from a parallel systematic review in which we found the magnitude of association between dietary patterns lower versus higher in red and processed meat and adverse cardiometabolic outcomes to be very similar to the estimates found in this review (10). If red meat and processed meat were indeed the primary drivers of the association between diet and adverse cardiometabolic outcomes, we would anticipate stronger associations in our analyses of red and processed meat compared with dietary patterns (7).

Strengths of this review include the prespecification of our methods in the review protocol and the inclusion of a large number of cohorts and participants. We conducted both linear and nonlinear dose–response meta-analyses, which provide the most compelling evidence for the association between red and processed meat consumption and health outcomes, in addition to secondary analyses comparing extreme categories of intake. Results from our dose–response analyses are presented for a realistic reduction of 3 servings per week, which corresponds to the elimination of red and processed meat from the typical North American and western European diet based on the average intake of these foods in these populations (38–40). We assessed risk of bias and, when results differed, based our estimates on studies with lower versus higher risk of bias. Finally, we used the GRADE approach to rate the certainty of evidence.

In evaluating risk of bias of the primary studies, we assessed whether studies adjusted for a set of important potential confounders for each outcome. However, our results are limited by the potential for residual confounding or measurement error in confounders. In addition, studies varied in their choice of adjustment variables. All included studies measured diet via recall-based methods, primarily food-frequency questionnaires, which are subject to measurement error that can both attenuate and overestimate observed associations (41, 42). Although food-frequency questionnaires may provide reliable information on relative intake, substantial error regarding absolute intake may compromise dose–response meta-analyses that rely on these estimates (41). We could not assess the effects of reduced intake of red meat and processed meat on the basis which foods were consumed in their place, and the associated health effects of these alternative food choices may differ.

Half the studies in our review did not report sufficient information to be included in the dose–response meta-analyses (19, 20). Nonetheless, we are more confident in our results from these meta-analyses because they account for differences in gradients of intake across cohorts (43). In secondary analyses comparing extreme categories of intake, studies omitted from dose–response meta-analyses produced smaller effect estimates. The reason may be that studies that could not be included in dose–response meta-analyses had a higher risk of bias and typically measured diet with methods not validated for red and processed meat and did not repeat diet measurements throughout the study; hence, they may have underestimated the association between red and processed meat and adverse cardiometabolic health outcomes.

We could not conduct 3 additional analyses that we had planned—a subgroup analysis on the effects of red versus white processed meat, a subgroup analysis on the effects of red meat intake in iron-deficient populations, and a sensitivity analysis to assess the robustness of results to loss to follow-up—because the primary studies did not report sufficient information (33). We converted effect estimates reported in grams to servings. Although we used typical serving sizes in our conversions, our estimates may have been unreliable (1–3, 21, 23–25).

Although we found no evidence of publication bias, given the lack of standard registration practices for observational studies, publication bias is possible. In addition, none of the included studies had a priori specified statistical analysis plans (44); therefore, analysts' modeling decisions may have been guided by the possibility of obtaining interesting results.

Previous reviews reported similar positive associations between red and processed meat intake and all-cause mortality, cardiovascular disease, stroke, MI, and type 2 diabetes (1, 3–6). Similar to our work, other reviews reported slightly stronger associations between processed meat versus unprocessed red meat and adverse health outcomes. We believe our review provides the most up-to-date evidence on the topic and adds to the existing literature by using a more rigorous evaluation of risk of bias and by providing an assessment of certainty of evidence. Our results, as well as those of other reviews of observational studies, contrast with findings from randomized trials, which have failed to demonstrate an effect of lower red and processed meat consumption on cardiometabolic outcomes (8).

Current dietary guidelines recommend limiting red and processed meat consumption (25, 45). Our results, however, demonstrate that the evidence implicating red and processed meat in adverse cardiometabolic outcomes is of low quality; thus, considerable uncertainty remains regarding a causal relationship. Moreover, even if a causal relationship exists, the magnitude of association between red and processed meat consumption and cardiometabolic outcomes is very small.

Reducing the consumption of unprocessed red and processed meat may result in a decrease in risk for cardiometabolic disease and mortality. The magnitude of absolute effect, if indeed it exists, is very small, and the certainty of evidence is low. Findings from our review raise questions regarding whether—on the basis of possible adverse effects on cardiometabolic outcomes—the evidence is sufficient to recommend decreasing consumption of red and processed meat.

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Annals of Internal Medicine CLINICAL GUIDELINE

Unprocessed Red Meat and Processed Meat Consumption: Dietary Guideline Recommendations From the NutriRECS Consortium

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Description: Dietary guideline recommendations require consideration of the certainty in the evidence, the magnitude of potential benefits and harms, and explicit consideration of people's values and preferences. A set of recommendations on red meat and processed meat consumption was developed on the basis of 5 de novo systematic reviews that considered all of these issues.

Methods: The recommendations were developed by using the Nutritional Recommendations (NutriRECS) guideline development process, which includes rigorous systematic review methodology, and GRADE methods to rate the certainty of evidence for each outcome and to move from evidence to recommendations. A panel of 14 members, including 3 community members, from 7 countries voted on the final recommendations. Strict criteria limited the conflicts of interest among panel members. Considerations of environmental impact or animal welfare did not bear on the recommendations. Four systematic reviews addressed the health effects associated with red meat and processed meat consumption, and 1 systematic review addressed people's health-related values and preferences regarding meat consumption.

Recommendations: The panel suggests that adults continue current unprocessed red meat consumption (weak recommendation, low-certainty evidence). Similarly, the panel suggests adults continue current processed meat consumption (weak recommendation, low-certainty evidence).

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Contemporary dietary guidelines recommend limiting consumption of unprocessed red meat and processed meat. For example, the 2015–2020 Dietary Guidelines for Americans recommend limiting red meat intake, including processed meat, to approximately 1 weekly serving (1). Similarly, United Kingdom dietary guidelines endorse limiting the intake of both red and processed meat to 70 g/d (2), and the World Cancer Research Fund/American Institute for Cancer Research recommend limiting red meat consumption to moderate amounts and consuming very little processed meat (3). The World Health Organization International Agency for Research on Cancer has indicated that consumption of red meat is "probably carcinogenic" to humans, whereas processed meat is considered "carcinogenic" to humans (4).

These recommendations are, however, primarily based on observational studies that are at high risk for confounding and thus are limited in establishing causal inferences, nor do they report the absolute magnitude of any possible effects. Furthermore, the organizations that produce guidelines did not conduct or access rigorous systematic reviews of the evidence, were limited in addressing conflicts of interest, and did not explicitly address population values and preferences, raising questions regarding adherence to guideline standards for trustworthiness (5–9).

A potential solution to the limitations of contemporary nutrition guidelines is for an independent group with clinical and nutritional content expertise and skilled in the methodology of systematic reviews and practice guidelines, methods that include careful management of conflicts of interest, to produce trustworthy recommendations based on the values and preferences of guideline users. We developed the Nutritional Recommendations (NutriRECS) (7) international consortium to produce rigorous evidence-based nutritional recommendations adhering to trustworthiness standards (10–12).

To support our recommendations, we performed 4 parallel systematic reviews that focused both on randomized trials and observational studies addressing the possible impact of unprocessed red meat and processed meat consumption on cardiometabolic and cancer outcomes (13–16), and a fifth systematic review addressing people's health-related values and preferences related to meat consumption (17). On the basis of these reviews, we developed recommendations for unprocessed red meat and processed meat consumption specific to health outcomes.

Methods

Guideline Development Process

We developed our recommendations by following the NutriRECS guideline development process (7),

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which includes use of GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology (18–20). To inform our guideline recommendations, systematic reviews were conducted on the basis of a priori methods (21, 22).

Guideline Team Structure

This work involved 3 teams:

1. A core NutriRECS leadership team was responsible for supervision and coordination of the project and for drafting of the research questions, guideline protocol, and manuscripts.

2. A guideline panel included experts in health research methodology, nutritional epidemiology, dietetics, basic and translational research, family medicine, and general internal medicine. The panel included 3 members from outside the medical and health care communities. Panelists resided in high-income countries (Canada, England, Germany, New Zealand, Poland, Spain, and the United States).

3. A literature review team drafted the protocols for the systematic reviews, completed the literature search and eligibility review, abstracted data and conducted data analysis, and produced narrative and tabular summaries of the results.

Framework for Panel Construction and Guideline Recommendations

The core leadership team applied safeguards against competing interests (7). After generating a list of potential panel members without perceived vested interests, we contacted prospective candidates from North America, Western Europe, and New Zealand. Those who expressed interest completed a detailed form enumerating potential financial or intellectual conflicts during the previous 3 years. If important competing issues were identified (1 interested individual had financial conflicts), the potential panelist was not invited to participate. The Appendix Table (available at Annals.org) shows a summary of the authors' conflict of interest forms; a full list of competing interests is available upon request from Dr. Johnston.

Before our initial guideline panel meeting, the methods editor and panel chair contacted panelists, shared the draft questions, and received and incorporated feedback. At the initial meeting, the guideline panel discussed the scope of the project and agreed on the research questions and subgroups of interest. The panel focused on health outcomes thought to be associated with consumption of unprocessed red meat and processed meat and chose not to consider animal welfare and environmental issues related to meat consumption in making recommendations. The panel chose to exclusively focus on health outcomes because environmental and animal welfare concerns are very different issues that are challenging to integrate with health concerns, are possibly more societal than personal issues, and vary greatly in the extent to which people find them a priority. Finally, to consider these issues rigorously would require systematic reviews that we were not resourced to undertake.

The panel also chose to make separate recommendations for unprocessed red meat and processed meat, given the potential for differential health effects and differing values and preferences of members of the public with regard to consumption of unprocessed meat versus processed meat.

Target Audience for Recommendations

The target audience for our guidance statement was individuals who consume unprocessed red meat or processed meat as part of their diet. The panel took the perspective of individual decision making rather than a public health perspective.

Key Principles for PICO Questions and Study Eligibility Criteria

Each NutriRECS project addresses a single nutrition question or topic, in this case guidance regarding the potential harms, benefits, and health-related values and preferences related to consuming unprocessed red meat and processed meat. We conducted a series of systematic reviews to inform our recommendations, addressing the following questions: 1) Among adults, what is the effect of diets and dietary patterns lower in red or processed meat versus diets higher in red or processed meat intake on the risk for outcomes important to community members? and 2) What are their health-related values and preferences for red and processed meat consumption?

The panel considered all-cause mortality, major cardiometabolic outcomes (cardiovascular mortality, stroke, myocardial infarction, and diabetes), cancer incidence and mortality (gastrointestinal, prostate, and gynecologic cancer), quality of life, and willingness to change unprocessed red or processed meat consumption as "critically important" for developing recommendations. "Important" outcomes included surrogate outcomes (weight, body mass index, blood lipids, blood pressure, hemoglobin, anemia) and reasons for eating unprocessed red meat and processed meat.

Methods for Systematic Reviews

In consultation with an expert librarian, we searched the major literature databases to identify all relevant studies on harms, benefits, and health-related values and preferences regarding unprocessed red meat and processed meat. Each database was searched from inception until July 2018 without restrictions on language or date of publication, with MEDLINE searched through to April 2019 (see the systematic reviews in this issue [13–17]).

For harms and benefits, we included any randomized trial, as well as cohort studies including 1000 or more adults, that assessed diets with varying quantities of unprocessed red meat (for example, as servings or times/wk, or g/d) or processed meat (meat preserved by smoking, curing, salting, or addition of preservatives) (23) for a duration of 6 months or more. Studies in which more than 20% of the sample was pregnant or had cancer or a chronic health condition, other than cardiometabolic disease, were excluded. The review articles report our methods for screening, data abstraction, risk of bias assessment, and data analysis (13–17).

Panelists considered 3 servings per week as a realistic reduction in meat consumption (for example, moving from 7 to 4 servings, or 4 to 1 serving) on the basis of the average intake of 2 to 4 servings per week in North America and Western Europe (24–28). We therefore framed the evidence regarding the potential reduced risks associated with a decrease of 3 servings per week of both unprocessed red meat and processed meat.

We used GRADEpro software to formulate GRADE summary of findings tables for each PICO (population, intervention, control, and outcomes) question (29). The overall certainty of evidence was evaluated by using the GRADE approach (18). For estimates of risk with current levels of meat consumption, we used population estimates from the Emerging Risk Factors Collaboration study for cardiometabolic outcomes (30) and population estimates from GLOBOCAN for cancer outcomes (31). Using these resources, we based our estimates for cardiometabolic mortality and incidence outcomes on an average of 10.8 years of follow-up, whereas for cancer mortality and incidence, our estimates are for the overall lifetime risk.

Complementing existing GRADE standards and to determine whether we should rate up for a dose–response effect, we assessed the plausibility of a causal relationship between meat and adverse health outcomes by contrasting results from 2 bodies of evidence (7, 22): cohort studies specifically addressing red meat and processed meat intake, and cohort studies addressing dietary patterns associated with varying red meat and processed meat consumption. We hypothesized that if red meat and processed meat were indeed causally related to adverse health outcomes, we would find stronger associations in studies that specifically addressed red meat and processed meat intake versus studies addressing dietary patterns (7).

To address health-related values and preferences regarding red meat and processed meat, we included qualitative (such as interviews and focus groups) and quantitative (such as cross-sectional surveys) studies conducted in adults. We independently screened studies, abstracted data, and assessed risk of bias (17). We then synthesized the data into narrative themes and tabulated summaries, and again assessed the certainty of evidence by using the GRADE approach (18, 32).

To assist our 3 public panel members without health science backgrounds, the method's editor conducted electronic meetings with them before the guideline panel meetings to explain the systematic review results and the GRADE approach for assessing the certainty of evidence and for moving from evidence to recommendations. During the guideline panel meetings, the leads of each of the systematic reviews shared the summary data and certainty of evidence for each of our outcomes with the guideline panel, and the panel chair answered any questions as necessary.

Moving From Evidence to Recommendations

Before our final guideline panel meeting, we asked each panelist to complete a GRADE Evidence to Decision (EtD) framework. The purpose of EtD frameworks is to help panelists use the evidence summaries in a structured and transparent way to develop the final recommendations. In doing so, the panelists considered evidence summaries for health effects, values, and preferences as well as cost, acceptability, and feasibility of a recommendation to decrease meat consumption (33). During the final meeting, the panel reviewed the results of the EtD survey and considered the implications of those judgments for their recommendations.

RESULTS

Recommendation for Unprocessed Red Meat

For adults 18 years of age or older, we suggest continuing current unprocessed red meat consumption (weak recommendation, low-certainty evidence). Eleven of 14 panelists voted for continuation of current unprocessed red meat consumption, whereas 3 voted for a weak recommendation to reduce red meat consumption.

Recommendation for Processed Meat

For adults 18 years of age or older, we suggest continuing current processed meat consumption (weak recommendation, low-certainty evidence). Again, 11 of 14 panel members voted for a continuation of current processed meat consumption, and 3 voted for a weak recommendation to reduce processed meat consumption.

Evidence Summary for Harms and Benefits of Unprocessed Red Meat Consumption

For our review of randomized trials on harms and benefits (12 unique trials enrolling 54 000 participants), we found low- to very low-certainty evidence that diets lower in unprocessed red meat may have little or no effect on the risk for major cardiometabolic outcomes and cancer mortality and incidence (15). Dose–response meta-analysis results from 23 cohort studies with 1.4 million participants provided low- to very low-certainty evidence that decreasing unprocessed red meat intake may result in a very small reduction in the risk for major cardiovascular outcomes (cardiovascular disease, stroke, and myocardial infarction) and type 2 diabetes (range, 1 fewer to 6 fewer events per 1000 persons with a decrease of 3 servings/wk), with no statistically significant differences in 2 additional outcomes (all-cause mortality and cardiovascular mortality) (16). Dose–response meta-analysis results from 17 cohorts with 2.2 million participants provided low-certainty evidence that decreasing unprocessed red meat intake may result in a very small reduction of overall lifetime cancer mortality (7 fewer events per 1000 persons with a decrease of 3 servings/wk), with no statistically significant differences for 8 additional cancer outcomes (prostate cancer mortality and the incidence of overall, breast, colorectal, esophageal, gastric, pancreatic, and prostate cancer) (13). Similar to studies directly addressing red meat, cohort studies assessing dietary patterns (70 cohort studies with just over 6 million participants) provided mostly uncertain evidence for the risk for adverse cardiometabolic and cancer outcomes. Although statistically significant, low- to very low-certainty evidence indicates that adherence to dietary

Table 1. Causal Inference Assessment Based on Summary of Evidence for Statistically Significant Effects for Red Meat, Processed Meat, and Dietary Patterns

Outcome	Unprocessed Red Meat		Processed Meat		Dietary Patterns	
	Risk Difference	Certainty of Evidence	Risk Difference	Certainty of Evidence	Risk Difference	Certainty of Evidence
Cardiovascular mortality*†	4 fewer per 1000 persons (from 5 fewer to 4 fewer) over 10.8 y	Very low	4 fewer per 1000 persons (from 7 fewer to 1 fewer) over 10.8 y	Very low	6 fewer per 1000 persons (from 9 fewer to 2 fewer) over 10.8 y	Very low
Type 2 diabetes*†	6 fewer per 1000 persons (from 7 fewer to 4 fewer) over 10.8 y	Low	12 fewer per 1000 persons (from 16 fewer to 9 fewer) over 10.8 y	Very low	14 fewer per 1000 persons (from 18 fewer to 8 fewer) over 10.8 y	Very low
Overall cancer mortality†‡	7 fewer per 1000 persons (from 9 fewer to 6 fewer) over lifetime	Low	8 fewer per 1000 persons (from 12 fewer to 6 fewer) over lifetime	Low	12 fewer per 1000 persons (from 18 fewer to 4 fewer) over lifetime	Very low

* Based on reference 16.
† Based on reference 14.
‡ Based on reference 13.

patterns lower in red or processed meat is associated with a very small absolute risk reduction in 9 major cardiometabolic and cancer outcomes (range, 1 fewer to 18 fewer events per 1000 persons), with no statistically significant differences for 21 additional outcomes observed (14). The tables in the Supplement (available at Annals.org) show the GRADE summary of findings for all systematic reviews on the harms and benefits associated with red and processed meat.

We summarize people's attitudes on eating meat below in a section on values and preferences. In short, omnivores enjoy eating meat and consider it an essential component of a healthy diet. There is also evidence of possible health benefits of omnivorous versus vegetarian diets on such outcomes as muscle development and anemia (34, 35), but we did not systematically review this literature.

Evidence Summary for Harms and Benefits for Processed Meat

No randomized trials differed by a gradient of 1 serving/wk for our target outcomes (15). With respect to cohorts addressing adverse cardiometabolic outcomes (10 cohort studies with 778 000 participants providing dose–response meta-analysis), we found low- to very low-certainty evidence that decreased intake of processed meat was associated with a very small reduced risk for major morbid cardiometabolic outcomes, including all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, and type 2 diabetes (range, 1 fewer to 12 fewer events per 1000 persons with a decrease of 3 servings/wk), with no statistically significant difference in 1 additional outcome (cardiovascular disease) (16). For cohort studies addressing adverse cancer outcomes (31 cohorts with 3.5 million participants providing data for our dose–response analysis), we also found low- to very low-certainty evidence that a decreased intake of processed meat was associated with a very small absolute risk reduction in overall lifetime cancer mortality; prostate cancer mortality; and the incidence of esophageal, colorectal, and breast cancer (range, 1 fewer to 8 fewer events per 1000 persons with a decrease of 3 servings/wk), with no statistically significant differences in incidence or mortality for 12 additional cancer outcomes (colorectal, gastric, and pancreatic cancer mortality; overall, endometrial, gastric, hepatic, small intestinal, oral, ovarian, pancreatic, and prostate cancer incidence) (13). For cohort studies assessing dietary patterns (70 cohort studies with over 6 million participants), although statistically significant we found low- to very low-certainty evidence that adherence to dietary patterns lower in red or processed meat was associated with a very small absolute risk reduction in 9 major cardiometabolic and cancer outcomes (range, 1 fewer to 18 fewer events per 1000 persons), with no statistically significant differences for 21 additional outcomes observed (14). Again, we assessed the risk for adverse cardiometabolic outcomes on the basis of an average of 10.8 years follow-up, and adverse cancer outcomes over a lifetime.

In our assessment of causal inferences on unprocessed red meat and processed meat and adverse health outcomes, we found that the absolute effect estimates for red meat and processed meat intake (13, 16) were smaller than those from dietary pattern estimates (14), indicating that meat consumption is unlikely to be a causal factor of adverse health outcomes (Table 1). We anticipated that if unprocessed red meat or processed meat was indeed a causal factor in raising the risk for adverse outcomes, the observed association between unprocessed red and processed meat and adverse outcomes would be greater in studies directly addressing the lowest versus highest intake of unprocessed red or processed meat versus studies in which meat was only one component of a dietary pattern (7, 22). Using our findings, in our assessment of the certainty of evidence, we did not rate up for dose–response, given the potential for residual confounding (36). The tables in the Supplement (available at Annals.org) show the GRADE summary of findings.

Evidence Summary of Health-Related Values and Preferences for Meat

Our systematic review on health-related values and preferences yielded 54 articles from Australia, Canada, Europe, and the United States, including 41 quantitative and 13 qualitative studies (17). Omnivores reported enjoying eating meat, considered meat an essential component of a healthy diet, and often felt they had limited culinary skills to prepare satisfactory meals without meat. Participants tended to be unwilling to change their meat consumption. The certainty of evidence was low for "reasons for meat consumption" and low for "willingness to reduce meat consumption" in the face of undesirable health effects, owing to issues of risk of bias (for example, unvalidated surveys), imprecision (small number of participants in qualitative studies), and indirectness (failure to specifically ask about the health benefits that would motivate a reduction in red or processed meat consumption) (Table 2).

Rationale for Recommendations for Red Meat and Processed Meat

The rationale for our recommendation to continue rather than reduce consumption of unprocessed red meat or processed meat is based on the following factors. First, the certainty of evidence for the potential adverse health outcomes associated with meat consumption was low to very low (13–16), supported by the similar effect estimates for red meat and processed meat consumption from dietary pattern studies as from studies directly addressing red meat and processed meat intake (13, 14, 16). Second, there was a very small and often trivial absolute risk reduction based on a realistic decrease of 3 servings of red or processed meat per week. Third, if the very small exposure effect is true, given peoples' attachment to their meat-based diet (17), the associated risk reduction is not likely to provide sufficient motivation to reduce consumption of red meat or processed meat in fully informed individuals, and the weak, rather than strong, recommendation is based on the large variability in peoples' values and preferences related to meat (17). Finally, the panel focused exclusively on health outcomes associated with meat and did not consider animal welfare and environmental issues. Taken together, these observations warrant a weak recommendation to continue current levels of red meat and processed meat consumption.

Table 2. Summary of Findings for Health-related Values and Preferences*

Outcomes	Studies (Participants), *n (n)*	Certainty of Evidence	Plain-Language Summary
Reasons for meat consumption	38 quantitative studies (62 963)	Low (rated down for risk of bias and indirectness)	Most omnivores were highly attached to their meat. Men had a more positive attitude than women toward meat consumption. Elderly omnivores were generally concerned about health with respect to their food choices. All vegetarians/low meat consumers reported health as one of the main reasons for not eating meat.
	10 qualitative studies (419)	Low (rated down for risk of bias, indirectness, and imprecision)	Most omnivores are highly attached to their meat consumption. Elderly omnivores believed that aging is associated with a decline in food intake. For many vegetarians, health concerns were the primary motivation to stop eating meat.
Willingness to change meat consumption in the face of undesirable health effects	5 quantitative studies (8983)	Low (rated down for risk of bias and indirectness)	Most omnivores reported low willingness to reduce meat consumption. In general, participants reported an overall mistrust related to the given information. Many participants believed that the presence of additives used in the production process was the real health problem rather than red meat consumption itself. Many participants already reduced their meat consumption in the past and did not plan any further changes.
	4 qualitative studies (616)	Low (rated down for risk of bias, indirectness, and imprecision)	Most omnivores reported low willingness to reduce meat consumption. Omnivores were concerned with reducing meat consumption because they perceived meat as an important component of a healthy diet, they enjoyed eating meat, and they believed they needed protein and the enjoyment of eating meat. Some omnivores believed they only ate small quantities of meat and did not need to reduce it (more often this referred to reducing red meat than all types of meat), and some believed they already reduced their meat consumption in the past. Some omnivores believed that the consequences of meat consumption were trivial compared with other behaviors (e.g., smoking tobacco). Some omnivores did not trust the available scientific information.

* Based on reference 17.

Other Considerations

The panel judged that although for some people in some circumstances, issues of cost, acceptability, feasibility, and equity may be relevant, these issues were not major considerations in making their judgments. Considerations of animal welfare, and particularly of environmental impact, will certainly be important to some individuals; the latter might be of particular importance from a societal perspective (37–41). The panel, at the outset, decided that issues of animal welfare and potential environmental impact were outside the scope of this guideline.

DISCUSSION

We developed recommendations for unprocessed red meat and processed meat by following the NutriRECS guideline development process, which adheres to the Institute of Medicine and GRADE working group standards. On the basis of 4 systematic reviews assessing the harms and benefits associated with red meat and processed meat consumption and 1 systematic review assessing people's health-related values and preferences on meat consumption, we suggest that individuals continue their current consumption of both unprocessed red meat and processed meat (both weak recommendations, low-certainty evidence).

Our weak recommendation that people continue their current meat consumption highlights both the uncertainty associated with possible harmful effects and the very small magnitude of effect, even if the best estimates represent true causation, which we believe to be implausible. Despite our findings from our assessment of intake studies versus dietary pattern studies suggesting that unprocessed red meat and processed meat are unlikely to be causal factors for adverse health outcomes (13, 14, 16), this does not preclude the possibility that meat has a very small causal effect. Taken together with other potential causal factors (for example, such preservatives as sodium, nitrates, and nitrites) (42) among dietary patterns with very small effects, this may explain the larger reductions among dietary patterns high in red meat and processed meat (14). The guideline panel's assessment was based on the available evidence regarding values and preferences suggesting that the majority of individuals, when faced with a very small and uncertain absolute risk reduction in cardiometabolic and cancer outcomes, would choose to continue their current meat consumption. People considering a decrease in their meat consumption should be aware of this evidence.

Our analysis has several strengths. We conducted 5 separate rigorous systematic reviews addressing both evidence from randomized trials and observational studies regarding the impact of unprocessed red meat and processed meat on cardiovascular and cancer outcomes (13–16), and community values and preferences regarding red meat and processed meat consumption (17). By using the GRADE approach, our reviews explicitly addressed the uncertainty of the underlying evidence. We present results focusing on absolute estimates of effects associated with realistic decreases in meat consumption of 3 servings per week (**Tables 4** through **7** in the **Supplement**), and these estimates informed our recommendations. Our panel included nutrition content experts, methodologists, health care practitioners, and members of the public, and we minimized conflicts of interest by prescreening panel members for financial, intellectual, and personal conflicts of interest and providing a full account of potential competing interests.

Our guideline also has limitations. We considered issues of animal welfare and potential environmental impact to be outside the scope of our recommendations. These guidelines may therefore be of limited relevance to individuals for whom these issues are of major importance. Related to this, we took an individual rather than a societal perspective. Decision makers considering broader environmental issues may reasonably consider evidence regarding the possible contribution of meat consumption to global warming and suggest policies limiting meat consumption on that basis.

Regarding the uncertainty of the evidence, randomized trials were limited by the small differences in meat consumption between the intervention and control groups, whereas observational studies were limited in the accuracy of dietary measurement and possible residual confounding related both to aspects of diet other than red meat and processed meat consumption and nondietary confounders, making decisions regarding meat consumption particularly value- and preference-dependent. With respect to our review on dietary patterns, studies did not typically report data separately for red and processed meat. Moreover, although all dietary patterns discriminated between participants with low and high red and processed meat intake, other food and nutrient characteristics of dietary patterns varied widely across studies (14). Evidence was also limited in that we found information insufficient to conduct planned subgroup analyses regarding the method of meat preparation (for example, grilling versus boiling) in terms of possible carcinogenic compounds from grilling, such as polycyclic aromatic hydrocarbons and heterocyclic amines (43). Finally, our panel was not unanimous in its recommendation: Three of the 14 panel members favored a weak recommendation in favor of decreasing red meat consumption.

As noted in our introduction, other dietary guidelines and position statements suggest limiting consumption of red and processed meat because of the reported association with cancer (1, 2, 44–46). There are 3 major explanations for the discrepancy between these guidelines and ours. First, other guidelines have not used the GRADE approach for rating certainty of evidence that highlight the low or very low certainty of evidence to support the potential causal nature of the association between meat consumption and health outcomes. As a result, we are less convinced of meat consumption as a cause of cancer. Because of the likelihood of residual confounding (that is, confounding that exists after adjustment for known prognostic factors) the GRADE approach we used for assessing causation considers that, in the absence of a large effect or a compelling dose–response gradient, observational studies provide only low- or very low-certainty evidence for causation (47, 48). Second, even if one assumes causation, other guidelines have not calculated, or if calculated have not highlighted, the very small magnitude of the absolute adverse effects over long periods associated with meat consumption. Third, other guidelines have paid little or no attention to the reasons people eat meat, and the extent to which they would choose to reduce meat consumption given small and uncertain health benefits. Indeed, no prior dietary guideline has attended with care to evidence bearing on values and preferences, and in particular has not conducted a systematic review addressing the issue.

Nutritional guidelines are challenging because each potential source of evidence has substantial limitations. Randomized trials are limited by sample size, duration of follow-up, and the difficulties participants have in adhering to prescribed diets. These limitations make showing an intervention effect very challenging. Observational studies are limited in the inevitable residual confounding (unmeasured differences in prognosis that remain after adjusted analyses). These limitations in randomized trials and observational studies are evident in studies addressing meat consumption and health outcomes. Studies focusing on intermediate outcomes (such as cholesterol and triglyceride levels) have additional limitations, in that changes in biomarkers often fail to deliver the anticipated benefits in patient-important health outcomes. Therefore, our reviews focused only on those outcomes important to patients. Nutritional recommendations must, therefore, acknowledge the low-certainty evidence and avoid strong "just do it" recommendations that can, as evidenced by the many low-fat recommendations worldwide (9, 12, 49), be very misleading.

In terms of how to interpret our weak recommendation, it indicates that the panel believed that for the majority of individuals, the desirable effects (a potential lowered risk for cancer and cardiometabolic outcomes) associated with reducing meat consumption probably do not outweigh the undesirable effects (impact on quality of life, burden of modifying cultural and personal meal preparation and eating habits). The weak recommendation reflects the panel's awareness that values and preferences differ widely, and that as a result, a minority of fully informed individuals will choose to reduce meat consumption.

Our studies have implications for future research. Generating higher-certainty evidence regarding the impact of red meat and processed meat on health outcomes would be, were it possible, both desirable and important. It may not, however, be possible. Randomized trials will always face challenges with participants complying with diets that differ sufficiently in meat consumption, adhering to these diets for very long periods, and being available for follow-up over these long periods (12). These challenges are all the more formidable because results of observational studies may well represent the upper boundary of causal effects of meat consumption on adverse health outcomes, and the estimated effects are very small. Observational studies will continue to be limited by challenges of accurate measurement of diet, the precise and accurate measurement of known confounders (50), and the likelihood of residual confounding after adjusted analyses (13, 14, 16).

This assessment may be excessively pessimistic; indeed, we hope that is the case. What is certain is that generating higher-quality evidence regarding the magnitude of any causal effect of meat consumption on health outcomes will test the ingenuity and imagination of health science investigators.

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Appendix Table. Summary of Panelists' Potential Conflicts of Interest

Panel Member	Role	Financial Conflicts	Intellectual Conflicts	Other Relevant Disclosures
Pablo Alonso-Coello	Voting panel member; methodologist	No	No	Consumes 3 to 4 servings of both red or processed meat per week
Malgorzata Bala	Voting panel member; methodologist	No	No	Consumes 0.5 serving of both red or processed meat per week
Carlos Brotons	Voting panel member; primary care physician	No	No	Consumes 1 to 2 servings of both red or processed meat per week
Faiz Bhatia	Voting panel member; nonmedical public-partner	No	No	Consumes 2 to 3 servings of both red or processed meat per week; does not eat pork
Russell de Souza	Voting panel member; nutrition epidemiologist	No	No	Consumes 3 to 4 servings of red or processed meat per week
Susan Fairweather-Taitt	Voting panel member; human nutritionist	No	No	Consumes 2 to 3 servings of red meat per week and 1 to 2 servings of processed meat per month
Gordon Guyatt	Chair of panel; voting panel member; general internist; methodologist	No	No	Pescatarian; does not consume red or processed meat
Bradley Johnston	Guideline methods editor; voting panel member; methodologist	No	No	Consumes 1 to 2 servings of both red or processed meat per week
Catherine Marshall	Voting panel member; nonmedical public-partner; guideline consultant	No	No	Consumes 3 to 4 servings of both red or processed meat per week
Joerg Meerpohl	Voting panel member; pediatrician; methodologist	No	No	Consumes 3 to 5 servings of both red or processed meat per week
Chirag Patel	Voting panel member; bioinformatician	No	No	Consumes 0.5 serving of both red or processed meat per week
Patrick Stover	Voting panel member; basic nutrition scientist	No	No	Consumes 2 to 3 servings of both red or processed meat per week
Grzegorz Wójcik	Voting panel member; nonmedical public-partner	No	No	Consumes 3 to 4 servings of both red or processed meat per week
Dena Zeraatkar	Voting panel member; PhD student; methodologist	No	No	Consumes 6 to 7 servings of red meat per week

Annals of Internal Medicine

REVIEW

Health-Related Values and Preferences Regarding Meat Consumption

A Mixed-Methods Systematic Review

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Background: A person's meat consumption is often determined by their values and preferences.

Purpose: To identify and evaluate evidence addressing health-related values and preferences regarding meat consumption.

Data Sources: MEDLINE, EMBASE, Web of Science, Centre for Agriculture and Biosciences Abstracts, International System for Agricultural Science and Technology, and Food Science and Technology Abstracts were searched from inception to July 2018 without language restrictions.

Study Selection: Pairs of reviewers independently screened search results and included quantitative and qualitative studies reporting adults' health-related values and preferences regarding meat consumption.

Data Extraction: Pairs of reviewers independently extracted data and assessed risk of bias.

Data Synthesis: Data were synthesized into narrative form, and summaries were tabulated and certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Of 19 172 initial citations, 41 quantitative studies (38 addressed reasons for meat consumption and 5 addressed willingness to reduce meat consumption) and 13 qualitative studies (10 addressed reasons for meat consumption and 4 addressed willingness to reduce meat consumption) were eligible for inclusion. Thirteen studies reported that omnivores enjoy eating meat, 18 reported that these persons consider meat an essential component of a healthy diet, and 7 reported that they believe they lack the skills needed to prepare satisfactory meals without meat. Omnivores are generally unwilling to change their meat consumption. The certainty of evidence was low for both "reasons for meat consumption" and "willingness to reduce meat consumption in the face of undesirable health effects."

Limitation: Limited generalizability of findings to lower-income countries, low-certainty evidence for willingness to reduce meat consumption, and limited applicability to specific types of meat (red and processed meat).

Conclusion: Low-certainty evidence suggests that omnivores are attached to meat and are unwilling to change this behavior when faced with potentially undesirable health effects.

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* For members of the NutriRECS Working Group, see the **Appendix**, available at Annals.org.

People need to choose from a wide range of foods on a daily basis to meet their nutritional requirements (1). Consumption of different foods may yield both desirable and undesirable health effects (2). In light of recent studies showing an association between consumption of unprocessed red meat and processed meat and adverse health consequences, including increased risk for cancer (3), all-cause (4) and cardiovascular mortality (5), and stroke (6), dietary guidelines have generally endorsed limiting meat intake (7–9). However, these guidelines have neglected to identify and incorporate their target populations' values and preferences on meat consumption (10–13), which are major influences on what foods people eat (14–16). Understanding people's health-related values and preferences on meat consumption may improve the trustworthiness of dietary recommendations (17).

Therefore, we conducted a systematic review addressing people's health-related values and preferences on meat consumption. This review was done as part of Nutritional Recommendations and Accessible Evidence Summaries Composed of Systematic Reviews (NutriRECS), an initiative that aims to develop trustworthy nutritional recommendations (18). We performed 4 parallel systematic reviews addressing the following: experimental (19) and observational evidence (20) on the effect of red and processed meat on cancer and cardiometabolic outcomes, observational studies on the effect of red and processed meat on cancer outcomes (21), and the effect of varying red and processed meat dietary patterns on cardiometabolic and cancer outcomes (22). On the basis of these reviews, we developed recommendations for red and processed meat and health outcomes (23).

Methods

We registered the protocol with PROSPERO (CRD42018088854) (24) and adhered to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (25).

See also:

Related articles
Editorial comment

Web-Only
Supplement

Data Sources and Searches

We designed and conducted a search in MEDLINE (via PubMed), EMBASE (via Ovid), Web of Science (Institute for Scientific Information), Centre for Agriculture and Biosciences Abstracts (via CABI), International System for Agricultural Science and Technology, and Food Science and Technology Abstracts from inception to July 2018, and an updated search of MEDLINE and EMBASE through June 2019. We combined search terms related to meat consumption, consumer behavior, and values and preferences with the controlled vocabulary from each database. We did not restrict our search by publication status, language, or date of publication (Supplement Table 1, available at Annals.org). We also reviewed reference lists of the included articles and relevant systematic reviews.

Study Selection

We included studies exploring health-related values and preferences on meat consumption if more than 80% of participants were adults (aged ≥18 years). We considered quantitative (that is, cross-sectional design), qualitative (that is, participant interviews, focus groups), and mixed-methods studies. If studies did not report the participants' ages, we assumed that more than 80% were aged 18 years or older. We included only studies done in Europe, Australia, Canada, the United States, and New Zealand because we considered them to be homogeneous countries reflecting similar socioeconomic characteristics and values. We excluded studies that focused on meat alternatives (for example, cultured, in vitro, functional products, or genetically modified), types (for example, organic), quality (composition, sensory quality or palatability factors, or origin), safety (for example, food handling, chemical hazards or contamination, or storing or preserving), industry (for example, market research to inform or meet consumers' demands), consumption trends, and specific populations (for example, cancer survivors or pregnant women).

Before beginning each aspect of the review process, we conducted calibration exercises in which reviewers assessed the same articles and discussed any disagreement, leading to a clarification and a common understanding of criteria and process. After calibration, teams of 2 reviewers independently screened titles and abstracts of all retrieved references. Subsequently, teams of 2 reviewers independently reviewed the full text of articles deemed potentially eligible during title and abstract screening. In cases of disagreement, reviewers reached consensus with assistance from a third reviewer.

Data Extraction and Quality Assessment

We used 2 ad hoc data extraction forms for quantitative and qualitative research (Supplement Tables 2 and 3, available at Annals.org). After calibration exercises similar to the ones described earlier, teams of reviewers independently abstracted information from each study, including study identification, objectives or research questions, population characteristics, design and methods, risk of bias or methodological limitations, and findings. In cases of disagreement, reviewers reached consensus with assistance from a third reviewer.

For quantitative studies, we used an adapted version of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to assess risk of bias of studies on importance of outcomes or values and preferences (26). We considered 5 items grouped in 3 domains: selection of participants, missing outcome data, and measurement instruments' validity. We rated studies as having high risk of bias if the measurement instrument was not validated or was unclear, and as having moderate risk if it was validated but 2 or more items had high risk of bias. For qualitative studies, we used the Critical Appraisal Skills Programme qualitative research checklist, which consists of the following items: aim of the research, qualitative methodology appropriateness, research design, appropriate recruitment strategy, data collection, investigator and participants' relationship, ethical issues, data analysis, findings, and value of the research (27). We rated studies as having "serious methodological limitations" if more than 2 items had serious concerns and as having "moderate methodological limitations" if they had 2 items with serious concerns. Reviewers independently assessed risk of bias or methodological limitations. In cases of disagreement, reviewers reached consensus with assistance from a third reviewer.

Data Synthesis and Analysis

We synthesized results from studies using a 4-step approach that involved simultaneous quantitative and qualitative data collection and analysis. First, we selected 2 to 3 eligible articles per study design, identified key themes, and coded them in categories. Second, we used these categories to design ad hoc data extraction forms. Third, using an iterative process, we compared the key themes of the categories identified across all studies and developed analytic themes. Fourth, we applied the critical meta-narrative synthesis to transform the quantitative data into qualitative data (28, 29). For the last step, we used 4 systematic profiles and several critical questions to extract the identified narratives and to guide our synthesis of data (Supplement Table 4, available at Annals.org).

We synthesized and narratively reported the findings according to participants' meat consumption. We defined those who consumed meat as omnivores and analyzed them separately from persons who typically avoided meat, whom we defined as vegetarians, including lacto-ovo vegetarians or low-meat consumers.

For quantitative studies, we assessed the certainty of evidence for each review finding according to GRADE domains (risk of bias, imprecision, inconsistency, indirectness, and publication bias) (30, 31). For qualitative studies, we assessed the certainty of evidence according to GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative Research) domains (methodological limitations, relevance, coherence, and adequacy) (32). Findings were initially considered as high certainty and were downgraded (from high to very low) by 1 or more levels if serious or several minor or moderate concerns were detected in 1 or more domains.

Role of the Funding Source

The study received no funding.

RESULTS

The search yielded 19 172 articles, of which 456 were deemed potentially eligible on the basis of title and abstract. We excluded 402 studies (**Supplement Table 5**, available at Annals.org). After full-text appraisal, we included 41 quantitative (33–73) and 13 qualitative studies (74–86). The **Figure** presents the flow diagram with the search results and selection of studies.

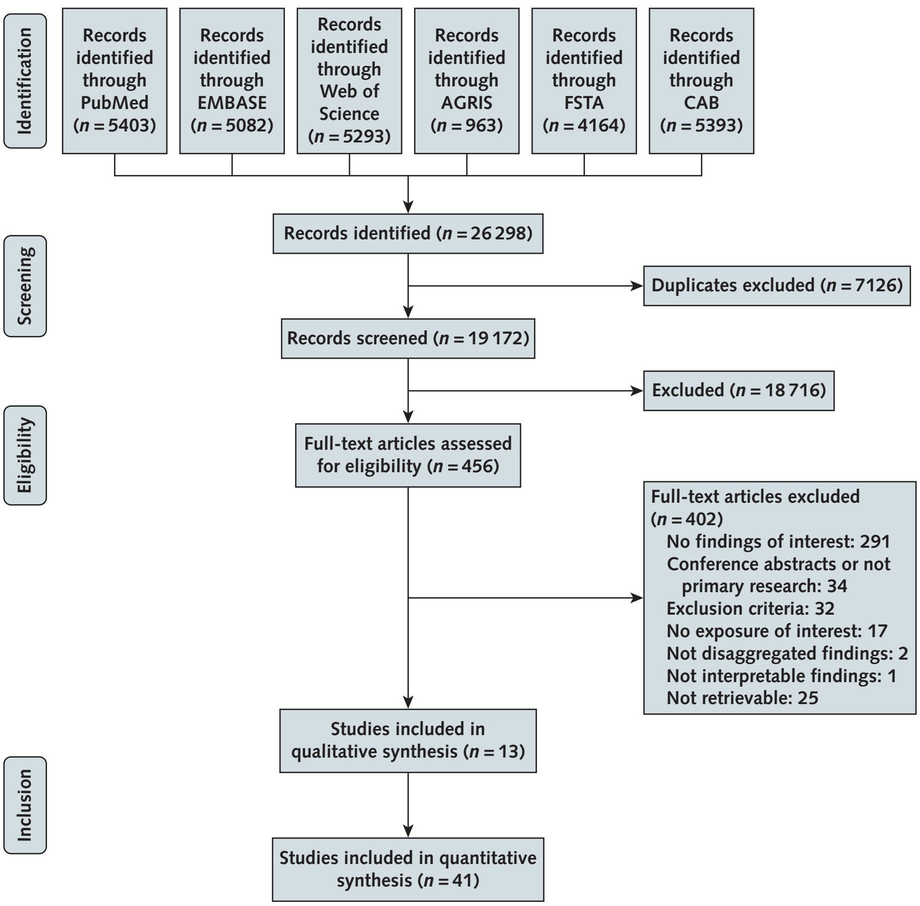
Study Characteristics

Table 1 presents the characteristics of the 54 included studies. Of the 41 quantitative studies, 21 were done in Europe, 11 in the United States, 7 in Australia, 1 in Canada, and 1 in New Zealand. Eighteen studies were done between 1988 and 2009, and 23 were done between 2011 and 2019. Of the 13 qualitative studies, 7 were done in Europe, 3 in the United States, and 3 in Australia. Six were done between 1991 and 2010, and 7 were done between 2011 and 2018. The number of participants ranged from 100 to 22 935 (aged 18 to >65 years) in the quantitative studies and from 19 to 460 (aged 16 to >75 years) in the qualitative studies. Among the included studies, 41 reported data on meat in general, 6 reported data on both meat in general and red meat, and 7 reported data on red meat only.

Findings

We identified 2 main themes: reasons for meat consumption (38 quantitative [62 963 participants] and 10 qualitative [419 participants]) and willingness to reduce meat consumption in the face of undesirable health effects (5 quantitative [8983 participants] and 4 qualitative [616 participants]). **Table 2** shows the main findings and their certainty (**Supplement Tables 6** and **7**, available at Annals.org). Of the quantitative studies, 23 of 38 (60.5%) reporting "reason for meat consumption" and 5 of 5 (100%) reporting "willingness to reduce meat consumption in the face of undesirable health effects" were assessed as having high risk of bias due to lack of validation of the measurement instruments (**Supplement Table 8**, available at Annals.org). Of the qual-

Figure. Evidence search and selection.



AGRIS = International System for Agricultural Science and Technology; CAB = Centre for Agriculture and Biosciences; FSTA = Food Science and Technology Abstracts.

Table 1. Characteristics of the Included Studies

Study, Year (Reference)	Primary Focus	Type of Study	Country	Data Collection Methods	Sampling	Participants, *n*	Female Sex, %	Type of Meat	Risk of Bias/ Methodological Limitations
Andrade et al, 2017 (53)	Self-perceived healthy eating attitudes after 10-y follow-up	Quantitative	Spain	FFQ and qualitative questions	NR	4572	56.6	Meat in general	High
The Realeat Survey Office, 1990 (34)	Survey on attitudes toward meat consumption	Quantitative	United Kingdom	Survey	NR	4162	NR	Meat in general	High
Beardsworth and Bryman, 1999 (35)	Changing patterns of meat consumption and meat avoidance	Quantitative	United Kingdom	Self-administered questionnaire	Convenience	350	80.3	Meat in general	High
Cordts et al, 2014 (36)	Effect of information on the negative attributes of meat consumption on demand for meat	Quantitative	Germany	Online survey	NR	590	48.1	Meat in general	High
Crnic, 2013 (37)	Prevalence of vegetarianism, learn about who and why persons become vegetarians	Quantitative	Slovenia	Survey	NR	800	NR	Meat in general	High
Decima Research, 2006 (44)	Survey to assess Canadians' level of awareness of the link between foods and disease	Quantitative	Canada	Computer-assisted telephone interview	NR	2029	52	Meat in general	High
Fessler et al, 2003 (43)	Meat consumption and reasons for meat avoidance	Quantitative	United States	Web-based survey	NR	945	65.5	Meat in general	High
Forestell et al, 2012 (39)	Dietary habits and lifestyle behaviors of vegetarians, pesco-vegetarians, semivegetarians, and flexitarians to omnivores	Quantitative	United States	NEO-FFI, FFQ, FN, VS, TFEQ/EI, EAT, FCQ, GEH questionnaires and follow-up online questionnaire	Convenience	240	100	Red meat	High
Gutkowska et al, 2018 (66)	Effect of consumer perception of beef values on consumer behavior toward this type of meat	Quantitative	Poland	Survey questionnaire	NR	1004	NR	Meat in general and beef	High
Haverstock and Forgays, 2012 (51)	Motivations for food choices	Quantitative	United States	Eating pattern questionnaire and FCQ	NR	247	85.4	Meat in general	High
Honkanen and Ottar Olsen, 2009 (58)	Russian food preferences: Fish lovers, fish haters, various food lovers, food indifferent, and red meat lovers	Quantitative	Russia	Face-to-face interview	Random	1081	50.2	Meat in general	Moderate
Izmirli and Phillips, 2011 (63)	Relationship between the consumption of animal products and attitudes toward animals	Quantitative	Australia	Online survey	Convenience	3433	NR	Meat in general	Moderate
Kayser et al, 2013 (54)	Attitudes toward meat; low-meat consumers differ from typical consumer behavior	Quantitative	Germany	Survey	Convenience	956	51.2	Meat in general	Low
Kovačićet al, 2016 (42)	Willingness to reduce meat consumption after the WHO report	Quantitative	Croatia	Survey	NR	169	60.4	Red meat	High
Latvala et al, 2012 (64)	Meat consumption patterns among Finnish consumers, considering both stated past changes and intended future changes	Quantitative	Finland	Online survey	NR	1623	50	Meat in general	High

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Table 1–Continued

Study, Year (Reference)	Primary Focus	Type of Study	Country	Data Collection Methods	Sampling	Participants, *n*	Female Sex, %	Type of Meat	Risk of Bias/ Methodological Limitations
Lea and Worsley, 2001 (65)	Meat consumption, beliefs about meat and nutrition, perceived difficulties with and benefits of vegetarian diets, personal values, number of vegetarian significant others, use in and trust of health/nutrition/food information sources, and demographic characteristics	Quantitative	Australia	Postal survey	Partly random and partly nonrandom	707	NR	Meat in general	Low
Lea and Worsley, 2002 (47)	Belief and demographic factors associated with the perception that meat is intrinsically unhealthy	Quantitative	Australia	Booklet with questionnaire	Partly random and partly nonrandom	698	56	Meat in general and red meat, specifically beef or lamb	Low
Lea and Worsley, 2003 (45)	Factors associated with the belief that vegetarian diets provide health benefits	Quantitative	Australia	Postal survey	Partly random and partly nonrandom	707	NR	Meat in general and red meat, specifically beef or lamb	Low
Lea and Worsley, 2003 (46)	Consumers' perceived benefits and barriers to consumption of a vegetarian diet	Quantitative	Australia	Postal survey	Random	601	56.8	Meat in general	Low
Lentz et al, 2018 (67)	To investigate New Zealand consumers' attitudes, motivations, and behaviors regarding meat consumption	Quantitative	New Zealand	Online survey	Random	841	50.4	Meat in general	Low
Love and Sulikowski, 2018 (68)	To measure implicit and explicit attitudes toward meat in men and women	Quantitative	Australia	Survey	NR	123	65	Meat in general	Low
McCarthy et al, 2003 (56)	Consumer perceptions toward beef and the influence of these perceptions on consumption	Quantitative	United Kingdom	Survey	Random	300	NR	Red meat (beef)	High
Mooney and Walbourn, 2001 (52)	Types of food college students actively avoid and some specific underlying sociocultural reasons for this rejection	Quantitative	United States	FAI, disgust and hedonic-restrained eating scales	Convenience	113	50.4	Meat in general	High
Mullee et al, 2017 (38)	Attitudes and beliefs about vegetarianism and meat consumption among the Belgian population	Quantitative	Belgium	Online questionnaire with multiple-choice questions	NR	2357	49.2	Meat in general	High
Neale et al, 1993 (62)	Study of the attitudes toward food, patterns of food consumption, and health of young vegetarian women	Quantitative	United Kingdom	Self-completed questionnaire with open and closed questions	Convenience	167	100	Meat in general	High
Neff et al, 2018 (69)	To learn about what is eaten in meatless meals, attitudes and perceptions toward meat reduction, and to build on and add depth to previous research on meat reduction behaviors in the United States and other high meat-consuming countries	Quantitative	United States	Web-based survey	Random	1112	51	Meat in general, red meat, and processed meat	High

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Table 1–Continued

Study, Year (Reference)	Primary Focus	Type of Study	Country	Data Collection Methods	Sampling	Participants, *n*	Female Sex, %	Type of Meat	Risk of Bias/ Methodological Limitations
Péneau et al, 2017 (70)	To investigate the existence of dilemmas between health and environmental motives when purchasing meat, fish, and dairy products; determining the sociodemographic profiles of persons reporting dilemmas; and comparing the dietary quality of these persons with those reporting no dilemma	Quantitative	France	Online survey	NR	22 935	75.2	Meat in general	Low
Phillips et al, 2010 (40)	Female and male students' attitudes toward use of animals	Quantitative	Australia	Online survey	Convenience	3444	55.4	Meat in general	Moderate
Piazza et al, 2015 (study 1a and 1b) (71)	To test whether the 4Ns would emerge as the lion's share of spontaneous justifications omnivores offer in defense of eating meat	Quantitative	United States	Survey	NR	295	55.2	Meat in general	Low
Pohjolainen et al, 2015 (59)	Barriers perceived by consumers to lowering their meat consumption levels and adopting a plant-based diet	Quantitative	Finland	Postal survey	Random	1890	56.3	Meat in general	Moderate
Richardson et al, 1993 (57)	Future events investigating meat eating and vegetarianism	Quantitative	United Kingdom	Postal survey	NR	1018	50	Meat in general	High
Ripoll and Panea, 2019 (72)	To identify the profiles of consumers of light lamb meat and the influence of involvement on consumers' attitudes, behaviors, beliefs, preferences, quality cues, and sensory perception regarding light lamb meat	Quantitative	Spain	Questionnaire	NR	100	54	Red meat (lamb)	Low
Rothgerber, 2014 (49)	Justifications that meat eaters use and how gender may be related to choice of meat-eating justification strategy and, secondarily, to diet	Quantitative	United States	MEJ and diet survey	NR	214	87	Meat in general	Moderate
Rothgerber, 2013 (48)	Reasons for the discrepancy and focuses on several dimensions that may demarcate semi- from strict vegetarians: belief in human–animal similarity and liking of and disgust toward meat	Quantitative	United States	Survey	NR	214	87	Meat in general	High
Rozin et al, 1997 (60)	Moralization and its consequences in the domain of vegetarianism	Quantitative	United States	Open-ended questionnaires/ratings of current attitudes/list of possible reasons to avoid meat	Convenience	104	66.3	Meat in general	High
Santos and Booth, 1996 (55)	The expectations that meat avoidance would follow a pattern of eliminating red meat, then white meat, and finally fish were tested	Quantitative	United Kingdom	Meat-avoidance questionnaire	NR	158	79.1	Meat in general	High

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Table 1–Continued

Study, Year (Reference)	Primary Focus	Type of Study	Country	Data Collection Methods	Sampling	Participants, *n*	Female Sex, %	Type of Meat	Risk of Bias/ Methodological Limitations
Spencer et al, 2007 (33)	Prevalence and correlates of U.S. medical students' self-identification as vegetarians	Quantitative	United States	Healthy Doc-Healthy Patient questionnaire and modified FFQ	NR	857	NR	Meat in general	High
Tobler et al, 2011 (41)	Consumers' beliefs about ecological food consumption and their willingness to adopt such behaviors and consumers' willingness to reduce meat consumption	Quantitative	Switzerland	Survey	Random	6189	52.4	Meat in general	High
Vainio, 2019 (73)	To explore why consumers of meat-based diets are not convinced by scientific evidence and to examine whether consumers of meat-based and plant-based diets attend to information in different ways	Quantitative	Finland	Online survey	NR	1279	55.7	Red meat	High
White et al, 1999 (61)	Prevalence and characteristics of vegetarians in the Women Physicians' Health Study and compared them with omnivores in the cohort	Quantitative	United States	Survey	Random	4362	NR	Meat in general	High
Woodward, 1988 (50)	Purchase of meat or meat products, in relation to other factors that may be gaining in influence	Quantitative	United Kingdom	Street intercept survey	Convenience	584	NR	Meat in general	High
Dowsett et al, 2018 (86)	To examine the meat–animal connection by presenting information about animals' intelligence and personality and details about the meat production process to induce cognitive dissonance and the negative affective state associated with it	Qualitative*	Australia	Open-ended responses	Convenience	460	59.6	Red meat (lamb)	No or very minor
Verbeke et al, 2010 (83)	European citizens' and consumers' attitudes and preferences regarding beef and pork	Qualitative*	Germany, Spain, France, and United Kingdom	Focus group discussion	Random	65	NR	Red meat (beef and pork)	Moderate
Beardsworth and Keil, 1991 (85)	Motivations, beliefs, and attitudes of practicing vegetarians and vegans	Qualitative	United Kingdom	Semistructured interview	Snowball sampling	76	NR	Meat in general	Moderate
Beardsworth and Keil, 1992 (81)	Cultural and sociological factors that influence patterns of food selection and food avoidance	Qualitative	United Kingdom	Interview	Snowball sampling	76	51	Meat in general	Moderate
Boyle, 2011 (82)	Eating patterns and vocabularies of motive for newly practicing, or developmental, vegetarians	Qualitative	United States	Semistructured interview	Snowball sampling	45	100	Meat in general and red meat	Serious

Continued on following page

Table 1–Continued

Study, Year (Reference)	Primary Focus	Type of Study	Country	Data Collection Methods	Sampling	Participants, *n*	Female Sex, %	Type of Meat	Risk of Bias/ Methodological Limitations
Brownie and Coutts, 2013 (76)	Perceptions and practices of older Australians in relation to a healthy diet	Qualitative	Australia	Focus group	Snowball sampling	29	79	Meat in general and red meat	No or very minor
Fox and Ward, 2008 (78)	Views of health in vegetarians	Qualitative	United Kingdom	Open-ended questions and follow-up interviews	Convenience	33	70	Meat in general	No or very minor
Graçca et al, 2014 (79)	Change habits toward less harmful choices	Qualitative	Portugal	Semistructured focus groups	Convenience	40	62.5	Meat in general	No or very minor
Guerin, 2014 (74)	Interpersonal interactions and conflicts between vegans and omnivores as the stage for deciphering underlying beliefs; omnivores construct ideas about veganism	Qualitative	United States	Interview	Snowball sampling	19	53	Meat in general	No or very minor
Hoek et al, 2017 (77)	Consumer perceptions, experiences, and attitudes toward health and environmental aspects in relation to foods	Qualitative	Australia	Semistructured virtual face-to-face interview	Quota sampling	29	56	Meat in general	No or very minor
Jabs et al, 1998 (75)	Factors involved in making dietary change and to develop theoretical understanding of the process	Qualitative	United States	In-depth, open-ended, semistructured interview	Snowball sampling	19	68	Meat in general	No or very minor
Kouris et al, 1991 (84)	Reasons for observed food habits and consumption of various foodstuffs	Qualitative	Greece	Interview	From electoral rolls	104	50	Meat in general	Moderate
Macdiarmid et al, 2016 (80)	The public's awareness of the environmental effect of food and its willingness to reduce meat consumption	Qualitative	United Kingdom	Focus groups and face-to-face and telephone interviews	Purposive sampling	87	54	Meat in general	No or very minor

4Ns = natural, normal, necessary, and nice; EAT = Eating Attitudes Test; FAI = Food Avoidance Inventory; FCQ = Food Choice Questionnaire; FFQ = food frequency questionnaire; FN = food neophobia; GEH = general eating habits; MEJ = meat-eating justification; NEO-FFI = NEO Five-Factor Inventory; NR = not reported; TFEQ/EI = Three-Factor Eating Questionnaire/eating inventory; VS = variety seeking; WHO = World Health Organization.
* Mixed-method study design, but only qualitative data were included.

itative studies, 1 of 12 (8.3%) reporting "reason for meat consumption" had serious methodological limitations due to lack of reporting of the investigator and participants' relationship, lack of detail about the data analysis process, and unclear reporting of findings (**Supplement Table 9**, available at Annals.org).

Reasons for Meat Consumption

Quantitative Studies

Nineteen studies reported on reasons for omnivores' meat consumption (35, 38, 42, 45–47, 56–59, 65–73). Most consumed meat because they enjoyed it (38, 46, 56–59, 65, 66, 71), they perceived it as being part of a complete and healthy diet (38, 42, 47, 56–59, 65, 66, 68–73), and they considered it part of their culture (58, 71). In addition, lack of food alternatives and lack of cooking skills to prepare a tasty dish without meat were often reported as barriers to reducing meat consumption (38, 45, 59, 65, 69).

Ten studies reported that, overall, men had a more positive attitude toward meat consumption than women (34–36, 38, 51, 52, 65, 66, 68, 69) and that they considered meat as part of a healthy diet and their culture (36, 38, 48, 69). Women were substantially more concerned about health consequences (34, 36, 38, 51, 65, 66) and more frequently avoided eating meat because of health and ethical concerns (34, 40, 52). Three studies reported inconsistent results on how elderly persons value meat consumption (51, 65, 66). In 2 studies, these persons noted potential undesirable health consequences (51) and the presence of diet-related diseases (66) as important reasons to reduce meat consumption. Another study, however, reported that older people were no more concerned about health than younger people, with both groups believing that meat was necessary for maintaining health (65).

Seventeen studies reported on reasons for avoiding meat among vegetarians or low-meat consumers. All participants reported health (for example, risk for cancer, heart diseases) as 1 of the main reasons for avoiding meat (37–39, 41, 43, 45, 46, 49–51, 54, 55, 60–63, 67). Other reasons for avoiding meat included animal welfare or environmental concerns (37, 43, 46, 51, 54, 55, 60–63, 67, 69).

The overall certainty of the evidence was rated as low because 20 of 38 (53%) studies proved to be at high risk of bias due to lack of validation of the measurement instruments and likely selectivity of study populations.

Qualitative Studies

Three studies reported on the reasons omnivores consume meat (74, 77, 83): enjoyment (74, 77), the perception that meat was part of a healthy diet (74, 77, 83), and the belief that it was part of their culture (77). Lack of food alternatives and cooking skills to prepare a tasty dish without meat were often mentioned as barriers to reducing consumption (74, 77).

Two studies reported that older people believe that aging is associated with a decline in food intake and thus a reduction in meat consumption, with a particular focus on red meat (76, 84). Many elderly participants viewed fish as a healthier alternative to red meat and were aiming to regularly incorporate fish into their diet (76). Most older people believed that people ate too much meat and that it was the cause of the increase

Table 2. Review Finding Table and Certainty of Evidence

Review Finding	Type of Research Evidence (Reference)	Certainty of Evidence
Reasons for meat consumption		
Most omnivores were highly attached to meat	Quantitative (35, 38, 42, 45–47, 56–59, 65–73)	Low: Risk of bias and indirectness
	Qualitative (74, 77, 83)	Low: Minor methodological limitations, minor relevance and adequacy concerns and limited information on the data analysis process
Men had a more positive attitude toward meat consumption than women	Quantitative (34–36, 38, 51, 52, 65, 66, 68, 69)	Low: Risk of bias and indirectness
Elderly omnivores were generally concerned about health in respect to their food choices	Quantitative (34, 40, 52)	Low: Risk of bias and indirectness
Elderly omnivores believed that aging is associated with a decline in food intake	Qualitative (76, 84)	Low: Minor methodological limitations, minor relevance and adequacy concerns and limited information on the data analysis process
All vegetarians or low-meat consumers reported health as 1 of the main reasons for not eating meat	Quantitative (37–39, 41, 43, 45, 46, 49, 50, 51, 54, 55, 60–63, 67)	Low: Risk of bias and indirectness
For many vegetarians, health concern was the primary motivation to stop eating meat	Qualitative (73–75, 78, 81, 85)	Low: Minor methodological limitations, minor relevance and adequacy concerns and limited information on the data analysis process
Willingness to change meat consumption in the face of undesirable health effects		
Most omnivores reported low willingness to reduce meat consumption	Quantitative (36, 42, 44, 53, 64)	Low: Risk of bias and indirectness
	Qualitative (77, 79, 80, 86)	Low: Minor methodological limitations, moderate concerns about relevance, minor adequacy concerns and limited information on the data analysis process

in the frequency of cancer, high blood pressure, diabetes, and heart disease (84).

Six studies explored reasons for avoiding meat among vegetarians and low-meat consumers and suggested that motivations for vegetarianism and meat avoidance vary and change over time (81, 85). Persons might initially avoid meat because of 1 motivation or concern (for example, health) and later integrate other beliefs or reasons to support their behavior (for example, animal welfare and environmental concerns) (78, 82). For many vegetarians, concern about health (for example, to avoid genetic health problems, such as heart disease) was the primary motivation to stop eating meat, but ethical concerns (for example, animal welfare) were also often reported as a major reason (73–75, 78, 81, 85).

The overall certainty of the evidence was rated as low because of methodological limitations due to lack of reporting of the investigator and participants' relationship (8 of 10 [80%] studies), limited information on the data analysis process and the likely selectivity of study populations (3 of 10 [30%] studies), and adequacy concerns (small number of participants).

Willingness to Change Meat Consumption in the Face of Health Concerns

Quantitative Studies

Five studies evaluated willingness to change meat consumption when faced with health concerns (36, 42, 44, 53, 64). One study provided participants with a World Health Organization report on the risk for colorectal cancer associated with red meat consumption (42). Another study provided participants with a fictional newspaper article reporting potentially undesirable health effects of meat consumption, including risk for stroke, heart attack, diabetes, and cancer (36). In both studies, most participants reported that they would not reduce meat consumption in the future, partially because they mistrusted the information provided (36, 42). In 1 study, many of the participants believed additives used in the production process were the real health problem rather than the meat consumption itself (42). Men attached greater importance to possible barriers for reducing meat consumption, considering it as part of a healthy diet and their culture, whereas most women expressed environmental concerns and animal welfare as motivations for reducing meat consumption (36).

Two additional studies asked participants what changes they would make to improve or maintain their health, and meat reduction was not among the most frequently reported; other dietary or lifestyle changes, such as exercise or eating more fruits and vegetables, were, among 10 options, selected more often (44, 53). One study that asked what future changes participants would make specifically regarding meat consumption found that most, especially men, had no intention of changing meat consumption (64). Many participants already believed that they had reduced their meat consumption in the past and did not plan any further reductions (64).

The overall certainty of the evidence was rated as low because all studies proved to be at high risk of bias due to lack of validation of the measurement instruments, and for indirectness because 3 of 5 (60%) studies did not inform participants about the undesirable health effects of meat consumption and the likely selectivity of populations.

Qualitative Studies

Four studies evaluated willingness to change meat consumption in the face of health concerns (77, 79, 80, 86). Two studies asked participants how they perceived the possibility of changing meat consumption habits to minimize undesirable health effects. Most participants reported that they would not reduce consumption (79, 80). One study asked participants their opinion about consumption of fewer animal-derived products and consuming more plant-based foods. Participants were concerned about reducing meat consumption because they perceived meat as an important component of a healthy diet (77). Reasons participants reported not desiring to change consumption included belief that they already ate small quantities and did not need to reduce further (this reason was more frequently cited when discussing reduction of red meat than other types of meat) (80), that they had already reduced meat consumption in the past (80), that the consequences of meat consumption were trivial compared with other behaviors (for example, smoking tobacco) (79, 80), and that they did not trust the available scientific information (79). In another study, participants were presented with nutritional information about lamb meat and then asked about their future meat consumption intentions. Most participants believed they would continue with their current consumption, with the most common reasons being the belief that they needed protein and the enjoyment of eating meat (86).

The overall certainty of the evidence was rated as low because of methodological limitations due to lack of reporting of the investigator and participants' relationship (3 of 4 [75%] studies), because of concerns in relevance due to not informing participants about the undesirable health effects of meat consumption and the likely selectivity of populations (4 of 4 [100%] studies), and because of adequacy concerns (small number of participants).

DISCUSSION

Key findings from our systematic review include the reasons omnivores consume meat: They consider meat an essential component of a healthy diet, they enjoy eating meat, they feel that meat is a part of their traditions, and they believe they lack the knowledge and cooking skills to prepare an adequate meal without meat. Study participants' willingness to change meat consumption in response to health concerns is generally low. Our findings were consistent across the 2 bodies of evidence (quantitative and qualitative research). The overall certainty of evidence was low, predominantly because of risk of bias or methodological limitations, lack of validation of the questionnaires, issues of indirectness or relevance, and issues of adequacy.

Strengths of this review include explicit eligibility criteria, an extensive search, and duplicate assessment of eligibility and risk of bias or methodological limitations. The use of 2 complementary bodies of evidence (mixed-methods) and the use of the GRADE approach to assess the certainty of the evidence allowed greater confidence in the interpretation of results (87).

This study also has limitations. We included studies done only in Europe, Australia, Canada, the United States, and New Zealand, reflecting food values and preferences of populations living in high-income countries. Therefore, we cannot generalize these findings to other populations. In addition, the studies reporting willingness to reduce meat consumption in the face of health concerns did not provide participants with sufficient information about the certainty of the evidence, nor about the effect meat consumption has on health. Studies failed to consistently report participants' socioeconomic status, educational level, and religious beliefs, precluding exploration of the effect of these characteristics on dietary values and preferences. Another limitation is related to the applicability of our results to the NutriRECS red meat recommendation because most of the included studies do not focus on red or processed meat, but rather meat in general. Finally, our systematic review focuses only on the influence of health effects and does not address other reasons that influence meat consumption, such as animal welfare and environmental concerns.

We performed a search of MEDLINE through June 2019 to identify relevant previous reviews. More recent study results are consistent with those of earlier studies: During the past 2 decades, omnivores have remained highly attached to meat, and willingness to change consumption has remained generally low (88, 89). Regarding prior systematic reviews, 1 review evaluated omnivores' perceptions and behaviors regarding protein consumption in general and not red meat in particular (88). That systematic review concluded that omnivores' willingness to change consumption in terms of reducing or substituting meat (for example, by eating insects or meat substitutes) is low. One recent narrative review evaluated psychological aspects of meat consumption in general and concluded that eating meat is entrenched in Western culture (89), which is consistent with our findings. Other existing narrative reviews explored motivations for consuming or avoiding meat and suggested, in keeping with our results, that the reasons for consuming meat are complex and diverse and may vary according to age and sex (90, 91).

Our findings have direct implications for stakeholders making both public health and clinical nutritional recommendations. Our results highlight the inappropriateness of assuming that informed persons would choose to reduce meat consumption on the basis of small and distant health benefits, particularly if the benefits are uncertain (10, 92). The results suggest that it may be similarly inappropriate to assume that informed persons would choose to modify their preferred diet in other ways on the basis of small and uncertain health benefits. However, studies generally did not present the possible adverse health consequences of meat consumption in ways that captured the current evidence and its uncertainty. Optimal insight into people's values and preferences, and in particular into willingness to reduce meat consumption, requires such a presentation. Subsequent research should address this issue.

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Annals of Internal Medicine

REVIEW

Reduction of Red and Processed Meat Intake and Cancer Mortality and Incidence

A Systematic Review and Meta-analysis of Cohort Studies

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Background: Cancer incidence has continuously increased over the past few centuries and represents a major health burden worldwide.

Purpose: To evaluate the possible causal relationship between intake of red and processed meat and cancer mortality and incidence.

Data Sources: Embase, Cochrane Central Register of Controlled Trials, Web of Science, CINAHL, and ProQuest from inception until July 2018 and MEDLINE from inception until April 2019 without language restrictions.

Study Selection: Cohort studies that included more than 1000 adults and reported the association between consumption of unprocessed red and processed meat and cancer mortality and incidence.

Data Extraction: Teams of 2 reviewers independently extracted data and assessed risk of bias; 1 reviewer evaluated the certainty of evidence, which was confirmed or revised by the senior reviewer.

Data Synthesis: Of 118 articles (56 cohorts) with more than 6 million participants, 73 articles were eligible for the dose-response meta-analyses, 30 addressed cancer mortality, and 80 reported cancer incidence. Low-certainty evidence suggested that an intake reduction of 3 servings of unprocessed meat per week was associated with a very small reduction in overall cancer mortality over a lifetime. Evidence of low to very low certainty suggested that each intake reduction of 3 servings of processed meat per week was associated with very small decreases in overall cancer mortality over a lifetime; prostate cancer mortality; and incidence of esophageal, colorectal, and breast cancer.

Limitation: Limited causal inferences due to residual confounding in observational studies, risk of bias due to limitations in diet assessment and adjustment for confounders, recall bias in dietary assessment, and insufficient data for planned subgroup analyses.

Conclusion: The possible absolute effects of red and processed meat consumption on cancer mortality and incidence are very small, and the certainty of evidence is low to very low.

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Cancer is the leading cause of morbidity and mortality worldwide (1). Authorities have postulated that diet—in particular, consumption of red meat and processed meat—may be a determinant of cancer risk (2). Many primary studies have reported an association between red and processed meat consumption and cancer mortality and incidence (3–12). In response, the International Agency for Research on Cancer classified consumption of processed meat as carcinogenic to humans on the basis of evidence about colorectal cancer (group 1) and classified that of red meat as probably carcinogenic on the basis of evidence about colorectal, pancreatic, and prostate cancer (group 2A) (13). The World Cancer Research Fund and American Institute for Cancer Research advise limiting red meat consumption to no more than about 3 portions per week (<500 g weekly) and consuming very little, if any, processed meat (14).

Many systematic reviews have supported the association between red or processed meat and cancer mortality or incidence. However, most have focused on specific types of cancer and have not provided a comprehensive overview (15–18). Some have limited their analyses to comparing extreme exposure categories rather than conducting the optimal dose–response analysis that uses the entirety of data from cohort studies (19–22). Few have formally rated the certainty of evidence supporting the inference that red and processed meat consumption is causally related to cancer.

We did this systematic review addressing the possible effect of red and processed meat on cancer as part of NutriRECS (Nutritional Recommendations and accessible Evidence summaries Composed of Systematic reviews), the goal of which is to develop trustworthy guideline recommendations on nutrition (23). We did 5 parallel systematic reviews (24–27) and developed the guideline for red meat and health outcomes (28). This current review focuses on observational studies addressing cancer outcomes; we summarized re-

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sults from cohort studies by conducting dose–response meta-analyses and used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (29) to rate the certainty of evidence supporting the absolute effects of meat consumption on cancer incidence and mortality.

METHODS

The protocol for this review was registered in PROSPERO (CRD42017074074) in August 2017.

Data Sources and Searches

We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science, CINAHL, and ProQuest from inception to July 2018 and updated our MEDLINE search to April 2019. An experienced librarian developed a search strategy (Supplement Table 1, available at Annals.org). We checked the reference lists of published systematic reviews to identify additional relevant studies.

Study Selection

We included cohort studies with more than 1000 participants aged 18 years or older that reported effect estimates and corresponding 95% CIs. Studies had to report associations between red or processed meat consumption and mortality from or incidence of any of the following: cancer overall, gastrointestinal cancer (oral, esophageal, gastric, small intestinal, colorectal, hepatic, pancreatic, or gallbladder), female cancer types (ovarian, endometrial, or breast), or prostate cancer. We applied no restrictions on language or publication status.

We excluded studies if they reported only on a specific type of red meat (such as beef or lamb) or a specific type of processed meat (such as hot dogs). Studies were excluded if more than 20% of the sample was pregnant or had a major chronic illness at baseline, including cancer, and participants without these conditions were not reported separately. We also excluded studies that asked participants to recall their diet at a previous point in their life (for example, if adults recalled their diet during adolescence and childhood or middle-aged adults recalled their diet during young adulthood).

After calibration exercises, teams of 2 reviewers independently screened titles and abstracts. Articles that either reviewer judged as potentially eligible then had full-text screening. Raters resolved disagreements by discussion or, if necessary, with a third reviewer. If authors published multiple reports from the same cohort, we selected the study with the longest follow-up.

Data Extraction and Quality Assessment

We did calibration exercises, and teams of 2 independent reviewers extracted data and addressed risk of bias, resolving discrepancies by discussion or consultation with a third reviewer. We used a predefined extraction form in Excel (Microsoft) for each study and included cohort name, country where the study was done, number of eligible participants at baseline, age and sex of participants, type of red and processed meat, amount of intake, type of cancer, years of follow-up, number of participants analyzed within exposure category, number of person-years, number of cases, and effect estimates and 95% CIs. If a study reported more than 1 adjusted effect estimate, we selected the most adjusted value.

We classified red and processed meat into the following 3 types: unprocessed red meat; processed meat; and mixed unprocessed red meat, processed meat, and unspecified red meat. Meat from mammals was classified as red meat. Processed meat was defined as meat that has been preserved by smoking, curing, salting, or adding preservatives (for example, hot dogs, charcuterie, sausage, ham, and cold-cut deli meats). Red meat was classified as unprocessed when authors explicitly described it as such and stated that processed red meat was not included. Without such a statement, we classified the exposure as an unspecified type of red meat.

To address risk of bias, we used a modified version of the Clinical Advances through Research and Information Technology risk of bias tool (30). After resolving discrepancies, we classified items rated "definitely low" and "probably low" as having low risk of bias and those rated "probably high" and "definitely high" as having high risk of bias. Through consultation with research methodologists and nutrition researchers, we developed criteria to evaluate each item (Supplement Table 2, available at Annals.org). We regarded all items as equally important and rated a study as having high risk of bias if 2 or more items had high risk of bias. This threshold, although somewhat arbitrary, represents a compromise between excessive stringency and problematic leniency.

Data Synthesis and Analysis

Using dose–response meta-analysis, as proposed by Greenland and Longnecker (31) and Orsini and colleagues (32), we calculated pooled relative risks (RRs) and 95% CIs for the effect of an intake reduction of 3 servings of red or processed meat per week on cancer mortality or incidence. We chose 3 servings per week because, on the basis of the average intake of red and processed meat (approximately 2 to 4 servings of each type per week [33]), this is likely to be a maximal realistic reduction in mean for most persons. For a study to be included in dose–response meta-analyses, it needed to state the quantity of intake, number of cases, number of person-years or participants, effect estimates, and 95% CIs across exposure categories or sufficient information to calculate these details. When quantity of exposure was reported as a range, the midpoint of the upper and lower boundaries was assigned as the exposure value. When the category was open-ended, we assumed that the interval between boundaries was the same as that of the adjacent category. When authors did not report the number of person-years or participants included in a specific category but instead reported exposure by quantile, such as quartile or quintile, we assumed that numbers of person-years or participants were approximately equal in each category. We preferred to use number of person-years but used number of participants in the absence of person-years. When studies used different units (such as servings and times) to report the exposure, we converted them into grams per day using standard conversions from the Food Standards Agency and other documents (34–41). One serving was 120 g for unprocessed red meat, 50 g for processed meat, and 100 g for mixed unprocessed red and processed meat. When studies used grams per 1000 kcal as the unit, we also converted into grams per day according to the average energy intake of the population included in the study. Studies reporting only risk estimates per unit increase in exposure (such as per 50 g/d) were also included in the dose–response meta-analysis; we calculated a regression coefficient based on the relative effect reported and meta-analyzed these regression coefficients with effects obtained from other studies (31). We examined the nonlinear association between red meat intake and cancer risk for analyses that included 5 or more studies by using restricted cubic splines with knots at 10%, 50%, and 90% and a Wald-type test, which tests the null hypothesis that the regression coefficient of the second spline is equal to 0. We presented an RR from the nonlinear model when we observed a statistically significant nonlinear association. The Appendix (available at Annals.org) gives details of the dose–response meta-analysis.

We also did meta-analyses comparing the lowest versus the highest category of intake using the Hartung–Knapp random-effects model (42) and presented DerSimonian–Laird random effects as a sensitivity analysis (43).

For both dose–response and lowest-versus-highest meta-analyses, we used meta-regression analysis to investigate whether the summary estimates are robust to risk of bias. Heterogeneity among studies was examined by inspecting forest plots for overlapping CIs, I^2 statistics, and Q statistics. Publication bias was assessed using the Egger test in meta-analyses with more than 10 studies. All statistical analyses were done using R software, version 3.5.1 (R Foundation).

Because we have greater confidence in results from dose–response meta-analysis, we based our inferences primarily on these results and preferentially present them in the included summary-of-findings tables. For outcomes with no studies eligible for dose–response meta-analysis, we present results from lowest-versus-highest meta-analyses.

Certainty of Evidence

We used GRADE to assess the certainty of evidence by rating each cancer outcome as high, moderate, low, or very low. One reviewer evaluated certainty of evidence, which was confirmed or revised by the senior reviewer. Evidence from observational studies begins at low certainty and may be increased to moderate or high certainty when a large effect is observed, when all plausible biases would work in a direction opposite to the observed effect, or when a dose–response gradient is present. Observational studies may be downgraded to very low certainty on the basis of risk of bias, inconsistency, indirectness, imprecision, or publication bias (44). We considered increasing certainty for dose response but ultimately decided not to do so because quantity of red meat consumption may track with other dietary and behavioral factors. This decision was influenced by the results of a parallel systematic review showing that the association between dietary patterns and cancer is similar in magnitude to that between red meat and cancer (26). We calculated the risk difference by multiplying the pooled RR reduction from the meta-analysis by the population risk for cancer incidence and mortality. Global cancer statistics (GLOBOCAN) produced by the International Agency for Research on Cancer (45) provided the cumulative risk for developing or dying of cancer before age 75 years using age-specific incidence and mortality rates based on 184 national data registries; we used these rates to estimate the population risk for cancer (lifetime risk). When the RR calculated from studies at low risk of bias differed from that from studies at high risk of bias, determined on the basis of a statistically significant test of interaction, we used the former rather than that from all eligible studies (46).

Role of the Funding Source

This study received no external funding or other support.

RESULTS

Study Selection

Of the 22 882 articles identified through database searches and other sources, 9724 were duplicates. We assessed full texts of 1505 studies for eligibility, of which 118 articles reporting on 56 cohorts with 6.1 million participants were eligible. Evidence for the dose–response meta-analyses came from 73 articles (40 cohorts), of which 18 (17 cohorts) addressed consumption of unprocessed red meat, 56 (31 cohorts) processed red meat, and 60 (30 cohorts) mixed unprocessed red and processed meat (Appendix Figure 1, available at Annals.org).

Study Characteristics

We found numerous reports addressing cancer mortality: 19 on cancer overall, 7 on gastric cancer, 8 on colorectal cancer, 3 on pancreatic cancer, 1 on ovarian cancer, 6 on breast cancer, and 11 on prostate cancer. We also found articles that reported cancer incidence: 5 on cancer overall, 2 on oral cancer, 3 on esophageal cancer, 8 on gastric cancer, 1 on small intestinal cancer, 35 on colorectal cancer, 2 on hepatic cancer, 15 on pancreatic cancer, 2 on ovarian cancer, 5 on endometrial cancer, 18 on breast cancer, and 12 on prostate cancer. Sample size in cohort studies varied from 1904 to 1 102 308 participants, followed from 3 to 34 years, and age at baseline from 36.4 to 77 years (Supplement Table 3, available at Annals.org). A total of 99 articles reported funding from public or private nonprofit organizations. Of the eligible reports addressing cancer mortality, the following proportions had high risk of bias due to lack of repeated measurement of diet and lack of adjustment for important con-

Table 1. Summary of Findings for Reduction of Unprocessed Red Meat Intake (3 Servings per Week) and Cancer Mortality and Incidence

Outcome	Studies, *n*	Participants, *n*	Follow-up, *y*	Relative Risk (95% CI)	Estimated Lifetime Population Risk per 1000 Persons*	Risk Difference per 1000 Persons (95% CI)	Certainty of Evidence (GRADE)	Plain-Language Summary
Overall cancer mortality	7	875 291	5–28	0.93 (0.91–0.94)	105	7 fewer (9 fewer to 6 fewer)	Low (due to observational design)	Reduction of unprocessed red meat intake may result in a very small decrease in cancer mortality.
Prostate cancer mortality†	1	Unknown‡	14	1.56 (0.93–2.63)	6	3 more (0 fewer to 10 more)	Very low (due to observational design, imprecision)§	We are uncertain of the effects of unprocessed red meat on prostate cancer mortality.
Overall cancer incidence	2	71 858	5–9	0.93 (0.83–1.04)	185	13 fewer (31 fewer to 7 more)	Very low (due to observational design, imprecision)‖	We are uncertain of the effects of unprocessed red meat on overall cancer incidence.
Esophageal cancer incidence	1	472 538	Mean, 11	1.00 (0.72–1.39)	7	0 fewer (2 fewer to 3 more)	Very low (due to observational design, risk of bias)¶	We are uncertain of the effects of unprocessed red meat on esophageal cancer incidence.
Gastric cancer incidence	1	8024	Mean, 6.7	0.86 (0.62–1.19)	14	2 fewer (5 fewer to 3 more)	Very low (due to observational design, risk of bias)**	We are uncertain of the effects of unprocessed red meat on gastric cancer incidence.
Colorectal cancer incidence	5	322 502	3–15	1.00 (0.92–1.09)	20	0 fewer (2 fewer to 2 more)	Low (due to observational design)	Reduction of unprocessed red meat intake may have little or no effect on colorectal cancer incidence.
Pancreatic cancer incidence	3	932 132	11–17	0.99 (0.98–1.01)	5	0 fewer (0 fewer to 0 fewer)	Low (due to observational design)	Reduction of unprocessed red meat intake may have little or no effect on pancreatic cancer incidence.
Breast cancer incidence	3	334 053	5–9	0.88 (0.72–1.06)	46	6 fewer (13 fewer to 3 more)	Low (due to observational design)	Reduction of unprocessed red meat intake may have little or no effect on breast cancer incidence.
Prostate cancer incidence	2	132 913	6–8	1.02 (0.95–1.10)	38	1 more (2 fewer to 4 more)	Low (due to observational design)	Reduction of unprocessed red meat intake may have little or no effect on prostate cancer incidence.

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* Lifetime cumulative risk from GLOBOCAN 2012 (45).
† Data are from highest-vs.-lowest meta-analysis.
‡ This study does not report the number of participants in the highest and lowest categories of intake.
§ CI around absolute effect includes both no effect and important harm.
‖ CI around absolute effect includes both important benefit and no effect.
¶ Study is at high risk of bias because diet was assessed only at baseline for 11 y of follow-up and because there was no adjustment for family history of cancer or alcohol consumption.
** Study is at high risk of bias because diet was assessed without validation and because there was no adjustment for family history of cancer.

founding variables: 9 of 19 on cancer overall, 6 of 7 on gastric cancer, 8 of 8 on colorectal cancer, 2 of 3 on pancreatic cancer, 1 of 1 on ovarian cancer, 6 of 6 on breast cancer, and 7 of 11 on prostate cancer. Of the eligible reports addressing cancer incidence, the following proportions had high risk of bias for the same reasons: 3 of 5 on cancer overall, 1 of 2 on oral cancer, 3 of 3 on esophageal cancer, 8 of 8 on gastric cancer, 0 of 1 on small intestinal cancer, 16 of 35 on colorectal cancer, 1 of 2 on hepatic cancer, 11 of 15 on pancreatic cancer, 1 of 2 on ovarian cancer, 5 of 5 on endometrial cancer, 5 of 18 on breast cancer, and 5 of 12 on prostate cancer (Supplement Table 4, available at Annals.org).

Dose–Response Meta-analysis of a Reduction in Unprocessed Red Meat Intake of 3 Servings per Week and Cancer Mortality and Incidence

An intake reduction in unprocessed red meat of 3 servings per week was associated with a very small decrease in overall cancer mortality. This reduction was not statistically significantly associated with overall incidence of cancer or incidence of esophageal, gastric, colorectal, pancreatic, breast, or prostate cancer. Data on prostate cancer mortality were available only for lowest-versus-highest meta-analysis, and no statistically significant association was found (Table 1). We did not find statistically significant differences between studies at lower and higher risk of bias (Supplement Table 5, available at Annals.org).

Overall cancer mortality and incidence of colorectal, pancreatic, breast, and prostate cancer had low-certainty evidence because of observational study design. The certainty of evidence was very low for prostate cancer mortality and overall cancer incidence because of observational design and imprecision and for esophageal and gastric cancer incidence because of observational design and risk of bias.

Dose–Response Meta-analysis of a Reduction in Processed Meat Intake of 3 Servings per Week and Cancer Mortality and Incidence

An intake reduction of 3 servings of processed meat per week was associated with very small reductions in overall cancer mortality and prostate cancer mortality but not with gastric or colorectal cancer mortality. The same intake reduction was also associated with very small decreases in incidence of esophageal and colorectal cancer but not with overall cancer incidence or incidence of oral, gastric, small intestinal, hepatic, pancreatic, endometrial, or prostate cancer. Only lowest-versus-highest meta-analyses were available for pancreatic cancer mortality and ovarian cancer incidence, and no statistically significant associations were found (Table 2). We observed a statistically significant interaction with risk of bias for overall cancer mortality; therefore, we present results only for studies at low risk of bias (Supplement Table 6, available at Annals.org). We found a nonlinear association between processed meat intake and breast cancer incidence (P = 0.015), and an intake reduction from 3 to 0 servings per week was associated with reduced risk for breast cancer incidence with low certainty. The RR estimates in the Figure are for processed meat consumption: Risk increased only marginally with intake greater than 3 servings per week.

The certainty of evidence was downgraded because of observational study design for overall cancer mortality; gastric and prostate cancer mortality; and incidence of small intestinal, colorectal, pancreatic, ovarian, breast, and prostate cancer. The certainty of evidence was very low for overall cancer incidence because of observational design and imprecision; it was also very low for colorectal and pancreatic cancer mortality and for incidence of oral, esophageal, gastric, hepatic, and endometrial cancer because of observational design and risk of bias (Table 2).

Dose–Response Meta-analysis of a Reduction in Mixed Unprocessed Red and Processed Meat Intake of 3 Servings per Week and Cancer Mortality and Incidence

An intake reduction of 3 servings of mixed unprocessed red and processed meat per week was associated with a very small reduction in overall cancer mortality but not with colorectal or prostate cancer mortality. Each intake reduction of 3 servings per week in mixed unprocessed red and processed meat was associated with a very small decrease in colorectal cancer incidence but not with overall cancer incidence or incidence of oral, esophageal, gastric, small intestinal, hepatic, pancreatic, endometrial, or prostate cancer. Only lowest-versus-highest meta-analyses were available for gastric, pancreatic, ovarian, and breast cancer mortality and ovarian cancer incidence, and no statistically significant associations were found (Supplement Table 7, available at Annals.org). We found no statistically significant differences between studies at lower and higher risk of bias (Supplement Table 8, available at Annals.org). We found a nonlinear association between intake of mixed unprocessed red and processed meat and breast cancer incidence (P = 0.018), and an intake reduction from 3 to 0 servings per week was associated with reduced risk for breast cancer incidence (Appendix Figure 2, available at Annals.org).

The certainty of evidence was downgraded because of observational study design for overall cancer mortality; pancreatic cancer mortality; and incidence of small intestinal, colorectal, hepatic, pancreatic, ovarian, breast, and prostate cancer. Overall cancer incidence had very-low-certainty evidence because of observational design and imprecision. Certainty of evidence was also very low for gastric, colorectal, ovarian, breast, and prostate cancer mortality; overall cancer incidence; and incidence of oral, esophageal, gastric, and endometrial cancer because of observational design and risk of bias (Supplement Table 7).

Lowest-Versus-Highest Meta-analysis of Red Meat Intake and Cancer Mortality and Incidence

We found that lowest-versus-highest meta-analyses of red meat intake and cancer mortality and incidence were similar to the dose–response meta-analysis (Supplement Tables 9 to 11, available at Annals.org).

Discussion

This systematic review of observational studies documented low-certainty evidence that an intake reduction of 3 servings per week may result in 7 fewer deaths from cancer overall per 1000 persons for unprocessed red meat (Table 1) and 8 fewer deaths per 1000 persons for processed meat (Table 2). We also found evidence of low or very low certainty for very small reductions in prostate cancer mortality and incidence of esophageal, colorectal, and breast cancer with reduced consumption of processed meat by 3 servings per week (Table 2). We found evidence of low or very low certainty for very small reductions in overall cancer mortality, colorectal cancer incidence, and breast cancer incidence with a reduction in consumption of mixed unprocessed red and processed meat (Supplement Table 7). We did not find statistically significant associations between either exposure and mortality from or incidence of other cancer types.

Our systematic review has many strengths. We rated the certainty of evidence for red and processed meat intake and cancer risk from the entire body of evidence using GRADE guidance, thus highlighting the remaining uncertainty regarding causal relationships

Table 2. Summary of Findings for Reduction of Processed Meat Intake (3 Servings per Week) and Cancer Mortality and Incidence

Outcome	Studies, *n*	Participants, *n*	Follow-up, *y*	Relative Risk (95% CI)	Estimated Lifetime Population Risk per 1000 Persons*
Overall cancer mortality†	3	666 995	10–28	0.92 (0.89–0.94)	105
Gastric cancer mortality	1	970 045	14	0.95 (0.86–1.04)	10
Colorectal cancer mortality	1	39 867	30	0.88 (0.67–1.14)	9
Pancreatic cancer mortality§	1	8817	20	0.67 (0.28–1.59)	4
Prostate cancer mortality	2	63 025	19–24	0.77 (0.66–0.90)	6
Overall cancer incidence	2	71 858	5–9	0.99 (0.89–1.09)	185
Oral cancer incidence	1	348 738	Mean, 11.8	0.85 (0.70–1.04)	5
Esophageal cancer incidence	1	348 738	Mean, 11.8	0.70 (0.56–0.88)	7
Gastric cancer incidence	4	565 285	5–18	0.89 (0.62–1.30)	14
Small intestinal cancer incidence	1	494 000	8	0.88 (0.55–1.39)	1
Colorectal cancer incidence	15	1 616 707	5–16	0.93 (0.89–0.95)	20
Hepatic cancer incidence	1	477 206	Mean, 11.4	1.10 (0.87–1.37)	11
Pancreatic cancer incidence	7	1 321 588	7–18	0.99 (0.89–1.09)	5
Ovarian cancer incidence§	1	Unknown‖‖	Mean, 6.8	0.81 (0.61–1.09)	7
Endometrial cancer incidence	2	172 251	11–21	0.95 (0.85–1.06)	10
Breast cancer incidence	8	907 764	6–17	0.90 (0.85–0.95)***	46
Prostate cancer incidence	6	484 029	8–15	0.99 (0.97–1.01)	38

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* Lifetime cumulative risk from GLOBOCAN 2012 (45).
† We found a statistically significant difference between studies at low and high risk of bias. Here, we report results from studies at low risk of bias.
‡ Study is at high risk of bias because diet was assessed only at baseline for 30 y of follow-up and because there was no adjustment for family history of cancer.
§ Data are from highest-vs.-lowest meta-analysis.
‖ Study is at high risk of bias because diet was assessed only at baseline for 20 y of follow-up and because there was no adjustment for family history of cancer.
¶ CI around absolute effect includes both important benefit and harm.
** Study is at high risk of bias because diet was assessed only at baseline for 11.8 y of follow-up and because there was no adjustment for family history of cancer.
†† 4 of 4 studies are at high risk of bias, primarily because of lack of periodic repeated measurement of diet in primary studies and lack of adjustment for family history.
‡‡ Study is at high risk of bias because diet was assessed only at baseline for 11.4 y of follow-up and because there was no adjustment for family history of cancer.
§§ I^2 = 66.4%; *P* for Q test = 0.03. However, the evidence was not downgraded for inconsistency because there is overlap between CIs of most studies.
‖‖ Does not report the number of participants in the highest and lowest categories of intake.
¶¶ 2 of 2 studies are at high risk of bias, primarily because of lack of periodic repeated measurement of diet in primary studies and lack of adjustment for family history.
*** Nonlinear relationship. Effect estimate presented represents reduction of intake from 3 to 0 servings/wk.

between meat consumption and cancer. We focused on dose–response analyses, which provide the most compelling evidence to assess these associations, and supported our findings with lowest-versus-highest analyses that provided similar results. Our review included an extensive search for all cohort studies with more than 1000 participants. We focused on studies that clearly separated unprocessed red meat from processed meat, but we also analyzed studies that did not make the distinction; these mixed analyses showed intermediate exposure effects compared with our estimates specific to unprocessed red and processed meat. Pairs of independent reviewers assessed eligibility, risk of bias, and data collection, with third-party adjudication of any discrepancies. When studies at low and high risk of bias produced discrepant results, we focused on those at low risk of bias. Presentation of results included not only relative but also absolute effects, which enabled us to document the very small reductions in cancer mortality and incidence over a lifetime associated with realistic decreases in meat consumption of 3 servings per week. These estimates

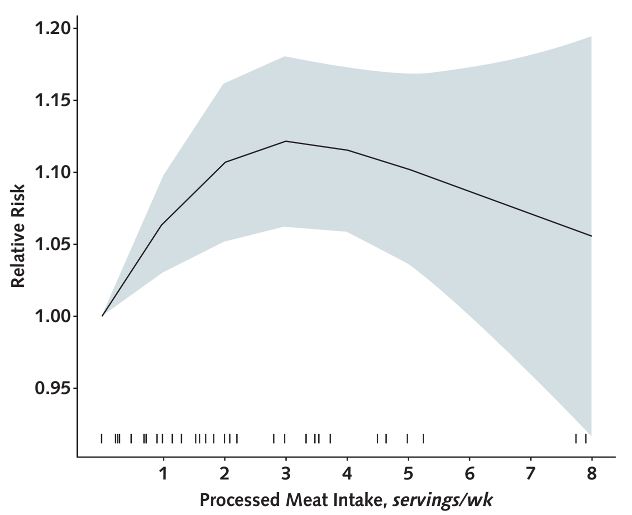
Table 2—Continued

Risk Difference per 1000 Persons (95% CI)	Certainty of Evidence (GRADE)	Plain-Language Summary
8 fewer (12 fewer to 6 fewer)	Low (due to observational design)	Reduction of processed meat intake may result in a very small decrease in cancer mortality.
1 fewer (1 fewer to 0 fewer)	Low (due to observational design)	Reduction of processed meat intake may have little or no effect on gastric cancer mortality.
1 fewer (3 fewer to 1 more)	Very low (due to observational design, risk of bias)‡	We are uncertain of the effects of processed meat on colorectal cancer mortality.
1 fewer (3 fewer to 2 more)	Very low (due to observational design, risk of bias)‖	We are uncertain of the effects of processed meat on pancreatic cancer mortality.
1 fewer (2 fewer to 1 fewer)	Low (due to observational design)	Reduction of processed meat intake may result in a very small decrease in prostate cancer mortality.
2 fewer (20 fewer to 17 more)	Very low (due to observational design, imprecision)¶	We are uncertain of the effects of processed meat on overall cancer incidence.
1 fewer (2 fewer to 0 fewer)	Very low (due to observational design, risk of bias)**	We are uncertain of the effects of processed meat on oral cancer incidence.
2 fewer (3 fewer to 1 fewer)	Very low (due to observational design, risk of bias)**	We are uncertain of the effects of processed meat on esophageal cancer incidence.
2 fewer (5 fewer to 4 more)	Very low (due to observational design, risk of bias)††	We are uncertain of the effects of processed meat on gastric cancer incidence.
0 fewer (0 fewer to 0 fewer)	Low (due to observational design)	Reduction of processed meat intake may have little or no effect on small intestinal cancer incidence.
1 fewer (2 fewer to 1 fewer)	Low (due to observational design)	Reduction of processed meat intake may result in a very small decrease in colorectal cancer incidence.
1 more (1 fewer to 4 more)	Very low (due to observational design, risk of bias)‡‡	We are uncertain of the effects of processed meat on hepatic cancer incidence.
0 fewer (1 fewer to 0 fewer)	Low (due to observational design)§§	Reduction of processed meat intake may have little or no effect on pancreatic cancer incidence.
1 fewer (3 fewer to 1 more)	Low (due to observational design)	Reduction of processed meat intake may have little or no effect on ovarian cancer incidence.
1 fewer (2 fewer to 1 more)	Very low (due to observational design, risk of bias)¶¶	We are uncertain of the effects of processed meat on endometrial cancer incidence.
5 fewer (7 fewer to 2 fewer)	Low (due to observational design)	Reduction of processed meat intake may result in a very small decrease in breast cancer incidence.
0 fewer (1 fewer to 0 fewer)	Low (due to observational design)	Reduction of processed meat intake may have little or no effect on prostate cancer incidence.

inform the general public, as well as researchers, policymakers, and guideline developers, about the effects they might expect if indeed a causal relationship exists between red and processed meat consumption and cancer.

The main limitation of this review was its basis in observational studies prone to confounding; even with appropriate adjusted analyses, causal inferences from such studies are necessarily limited. Additional limitations included high risk of bias in some studies due to limited assessment of dietary intake and lack of adjustment for known confounders. Limitations in dietary assessment included measurement error due to recall-based methods and failure to report the alternative diets of patients with low consumption of red meat. Lack of adequate adjustment for potential confounders was one of the main sources of potential bias among eligible studies (47). We dealt with this issue by considering the possibility that studies at low and high risk of bias yielded systematically different estimates of effect; when this was the case, we focused on those at low risk of bias. Studies most often did not report sufficient data to inform our a priori planned subgroup analyses (that is, analyses of red vs. white processed meat and method of red meat preparation). Many studies did not

Figure. Nonlinear association between processed meat intake and breast cancer incidence.



The solid black line represents the point estimate, the shaded region represents the 95% CIs, and the tick marks represent the positions of the study-specific estimates.

report complete information for the purpose of dose–response meta-analysis.

Our results were consistent with those of previous systematic reviews of the RRs of cancer incidence and mortality associated with processed meat intake, which we identified in MEDLINE searches to April 2019. A recent systematic review summarized results from a meta-analysis on meat consumption and risk for 15 types of cancer, including 24 meta-analyses for total red meat and 39 for processed meat published between 2005 and 2015 (48). The authors concluded that a convincing association existed between larger intake of red meat and cancer, especially for colorectal, lung, esophageal, and gastric cancer. Similarly, they concluded that increased consumption of processed meat was associated with colorectal, esophageal, gastric, and bladder cancer. Several recent systematic reviews have also reported an association between red meat and specific cancer risks (49–53). Some of the meta-analyses relied on extreme exposure categories (48–50) and pooled case–control studies together with cohort studies (48), and many did not consider absolute effects or certainty of evidence on an outcome-by-outcome basis (15, 16, 49–54). Evidence of an association between unprocessed meat consumption and risk for cancer, however, proved difficult to compare between our review and previous systematic reviews, even for relative effects. Most primary studies did not distinguish between unprocessed and processed red meat, and most previous systematic reviews focused on total red meat, which included both unprocessed and processed meat (18–21, 55, 56). Our review provides up-to-date evidence separately for unprocessed red meat and processed meat, including the absolute effect and certainty of evidence for each outcome.

Regarding the implications of the results of our own and prior reviews, decision makers might expect that if red meat itself has a sufficient concentration of carcinogenic compounds to be causally related to cancer, the relative increases in incidence and mortality would be similar across cancer types regardless of whether meat was unprocessed or processed. Therefore, as noted in prior reviews (57, 58), results suggest that carcinogens may be added during meat processing procedures, such as curing, smoking, salting, or adding chemical preservatives (13, 57, 59). This suggests the desirability of future research addressing preservatives and processing procedures of red meat. For example, such research could focus on the direct relationship between preservatives and health outcomes (60, 61). On the other hand, differential levels of confounding may instead explain the gradient in cancer incidence and mortality between unprocessed and processed meat: For instance, lower socioeconomic status might be more strongly associated with consumption of processed than unprocessed red meat (62, 63).

Given the widespread consumption of red and processed meat and the large burden of cancer worldwide, this systematic summary provides relevant and useful information about important health concerns. Our systematic review and meta-analysis of cohort studies supports the association between red and processed meat intake and increased risk for cancer. The magnitude of red meat's effect on cancer over a lifetime of exposure was, however, very small, and the overall certainty of evidence was low or very low. Persons making recommendations about consumption of red and processed meat should be mindful of the remaining uncertainty regarding causation and, if indeed causal mechanisms are at play, the very small absolute effects.

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Appendix: Technical Appendix

This appendix presents additional details on dose–response meta-analysis. We use our analysis addressing the association between unprocessed red meat intake and fatal stroke as an example.

Our systematic review identified 3 cohort studies reporting the association between unprocessed red meat and fatal stroke. The first 2 studies presented results across categories of exposure. The third reported results from a regression in which intake of unprocessed red meat was treated as a continuous variable. The relative effect presented in the third study corresponds to an increase in intake of 120 g/d.

Data are presented in Supplement Table 12, along with definitions of variables.

The following code loads the data and the necessary packages for the analysis.

```
library(dosresmeta)
library(metafor)
library(rms)
attach(filename)
```

The following code generates the natural logarithm of effect estimates and the associated SEs, which are stored in variables called log_point and se_point, respectively.

```
filename$log_point<-log(Adj_point)
filename$se_point<-(log(filename$CI_upper)-log
(filename$CI_lower))/(2*1.96)
```

The following code approximates covariances of relative effects from the first 2 studies using the method proposed by Greenland and Longnecker (31) and estimates a corrected trend using generalized least-squares regression.

```
twostageresults <- dosresmeta(formula = log_point
~ Quantity, id = Ref, type = RType,
cases = Events, n = PY, data = filename,
se = se_point, proc = "2stage", method="reml")
summary(twostageresults)
```

The estimated trend (that is, the regression coefficient) for the first 2 studies can be extracted from the above dose–response meta-analysis. Note that regression coefficients extracted from the dose–response meta-analysis correspond to 1 unit of intake (in this case, 1 g/d) but can be converted to correspond with any quantity of intake and can subsequently be meta-analyzed with the third study that treats the exposure as a continuous variable.

Here, we calculate effects for 1 serving per day and assume that each serving is equal to 120 g.

The following code meta-analyzes the relative effect from the third study with the relative effects from the first 2 studies that were derived on the basis of the method of Greenland and Longnecker (31).

```
serving <- 120
point1 <- 1.17
```

```
upperci1<- 1.33
lowerci1<- 1.03
bi1<-log(point1)/serving
si1<-((log(upperci1)-log(lowerci1))/(2*1.96*serving))^2
contbi<-c(bi1)
contsi<-c(si1)
Si<-unlist(twostageresults$Si)
newbi<-c(twostageresults$bi, contbi)
newsi<- c(Si, contsi)
meta<- rma.uni(yi=newbi*serving, vi=(sqrt(newsi)*serving)^2)
summary(meta)
```

The results from this analysis can be converted from 1 serving per day to a reduction of 3 servings per day by calculating the inverse of the effect, dividing by 7, multiplying by 3, and then subsequently exponentiating. This process can also be replicated for the upper and lower bounds of the CIs. This yields relative effect estimates corresponding to a reduction of 3 servings per week.

```
exp(-meta$beta/7*3)
exp(-meta$ci.lb/7*3)
exp(-meta$ci.ub/7*3)
```

The following code tests for nonlinearity using restricted cubic splines with knots at 10%, 50%, and 90%.

```
knots <- quantile(filename$Quantity, c(0.10, 0.50, 0.90))
nonlinear <-dosresmeta(formula = log_point ~ rcs(Quantity, knots), id = Ref,
type = RType, cases = Events, n = PY,
data = filename, se = se_point)
summary(nonlinear)
waldtest(b=coef(nonlinear), Sigma=vcov(nonlinear), Terms = 2)
```

Web-Only Reference

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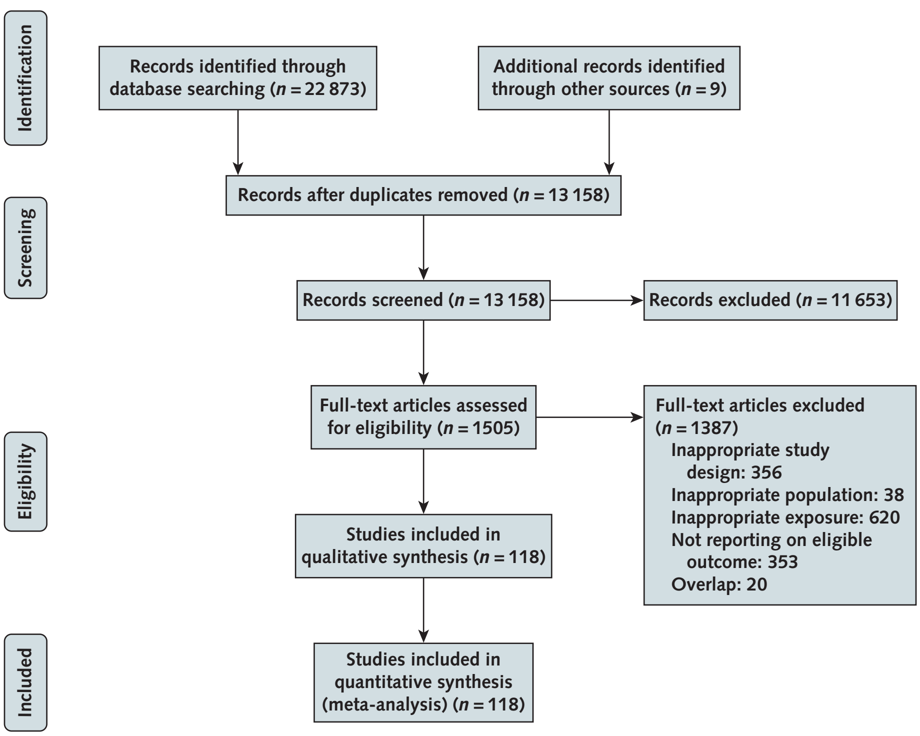
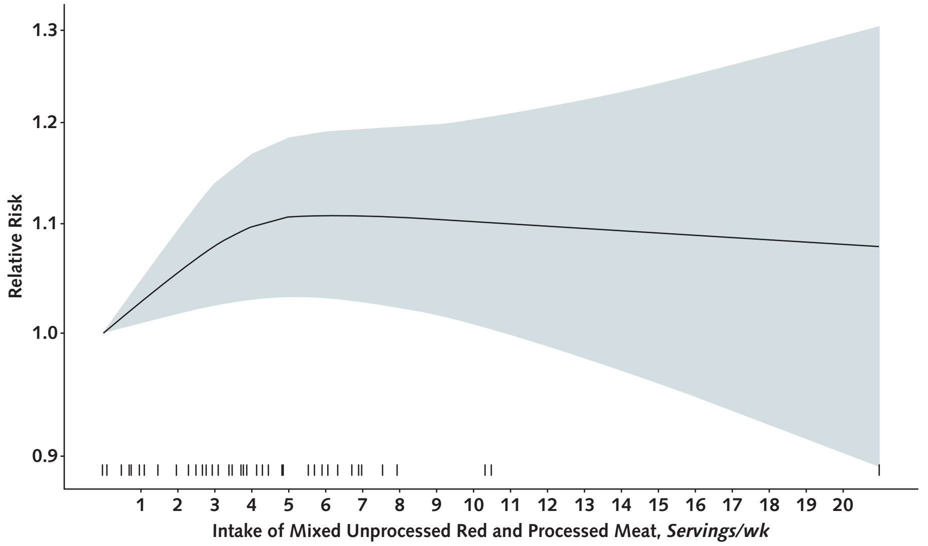
Appendix Figure 1. Evidence search and selection.



Appendix Figure 2. Nonlinear association between intake of mixed unprocessed red and processed meat and breast cancer incidence.



The solid black line represents the point estimate, the shaded region represents the 95% CIs, and the tick marks represent the positions of the study-specific estimates.

Effect of Lower Versus Higher Red Meat Intake on Cardiometabolic and Cancer Outcomes

A Systematic Review of Randomized Trials

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Background: Few randomized trials have evaluated the effect of reducing red meat intake on clinically important outcomes.

Purpose: To summarize the effect of lower versus higher red meat intake on the incidence of cardiometabolic and cancer outcomes in adults.

Data Sources: EMBASE, CENTRAL, CINAHL, Web of Science, and ProQuest from inception to July 2018 and MEDLINE from inception to April 2019, without language restrictions.

Study Selection: Randomized trials (published in any language) comparing diets lower in red meat with diets higher in red meat that differed by a gradient of at least 1 serving per week for 6 months or more.

Data Extraction: Teams of 2 reviewers independently extracted data and assessed the risk of bias and the certainty of the evidence.

Data Synthesis: Of 12 eligible trials, a single trial enrolling 48 835 women provided the most credible, though still low-certainty, evidence that diets lower in red meat may have little or no effect on all-cause mortality (hazard ratio [HR], 0.99 [95% CI, 0.95 to 1.03], cardiovascular mortality (HR, 0.98 [CI, 0.91 to 1.06]), and cardiovascular disease (HR, 0.99 [CI, 0.94 to 1.05]). That trial also provided low- to very-low-certainty evidence that diets lower in red meat may have little or no effect on total cancer mortality (HR, 0.95 [CI, 0.89 to 1.01]) and the incidence of cancer, including colorectal cancer (HR, 1.04 [CI, 0.90 to 1.20]) and breast cancer (HR, 0.97 [0.90 to 1.04]).

Limitations: There were few trials, most addressing only surrogate outcomes, with heterogeneous comparators and small gradients in red meat consumption between lower versus higher intake groups.

Conclusion: Low- to very-low-certainty evidence suggests that diets restricted in red meat may have little or no effect on major cardiometabolic outcomes and cancer mortality and incidence.

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Observational studies have reported that intake of red meat is associated with cardiometabolic disease and cancer (1–8). Dietary guidelines from the United States, United Kingdom, and the World Cancer Fund/American Institute for Cancer Research recommend limiting intake of red and processed meat (8–10). Such recommendations are primarily based on observational studies that are at high risk for confounding.

Randomized trials generally provide higher-certainty evidence supporting causal relationships (11, 12). The few systematic reviews of trials addressing red meat consumption have evaluated only surrogate outcomes, such as blood pressure and lipid levels (13–15).

In this systematic review of randomized trials, we investigate the effect of lower versus higher red meat intake on the incidence of major cardiometabolic and cancer outcomes. The review was performed by the Nutritional Recommendations (NutriRECS) working group as part of a new initiative to develop trustworthy guideline recommendations in nutrition (16). In addition to this review, we performed 4 parallel systematic reviews that focused on observational studies addressing the effect of red and processed meat consumption on cardiometabolic and cancer outcomes (17–19), and a review of health-related values and preferences related to meat consumption (20). These reviews were used to underpin guideline recommendations for consumption of red and processed meats (21).

Methods

We registered the systematic review protocol in PROSPERO (CRD42017074074) on 10 August 2017 (22).

Data Source and Searches

We searched MEDLINE, EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Web of Science from inception until July 2018, and MEDLINE from inception through to April 2019, with no restrictions on language or date of publication (Section I of the Supplement, available at Annals.org). We also searched ProQuest Dissertations and Theses Global (1989 to 2018); trial registries, in-

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cluding ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform Search Portal, to April 2019; and bibliographies of eligible studies and relevant systematic reviews.

Study Selection

We included English-language and non–English-language reports of randomized trials of adults allocated to consume diets that included varying quantities of unprocessed red meat (measured as servings or times/week, or as g/d) or processed meat (meat preserved by smoking, curing, salting, or adding preservatives) for 6 months or more (23). Eligible trials compared diets lower in red or processed meat with diets higher in red or processed meat that differed by a gradient of at least 1 serving per week (Table 1). If a trial reported more than 2 study groups (24, 25), we used the groups with the largest gradient in red meat intake or combined groups if red meat intake was equal. Studies in which more than 20% of the participants were pregnant or had cancer or a chronic health condition, other than cardiometabolic diseases, were excluded.

Outcomes of interest, which were determined a priori and in consultation with the guideline panel, were all-cause mortality, cardiovascular mortality, adverse cardiometabolic events and major morbidity, cancer mortality and incidence, quality of life, and surrogate outcomes (weight, body mass index, blood lipid levels, blood pressure, and hemoglobin level) (22). Pairs of reviewers screened titles and abstracts for initial eligibility and reviewed the full text of potentially eligible studies, independently and in duplicate. Reviewers resolved disagreements by discussion and third-party adjudication if needed.

Data Extraction and Quality Assessment

Using standardized, piloted forms, pairs of reviewers conducted calibration exercises and independently extracted information on study design, participant characteristics, interventions, comparators, and outcomes of interest and resolved disagreement by discussion or, if necessary, third-party adjudication. When details related to methods or results were unavailable or unclear, we contacted study authors for additional information.

Reviewers, independently and in duplicate, assessed the risk of bias of eligible trials by using a modified version of the Cochrane Collaboration's risk of bias instrument for randomized trials (26–28). The modified version categorizes risk of bias as “definitely low,” “probably low,” “probably high,” or “definitely high” for each of the following domains: sequence generation, allocation sequence concealment, blinding, missing participant outcome data, selective outcome reporting, and other bias (for example, prematurely terminated studies). We resolved any disagreements by discussion or, if necessary, third-party adjudication. We collapsed ratings of “probably low” and “definitely low” into “low risk of bias” and ratings of “probably high” and “definitely high” into “high risk of bias.” Among the 8 risk of bias domains, we considered a study to be at high risk of bias if, at the outcome level, 2 or more domains were at high risk of bias (Section I of the Supplement).

Data Synthesis and Analysis

We reported risk ratios (RRs), hazard ratios (HRs), and mean differences (MDs) with their 95% CIs for the lowest versus highest category of red meat intake, at the last reported time point. We used the Hartung–Knapp–Sidik–Jonkman approach to pool data (29, 30). To calculate absolute risk differences, we multiplied the effect estimate for each outcome with the population risk estimates from the Emerging Risk Factors Collaboration study for cardiometabolic outcomes (31) or from GLOBOCAN for cancer outcomes (32, 33) and, when this was not available, the control group estimate from the largest study (Section I of the Supplement).

We investigated heterogeneity by using the Cochran *Q* test and the I^2 statistic (34). We used R Project, version 3.3.0 (R Foundation for Statistical Computing), for all analyses.

To rate the certainty of the evidence for each outcome, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach (11, 35–39). Reviewers, independently and in duplicate, assessed the certainty of evidence for each outcome, and resolved disagreements by discussion.

Role of the Funding Source

This systematic review was conducted without financial support.

RESULTS

Study Selection

Electronic searches yielded 13 190 unique articles (Appendix Figure, available at Annals.org). Of these, 24 articles (24, 25, 40–62) reporting on 12 unique randomized trials met eligibility criteria. In 2 instances, authors provided clarification about study characteristics or outcomes: Turner-McGrievy and colleagues (24) clarified the aggregated change in weight for vegan/vegetarian and semi-vegetarian/omnivorous groups, and Griffin and associates (44) clarified reported effect estimates.

Study Characteristics

Trials ranged in size from 32 to 48 835 participants (Table 1). The mean age of participants ranged from 22.4 to 70.9 years. The largest study, the Women's Health Initiative (WHI), enrolled postmenopausal women (45). Five trials, including the WHI, enrolled overweight and obese participants (24, 25, 41, 45, 59, 60); 5 focused on participants with medical conditions, such as diabetes or hypercholesterolemia (42, 43, 57, 58, 61); and 1 enrolled older (>64 years) healthy individuals (41). Only 1 trial explicitly reported participants' consumption of both unprocessed red meat and processed meat (62).

All trials used parallel designs, except for a small crossover trial in patients with hypercholesterolemia (57). Intervention and control diets varied widely. The primary protein intake in the low red meat group was from plant sources in 4 trials (40, 60, 58, 61); from animal protein sources in 5 trials (25, 43, 44, 57, 59); and from a mix of plant and animal protein in 3 trials (24, 41, 42). The largest trial, the WHI trial, compared a low-fat

Table 1. Study Characteristics

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Benassi-Evans et al, 2009 (40)	NR; NR	Meat and Livestock Australia medical research grant	High-carbohydrate diet: 17 High-protein diet: 16	0.0	Overweight or obese (Australia)	High-carbohydrate, low-red-meat weight loss diet: red meat <1 time/wk High-protein, high-red-meat weight loss diet: red meat 4 times/wk	Actual between-group difference in meat gradient NR	12	12
Davis et al, 2017 (41)	MedLey; NR	National Health and Medical Research Council; Cobram Estate (extra-virgin olive oil); Peanut Company of Australia (peanuts); Grains & Legumes Nutrition (legumes); Simplot Australia Pty. Ltd (legumes and tuna); Goodman Fielder Ltd (canola oil); Almond Board of Australia (almonds)	Mediterranean diet: 85 Habitual diet: 81	56.4	Healthy elderly (Australia)	Mediterranean diet with abundant extra-virgin olive oil, vegetables, fresh fruit, whole-grain cereals, nuts, legumes, fish, <1 serving of red meat/wk Control diet: Participants were asked to maintain their habitual diet	At 4 mo, the between-group difference in gradient of red and white meat was approximately 4.2 servings/wk (excluded ham, salami, bacon)	6	6
de Lorgeril et al, 1999 (42)	Lyon Diet Heart Study; NR	INSERM (Reseau Clinique); Ministry of Research; CNAMTS; CETIOM; ONIDOL; Astra-Calve BSN; Fondation pour la Recherche Médicale	Mediterranean diet: 1467* Prudent diet: 1383*	9.2	Survivors of a first myocardial infarction (France)	Mediterranean diet with more bread, more root vegetables and green vegetables, more fish, less meat (beef, lamb, and pork to be replaced with poultry), no day without fruit, and butter and cream to be replaced with a canola oil–based margarine supplied to patients Prudent Western-type diet: Participants received no dietary advice from the investigators and were advised by their attending physicians to follow a prudent diet	At 4 y, the between-group difference in gradient of red and processed meats was approximately 1.9 servings/wk	27–36	48
de Mello et al, 2008 (43)	NR; NR	Ministry of Science and Technology; National Council for Scientific and Technological Development; Hospital de Clínicas	Chicken-based diet plus active placebo: 16 Enalapril plus usual diet: 16	57.1	Type 2 diabetes (Brazil)	Chicken-based diet plus placebo: All meat in the usual diet was replaced with dark chicken meat (skinless leg quarter), without changing the total amount of protein intake Enalapril (10 mg/d) plus usual diet: usual diet according to recommendations of the American Diabetes Association (about 50% of protein from red meat)	Actual between-group difference in meat gradient NR	12	12

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Table 1–Continued

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Griffin et al, 2013 (44)	NR; ACTRN12609000030720	Meat and Livestock Australia	High-carbohydrate diet: 35 High-protein diet: 36	100.0	Young overweight or obese women (Australia)	High-carbohydrate diet: 100 g (raw) of any type of meat during the day; set amounts of red (beef or lamb) and white (poultry or pork) meat (80 g raw weight) prescribed for evening meal—red meat, 1 serving or 1 time/wk; white meat, 4 times/week; fish, 2 times/wk High-protein diet: 100 g (raw) of any type of meat during the day; set amounts of red (beef or lamb) and white (poultry or pork) meat (200 g raw weight) prescribed for evening meal—red meat, 4 servings or 4 times/wk; white meat, 1 time/wk; fish, 2 times/wk	Actual between-group difference in meat gradient NR	12	12
Women's Health Initiative trial (45–56)	Women's Health Initiative Dietary Modification Trial; NCT00000611	National Institutes of Health, U.S. Department of Health and Human Services	Low-fat diet: 19 541 Habitual diet: 29 294	100.0	>70% overweight or obese; >30%–40% hypertensive women (United States)	Low-fat diet group had extensive behavioral support (≥4 sessions/y for duration of study) to reduce total dietary fat to 20% and to increase intake of vegetables and fruit to ≥5 servings and grains to ≥6 servings daily Habitual diet received a copy of the Dietary Guidelines for Americans as well as other diet and health-related educational materials	At 3 years, the between-group difference in gradient of red meat was approximately 1.4 servings/wk (approximately 20.2% [95% CI, 14.8%–25.5%])	72–144	72–204.6
Hunninghake et al, 2000 (57)	NR; NR	National Cattlemen's Beef Association	Lean white meat diet: 107 Lean red meat diet: 95	42.7	Hypercholesterolemia (United States)	Patients were instructed to consume up to 170 g per day of lean meat, including red meat, poultry, fish, or shellfish Lean white meat group: Participants were instructed to consume ≥80% of their meat consumption as lean white meat, defined as poultry or fish Lean red meat group: Participants were instructed to consume ≥80% of their total meat in the form of lean beef, veal, or pork	Actual between-group difference in meat gradient NR	9	9

Continued on following page

Table 1–Continued

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Lanza et al, 2007 (58)	Polyp Prevention Trial; NR	NR	Low-fat and high-fiber diet: 1037 Usual diet: 1042	35.0	Large-bowel adenomatous polyp (United States)	Diet low in fat (20% of calories from fat) and high in fiber (18 g of dietary fiber per 1000 kcal) and fruits and vegetables (3.5 servings/1000 kcal) Usual diet group given a standard brochure on healthy eating	At 4 y, the between-group difference in gradient of red and processed meats was approximately 1.7 servings/wk	48	96.8
Murphy et al, 2012 (59)	NR; ACTRN1260800019030	Australian Pork Ltd., Pork Cooperative Research Centre	Pork diet: 84 Habitual diet: 80	NR	Overweight or obese (Australia)	Pork diet group: Participants were instructed to consume 7 servings (men) or 5 servings (women) of pork per week. Control group: Participants were asked to maintain their habitual diet	At 6 mo, the between-group difference in gradient of red meat was approximately 3.6 servings/wk	6	6
Poddar et al, 2013 (60)	NR; NR	Mushroom Council; Australian Mushroom Growers' Association	Mushroom diet: 36 Meat diet: 37	87.7	Overweight or obese (United States)	Mushroom diet: Mushrooms (8 oz) were substituted for meat at 3 servings/wk Meat diet: Participants were asked to eat 3 servings/week of ≥90% lean ground beef	Actual between-group difference in meat gradient NR	12	6–12
Turner-McGrievy et al, 2015 (24)	New Dietary Interventions to Enhance the Treatments for weight-loss (New DIETs); NR	NR	Vegan diet: 12 Vegetarian diet: 13 Pesco-vegetarian diet: 13 Semi-vegetarian diet: 13 Omnivorous diet: 12	73.0	Overweight or obese (United States)	Vegan diet: Did not contain any animal products; emphasized plant-based foods Vegetarian diet: Did not contain meat, fish, or poultry but did contain eggs and dairy, in addition to plant-based foods Pesco-vegetarian diet: Did not contain meat or poultry but did contain fish and shellfish, eggs, and dairy, in addition to plant-based foods Semi-vegetarian diet: Contained all foods, including meat, poultry, fish and shellfish, eggs, and dairy, in addition to plant-based foods; red meat limited to once per week, poultry ≤5 times/wk Omnivorous diet: Contained all foods	Actual between-group difference in meat gradient NR	6	6

Continued on following page

Table 1–Continued

Study, Year (Reference)	Study Name; Registration Number	Funding Source	Participants, *n*	Women, %	Sample (Country)	Study Group Definition	Gradient in Meat Reduction Between Groups	Duration of Intervention, *mo*	Duration of Follow-up, *mo*
Yaskolka-Meir et al, 2019 (25)	DIRECT-PLUS; NR	German Research Foundation; Deutsche Forschungsgemeinschaft, Obesity Mechanism; Israel Ministry of Health; Israel Ministry of Science and Technology; California Walnut Commission	Mediterranean diet: 98 Control diet: 98	22.0	Abdominal adiposity (Israel)	Mediterranean diet: Participants were guided to follow a calorie-restricted diet low in simple carbohydrates; rich in vegetables; and low in red meat, with poultry and fish replacing beef and lamb. Main sources of added fat were 30–45 g of olive oil and a handful of nuts (5–7 nuts, <20 g) per day, including 28 g walnuts/d (84% fat, mostly ω-3 α- linolenic acid) Control group: Participants were not guided to restrict calories, but received basic health-promoting guidelines for a healthy diet	Actual between-group difference in meat gradient NR	6	6

NR = not reported.
* Person-years.

dietary intervention aimed at reducing total dietary fat to 20% with a usual diet group given diet and health-related materials (45–56). The duration of interventions ranged from 6 months (24, 25, 41, 59) to 12 years (51).

Risk of Bias

Trials were most often rated as high risk of bias for lack of blinding (not possible for participants) and missing outcome data overall (Supplement Table 1, available at Annals.org). However, some trials were rated as low risk of bias for specific outcomes (all-cause mortality, cardiovascular disease, type 2 diabetes, adenocarcinoma) because there were either more outcome events than missing data for dichotomous outcomes or there were less than 10% missing data for continuous outcomes. Selective reporting bias was detected in 4 trials (40, 42, 44, 57). Other biases included a non-paired analysis of data from a crossover trial (57) and early termination for benefit in the Lyon Diet Heart Study (42).

Outcomes

None of the trials reported on a combination of fatal and nonfatal myocardial infarction, fatal infarction, nonfatal coronary heart disease, prostate cancer, and satisfaction with diet. Only 2 trials, the Lyon Diet Heart Study and the WHI trial (42, 54), addressed all-cause mortality and other patient-important, major morbid cardiovascular outcomes. The Lyon Diet Heart Study reported an implausibly large treatment effect, potentially due to stopping the trial early for benefit, and had a sample size (605 participants) more than 80 times smaller than the WHI trial (48 835 participants); for this reason the 2 trials were not pooled (63). Results presented below and in Table 2 regarding all-cause mortality and cardiovascular outcomes are based on the WHI trial results. Results of the Lyon Diet Heart Study are presented in Section II of the Supplement (available at Annals.org).

All-Cause Mortality and Cardiometabolic Outcomes

Low-certainty evidence from the WHI trial showed that a diet lower in red meat may have little or no effect on all-cause mortality (HR, 0.99 [95% CI, 0.95 to 1.03]) (54). The certainty of evidence was rated down for serious indirectness. The trial investigated reducing dietary fat intake, which led to reduction of red meat intake (rather than directly investigating reduction of red meat intake). Compared with the usual diet control group, the low-fat dietary intervention group reduced their consumption of red meat by about 20% (approximately 1.4 servings per week).

Evidence showing little or no effect on cardiovascular mortality (HR, 0.98 [CI, 0.91 to 1.06]), fatal and nonfatal cardiovascular disease (HR, 0.99 [CI, 0.94 to 1.05]), nonfatal myocardial infarction (RR, 1.05 [CI, 0.96 to 1.16]), fatal and nonfatal stroke (RR, 0.98 [CI, 0.89 to 1.07]), fatal stroke (HR, 0.97 [CI, 0.69 to 1.36]), nonfatal stroke (HR, 1.03 [CI, 0.90 to 1.17]), and risk for type 2 diabetes (HR, 0.96 [95% CI, 0.90 to 1.03]) was consid-

Table 2. Summary of Findings for Lower Intake of Red Meat* and Mortality Outcomes

Outcome	Trials, *n*	Participants, *n*	Follow-up, *y*	Hazard Ratio (95% CI)	Population Risk Over 10.8 y for Cardiometabolic Outcomes and Over a Lifetime for Cancer Outcomes, *n/n (%)*	Risk Difference per 1000 Persons (95% CI)	GRADE Certainty of Evidence	Plain-Language Summary
All-cause mortality	1	48 835	Up to 17.05 y	0.99 (0.95–1.03)	113/1000 (11.3)†	2 fewer cases (12 fewer to 7 more cases)	Low‡	Reduction of red meat may have little or no effect on all cancer mortality.
Cardiovascular mortality	1	48 835	Up to 13.8 y	0.98 (0.91–1.06)	41/1000 (4.1)†	3 fewer (11 fewer to 8 more cases)	Very low‡§	We are uncertain of the effects of red meat on cardiovascular mortality.
Fatal myocardial infarction	NR	NR	NR	NR	NR	NR	NR	NR
Fatal stroke	1	48 835	Up to 8.0 y	0.97 (0.69–1.36)	19/1000 (1.9)†	2 fewer cases (16 fewer to 35 more cases)	Very low‡‖¶	We are uncertain of the effects of red meat on fatal stroke.
Breast cancer mortality	1	48 835	Up to 16.1 y	0.91 (0.72–1.15)	14/1000 (1.4)**	5 fewer cases (11 fewer to 10 more cases)	Very low‡††	We are uncertain of the effects of red meat on breast cancer mortality.
Total cancer mortality	1	48 835	Up to 12.3 y	0.95 (0.89–1.01)	105/1000 (10.5)**	12 fewer cases (26 fewer to 2 more cases)	Very low‡¶‡‡	We are uncertain of the effects of red meat on breast cancer mortality.

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; NR = not reported.
* Studies did not differentiate between red and processed meat. Most red meat is consumed as unprocessed, and our estimates of effect are therefore likely to apply predominantly to red meat.
† Data from reference 31.
‡ Downgraded twice for indirectness (trial investigated reducing dietary fat, which led to reduction of red meat, and not red meat directly) and there was a very small between-group gradient in red meat consumption (difference of approximately 1.4 servings/wk).
§ Downgraded for risk of bias related to missing participant outcome data; although the total number of events in the Women's Health Initiative trial was not reported, it is highly likely that the number of events was substantially lower than the number of missing participant outcomes.
‖ Downgraded for high risk of bias related to missing participant outcome data because there were far more missing participant outcomes (4484) than total events (141).
¶ Downgraded for imprecision because the CI around the absolute effect includes both appreciable benefit and no appreciable benefit.
** Data from reference 33.
†† Downgraded for risk of bias related to missing participant outcome data because there were far more outcome data missing (18 145) than total number of cancer events (296).
‡‡ Downgraded for risk of bias related to missing participant outcome data because there were far more outcome data missing (11 125) than total number of cancer events (2049).

ered of low or very low certainty owing to indirectness, risk of bias, or imprecision (**Table 2** and **Supplement Table 2**, available at Annals.org).

Cancer

Because of risk of bias, imprecision, and serious indirectness, the WHI trial (53) provided very-low-certainty evidence that a diet lower in red meat may have little or no effect on cancer mortality (HR, 0.95 [CI, 0.89 to 1.01]) (**Table 2**). Similarly, the WHI trial provided very-low-certainty evidence that a diet lower in red meat may have little or no effect on colorectal, pancreatic, esophageal, and stomach cancer in women (51, 53, 55). This evidence was rated down to very low certainty owing to risk of bias, imprecision, or serious indirectness (**Supplement Table 3**, available at Annals.org). The WHI trial (46, 53, 55) also found that a diet lower in red meat may have little or no effect on the risk for invasive breast cancer (HR, 0.97 [95% CI, 0.90 to 1.04]); breast cancer mortality (HR, 0.91 [95% CI, 0.72 to 1.15]); or risk for gynecologic, ovarian, endometrial cancer, and ductal carcinoma in situ (**Table 2** and **Supplement Table 3**). Such evidence was considered low or very low certainty owing to risk of bias, imprecision or serious indirectness (**Supplement Table 3**).

One trial of 2079 participants (58) provided very-low-certainty evidence (imprecision and serious indirectness) that a diet lower in red meat may have little or no effect on the risk for adenoma recurrence (HR, 1.04 [CI, 0.98 to 1.09]) (**Supplement Table 3**).

Quality of Life

The WHI trial (39 416 participants) provided very-low-certainty evidence, owing to risk of bias and serious indirectness, that a diet lower in red meat may have little or no effect on quality of life as measured by the RAND 36-Item Health Survey: general health (MD, 1.7 units [CI, 1.5 to 2.0 units]), physical functioning (MD, 2.0 units [CI, 1.7 to 2.3 units]), vitality (MD, 1.9 units [CI, 1.6 to 2.2 units]), and global quality of life (MD, 0.09 unit [CI, 0.07 to 0.12 units]) (45) (**Supplement Table 4**, available at Annals.org). The judgment of little or no effect is based on the minimal important difference estimates for the domain scores on the RAND-36 instrument, which range from 3.5 to 7, whereas the important difference for the global score is 1.7 (64).

Surrogate Outcomes

Aside from a trivial effect on high-density lipoprotein (HDL) cholesterol based on 6 trials (2320 participants) (0.77 mg/dL [CI, 0.07 to 1.54 mg/dL]; 0.02 mmol/L [CI, 0.002 to 0.04 mmol/L]; I^2 = 0%), low- to very low-certainty evidence suggests diets lower in red meat may have little or no effect on surrogate outcomes, such as cholesterol, weight, blood pressure, and hemoglobin (**Supplement Table 4**).

DISCUSSION

On the basis of evidence from 24 articles reporting on 12 randomized trials, our review shows that diets lower in red meat may have little or no effect on all-cause mortality, nonfatal cardiovascular disease, and diabetes (low-certainty evidence) and, although we are very uncertain, may have little or no effect on cancer mortality and incidence. Although no effect estimates for the major cardiometabolic or cancer outcomes met conventional criteria for statistical significance, 13 of 21 outcomes demonstrated a trivial to very small absolute risk reduction (range, 1 to 12 fewer events per 1000 persons over 8 to 17 years) in those who consume approximately 1 to 3 fewer servings of red meat per week. We found some improvements in quality of life and HDL cholesterol level, but the effects were very small: For HDL cholesterol level, the MD was 0.77 mg/dL (0.02 mmol/L), and for quality of life, the effects on the RAND-36 Health Survey ranged from 1.7 to 2.0 on 3 domains in which the minimally important differences ranges from 3.5 to 7.0.

Strengths of our review include adherence to a priori methods based on a registered protocol (22); a comprehensive search strategy without language restrictions; and inclusion of evidence on 8 cardiometabolic outcomes, 13 cancer outcomes, and 10 surrogate outcomes. We used explicit eligibility criteria, duplicate screening, abstraction of data, and risk-of-bias assessments with third-party adjudication of discrepancies and GRADE guidance to rate the certainty of evidence for each outcome.

Our review had limitations. First, many of the data were derived from a single large study in postmenopausal women: the WHI trial. Although 12 trials proved eligible, only 2 reported on the most patient-important outcomes—cardiovascular mortality and major morbidity, diabetes, and cancer mortality and incidence—and we considered only the WHI trial to have trustworthy results. Eleven studies proved at high risk of bias overall, primarily because of lack of blinding and substantial missing participant outcome data.

In addition, participants consuming alternative diets may have made different choices regarding smoking, exercise, or other lifestyle factors. In clinical trials of dietary interventions, particularly primary prevention trials, studies must follow participants for decades to capture important outcomes, such as cancer incidence (65). Of trials that met our eligibility criteria, only the WHI and the less trustworthy Lyon Diet Heart Study followed participants for 2 or more years. The choice to substitute red meat with poultry, fish, plant sources of protein, or whole or refined carbohydrates may result in different effects for some outcomes (66, 67). Thus, failure to demonstrate effects of decreased meat consumption may be related to trials' varying sources of protein replacement (for example, fish) in the diets lower in red meat (68). We had planned to address these issues through subgroup analyses (22, 69), but the paucity of trials made this impossible. The trials achieved only small differences between red meat intake in the intervention and control groups, equivalent to about 1 to 3 servings per week. In particular, the WHI study (61), on which we relied for our most important estimates, achieved a difference of 1.4 servings per week between the low-fat and the usual diet group (70). The failure to find differences in outcomes may be a result of the small gradient in red meat intake between the experimental and control groups. Had studies achieved larger gradients in consumption, researchers might have observed statistically significant and possibly an important effect on health outcomes.

Finally, only 1 study specified the proportion of red meat that was consumed as processed (42, 62). Observational studies have suggested that processed meat may have a larger adverse effect than unprocessed red meat (3, 6, 17, 19). Most red meat is, however, consumed as unprocessed (71), and our estimates therefore are likely to apply predominantly to red meat.

Our review of randomized trials relies largely on the WHI trial for estimates of effect on important major morbid cardiometabolic and cancer outcomes. Our results for surrogate outcomes are consistent with those of previous systematic reviews of trials, suggesting that red meat has little or no effect on blood pressure and blood lipids (13–15) (Supplement). Regarding important outcomes, systematic reviews of observational studies assessing diets that vary in red meat have, in contrast, reported positive associations between red meat intake and all-cause (6, 7, 19), cardiovascular (4, 6), and cancer (6, 17) mortality.

The discrepancy between results from randomized trials and observational studies may be explained by unadjusted confounders in the observational studies or by smaller gradients in red meat intake in trials and, thus, lower power, or the shorter follow-up in trials. Furthermore, compared with randomized trials, observational studies do not face the same limitations caused by poor adherence, missing end points, and financing, allowing investigators to better capture and evaluate important outcomes (such as cancer) that often take decades to develop (65).

Our results from the evaluation of randomized trials do not support the recommendations in the United Kingdom, United States, or World Cancer Research Fund guidelines on red meat intake (8–10). One could argue, however, that neither do they seriously challenge those recommendations: We found only low- to very-low-certainty evidence that diets lower in red meat compared with those higher in red meat have minimal or no influence on all-cause mortality, cancer mortality, cardiovascular mortality, myocardial infarction, stroke, diabetes, and incidence of gastrointestinal and gynecologic cancer. Our results highlight the uncertainty regarding causal relationships between red meat consumption and major cardiometabolic and cancer outcomes.

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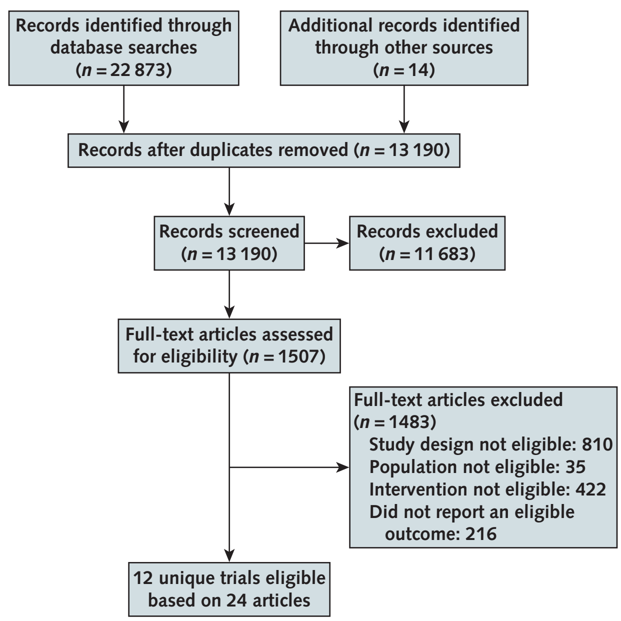
Appendix Figure. Evidence search and selection.



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The obesity wars and the education of a researcher: A personal account

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ABSTRACT

A naïve researcher published a scientific article in a respectable journal. She thought her article was straightforward and defensible. It used only publicly available data, and her findings were consistent with much of the literature on the topic. Her coauthors included two distinguished statisticians. To her surprise her publication was met with unusual attacks from some unexpected sources within the research community. These attacks were by and large not pursued through normal channels of scientific discussion. Her research became the target of an aggressive campaign that included insults, errors, misinformation, social media posts, behind-the-scenes gossip and maneuvers, and complaints to her employer. The goal appeared to be to undermine and discredit her work. The controversy was something deliberately manufactured, and the attacks primarily consisted of repeated assertions of preconceived opinions. She learned first-hand the antagonism that could be provoked by inconvenient scientific findings. Guidelines and recommendations should be based on objective and unbiased data. Development of public health policy and clinical recommendations is complex and needs to be evidence-based rather than belief-based. This can be challenging when a hot-button topic is involved.

I was a senior scientist at the Centers for Disease Control and Prevention (CDC) for almost 30 years. Beginning in 2000, I began working with a CDC colleague and two expert statisticians from the National Cancer Institute (NCI) on a method to estimate the number of deaths associated with overweight and obesity. We thought the topic was interesting and the previous literature inadequate. As federal employees, we had no outside funding or conflicts of interest. Our intent was to use more recent data and better statistical methods to provide more accurate estimates than hitherto available.

Unbeknownst to us, a somewhat similar project was underway elsewhere within CDC. That project resulted in the 2004 publication in JAMA of an article by Mokdad and other CDC authors, including the then-CDC director.[1] Their article concluded that obesity was poised to overtake smoking as a leading cause of death in the US. These findings were widely publicized although they met with some controversy, including concerns from anti-tobacco activists.[2] The Mokdad et al. article had many flaws, however, including older and largely unrepresentative data sets, erroneous coding of smoking data in one data set,[3] a statistical method that failed to adjust correctly for confounding factors,[4] and easily identifiable calculation errors that required a correction to be published.[5]

For our project, we developed a method that provided appropriate statistical adjustment for confounding factors. In addition, we used recent and nationally representative data sets from CDC surveys. Our results were published in JAMA in 2005.[6] A comparison of some features of our article with the 2004 Mokdad et al. article is shown in Table 1. We found that obesity was indeed associated with excess deaths relative to normal weight, although our estimate of less than 5% of deaths was considerably lower than the 2004 Mokdad et al. estimate of over 15%. CDC accepted our results for obesity as the better estimate a month after our article was published.[7] We also found that overweight was associated with slightly but significantly *fewer* deaths than normal weight. A quick glance at the literature suggested that our findings about overweight were not particularly unusual. We were unprepared for the firestorm that followed.

Our article attracted attention because it appeared to be inconsistent with the dramatic conclusions of the 2004 Mokdad et al. article.[8] I fielded dozens of press calls as soon as our article was published. To my surprise, after the first few hours, many of the journalists who called me had already spoken to a professor, Walter Willett, (let's call him Professor 1) from a prestigious school of public health (PSPH). He was not a statistician and had no expertise in estimating the number of deaths associated with obesity. Our article was not intended to have anything to do with his work. He had apparently begun pre-emptively contacting the press, inserting himself into the discussion, positioning himself as an expert, and providing negative and antagonistic comments on our article before reporters had spoken to me. He used strong language to disparage our article, describing it as “really naive, deeply flawed and seriously misleading”.[9] At a scientific conference, a little over a week after our article appeared, Frank Hu (let's call him Professor 2), another professor from PSPH, took the unusual step of pre-empting a planned presentation by someone else to take the stage and deliver a critique of our just-published article. When I presented a seminar at UC Berkeley

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Table 1
Comparison of Mokdad et al.[1] and Flegal et al.[6] articles.

	Mokdad et al., 2004	Flegal et al., 2005
Results	Estimated overweight and obesity-associated deaths in 2000 as 365,000	Estimated obesity-associated deaths in 2000 as 112,000
Features in common	Used BMI measured once at the beginning of each study Did not limit sample to healthy never-smokers	Used BMI measured once at the beginning of each study Did not limit sample to healthy never-smokers
Data	6 data sets, older data, not representative, only one from NHANES	The 3 most recent nationally representative data sets from NHANES
Weight and height data	3 studies with measured weight and height and 3 with self-reported data	All height and weight data were measured
Hazard ratios adjusted for	Age, sex and smoking	Age, sex, race, smoking, alcohol consumption
Estimates of variability	None	Standard errors for estimates
Attributable fraction method	Method that did not adjust for effects of age, sex, smoking or other factors on mortality[4,19,51–54]	Method that adjusted for the effects of age, sex, race, smoking and alcohol consumption on mortality
Errors in smoking data	Smoking data for NHANES I were incorrect[3]	Correct smoking data used for NHANES I
Calculation errors	Article contained simple calculation errors that anyone could have identified from the published data	No identified calculation errors

a week after our article appeared, an unidentified young woman stood at the door giving out a handout of 4 pages of faxed and photocopied material that included an abstract from PSPH and several news articles that discussed PSPH research on obesity.

Our 2005 article had been reviewed extensively by scientists within CDC and NCI, cleared for publication by both agencies, reviewed by peer reviewers at the journal and accepted by the JAMA editors. Nonetheless, less than a month after its publication, a speaker from the American Cancer Society (a PSPH graduate) suggested in a talk at NCI that our article should not even have been published, with one of his PowerPoint slides saying: "Because of the importance of these estimates, scientific controversies should be addressed in a scientific forum that seeks consensus, rather than immediately publicizing widely divergent estimates through the media."

Perhaps feeling that lower estimates of obesity-associated deaths were detrimental to public health goals, some began casting around for explanations that would show that our estimates were less valid than the 2004 estimates by Mokdad et al. "Fact sheets" and lists of "talking points" (one entitled "Damage Control for the Flegal article") began to circulate from various public health-oriented groups describing our estimates as problematic and giving misleading arguments as to why the 2004 estimates were better. The "Damage Control" talking points, for example, asserted that the 2004 paper was superior because it had used data on "diet and physical activity" even though the 2004 paper had not in fact used any data on diet and physical activity. A group from PSPH, including both Professor 1 and Professor 2, published a long speculative article[10] in 2007 about "reconciling the differences" that failed to mention the errors in the previous statistical method or the inadequacies of the data sets used in the 2004 Mokdad et al. paper and ended up announcing that the real problem was that we had asked the wrong question (although it was the same question that the 2004 Mokdad article had asked).

Almost as soon as our article appeared, a symposium was scheduled at PSPH for the express purpose of criticizing our article.[11] One of the organizers wrote to me to say that they viewed this as an opportunity to engage in a respectful and constructive examination of the issues and provide a more in-depth view for the media so they could acquire a deeper understanding. The line-up consisted of a small number of vocal critics, mostly from PSPH itself, all attacking our work and asserting that their previous research somehow showed that our estimates should have been higher, although their previous research had not even addressed the topic of estimating numbers of deaths. The presentations at the symposium did not mention the multiple errors in the 2004 Mokdad et al. article. One speaker described us as having no biomedical background, even though the four authors of our article were well-published senior scientists, all with doctoral degrees in nutrition or statistics and one with a medical degree from Harvard Medical School. Seeking to maximize media coverage, the organizers arranged for the entire symposium to be web-cast live and encouraged reporters to view and report on it.

Further attacks, many but not all emanating from PSPH and its alumni, continued over a number of years. These ranged over a broad gamut: criticisms that we repeatedly refuted, generic minor criticisms that would apply to most articles in this general field (for example that, like the 2004 Mokdad et al. paper, we had used body mass index instead of a more precise measure of adiposity), misinformation, content-free insults and name calling, and sometimes outright falsehoods. It took me far too long to understand that our findings were being treated by some as a partisan issue rather than as a topic of scientific discussion. Our work was attacked in a surprising variety of non-scientific forums, including internet blog posts, social media posts, in-house newsletters, widely distributed fact sheets, and Wikipedia entries. Trying to get errors corrected was stressful and time-consuming. We repeatedly demonstrated that the criticisms being raised would have little or no effect on our results, but these demonstrations were ignored or dismissed.

A number of researchers prepared papers to attack our work, employing convoluted analyses of unclear validity. I began to call these "Flegal is wrong" papers because their primary intent appeared to be to prove that something was wrong with our paper that had caused our estimates to be too low. Such papers often contained a speculative "rescue hypothesis" – claiming with no evidence that if some particular feature of our research had been different, our estimates would have been higher. In several cases, we went to the effort of writing and publishing a new article to demonstrate that one or another speculative hypothesis did not explain our results.[3,12–19] For example, Manson et al.[10] had incorrectly speculated that older ages at measurement had led to downward bias in our estimates; we published an article that showed that their speculation was incorrect.[16] One research group repeatedly tried to publish a paper with the claim that although we had used age as the time line, if we had also included age in our models, we would have gotten different results. To forestall the eventual publication of this erroneous claim, we published a brief article to demonstrate that such an inclusion would not have changed our results.[13]

Although the "Flegal is wrong" papers referred specifically to our article, they often misunderstood key details. These papers tended to focus on analytic methods rather than on data, but in fact our use of more updated and better-quality data sets accounted for much of the difference. We had used nationally representative survey data with measured weights and heights. Critics rarely if ever noted that our findings might be due to our use of better data.

Some criticisms employed a rhetorical approach known as "paltering," defined as the active use of truthful statements with the intent to deceive.[20] Critics would emphasize that our article found different results than previous articles had and then mention some criticism of our article, with the implication that this was the reason for the differences. However, they would not mention that the same criticism would apply equally well to the 2004 Mokdad et al. article and thus could not explain the differences. For example, a laboratory exercise for graduate students in epidemiology at Johns Hopkins University compared our results unfavorably to those of Mokdad et al., stated four different times that our study had only used a single measure of BMI and then asked students to "Discuss the appropriateness and effect of using a single measure of BMI in attributing subsequent deaths to obesity" without noting that Mokdad et al. had also used a single measure of BMI. Other examples of paltering are shown in Table 2.

Attacks on our paper continued and appeared in some unexpected places. A 2007 story appeared in Scientific American[21] by a leading health journalist who had never even contacted the CDC press office or spoken to me but nonetheless asserted that our conclusions were "probably wrong," quoting two PSPH faculty at length. "It's complete nonsense, and it's obviously complete nonsense, and it's very easy to explain why some people have gone astray," said one.

In the same year, a post-doc at PSPH posted the following on a blog: "Numbers from Flegal's paper had been subsequently RETRACTED [sic] by the CDC, and she has subsequently been demoted at the CDC for writing the erroneous paper." Every single one of these statements was false. CDC had not retracted our findings, and I had not been demoted. In fact, our paper had received CDC's highest science award, the Shepard award, in 2006. After I called the post-doc to point out his errors, he apologized and deleted the post. He was unable or unwilling to tell me where he had gotten his misinformation, although he assured me it was not from anyone at PSPH.

A 2007 article[22] from a different PSPH group claimed falsely that CDC had "recanted" our 2005 article. I was impressed that this unreferenced statement could have been written to begin with and then could get through reviewers, editors and copy editors without anyone asking for clarification or evidence. At our request and after some negotiations, the authors reluctantly published an erratum.[23]

Around the same time, some unusual statements were anonymously inserted in the Wikipedia entry on "overweight." These statements asserted with no references that our article had been "widely discredited and regarded as fatally flawed by researchers from the Harvard School of Public Health, Harvard Medical School, American Cancer Society, and even the CDC agency itself, which has backtracked on the findings from the Flegal report." This was part of what appeared to be an ongoing campaign to present our article incorrectly as having been repudiated by reputable sources.

In 2007, I accepted an invitation to give a named lecture at the 2008 meeting of a scientific society. The invitation included no mention of a rebuttal. When I received the final program a month before the meeting, to my surprise Professor 2 from PSPH had been added as a rebuttal speaker. This is an unusual way to treat an invited lecturer. As part of Professor 2's rebuttal, he presented a slide supposedly "based on" our research that strangely showed precisely the opposite of what we had found. It turned out that Professor 2 and his group had misunderstood a table in our published article and misinterpreted the results. Although I wrote him an email to clarify the table, Professor 2 and his colleagues nonetheless submitted an article for publication with the same erroneous analysis. Fortunately, their article was rejected. This led me to realize that if such an article were to get published with such an erroneous analysis, it would likely be quite difficult for me to ever correct the situation. This episode as well as others also led me to realize that some, perhaps many, of our critics had very little understanding of our article. For example, Professor 2 gave a completely incorrect description of our method on page 46 in his book published in 2008.[24]

Another line of attack was something like "this is just one study." According to the 2007 hit piece in Scientific American, "Decades of research and thousands of studies have suggested precisely the opposite …", adding "Flegal is not necessarily wrong, but the preponderance of evidence clearly points in the other direction." In fact, many other studies had already shown no excess mortality associated with overweight. The 2013 obesity guidelines[25] put out jointly by the American Heart Association, the American College of Cardiology and The Obesity Society, also reported the finding that overweight did not appear to be associated with excess mortality, rating the strength of the evidence as "moderate." Professor 2 was a coauthor of these guidelines.

A study using nationally representative Canadian data appeared in 2010 with findings similar to ours.[26] Subsequently, CDC and NIH coauthors, the Canadian researcher and I carried out a systematic literature review,[27] which was published in JAMA in 2013. Before publication, our article had been reviewed extensively by scientists within CDC and NCI and cleared for publication by both agencies. The summary results from 97 published studies with a total of almost 3 million participants

Table 2
Examples of "paltering" – using true statements in a deceptive way.

	Step 1, emphasize that our article found different results than previous articles had	Step 2, mention some criticisms of our article with the indirect implication that these criticisms might explain the differences	Step 3. Do not mention that the criticisms of our article apply equally well to the previous articles.
Willett[55]	"In their study of deaths associated with underweight, overweight, and obesity, Dr. Flegal and colleagues conclude that excess mortality due to obesity and overweight is much lower than previously reported."	We believe that their analysis is flawed and misleading…. In the main analyses, the study apparently did not exclude persons with known chronic disease at baseline	Willett does not mention that the previous estimates also did not exclude persons with known chronic disease at baseline.
Moore[56]	In 2005 a controversial study by Flegal et al. estimated that 26,000 deaths per year in the United States were attributable to excessive body weight, which contrasted strikingly with a previous estimate of 280,000 deaths due to excess body weight.	Flegal et al. may underestimate the proportion of deaths attributable to excess adiposity because they do not exclude persons with a history of smoking or preexisting disease.	Moore does not mention that the "previous estimate" also did not exclude persons with a history of smoking or pre-existing disease.
Harvard Health Letter[57]	In April, a study published in the Journal of the American Medical Association (JAMA) reported that obesity increased the risk of premature death much less than previously estimated.	Other researchers (including several at Harvard) believe the unexpected findings came from methodological errors in the study. These critics say the CDC researchers didn't take into account two important variables: smoking and illness. That arise when attributing death to excess weight.	The report does not mention that the values previously estimated did not take smoking and illness into account.
CA-Cancer journal for clinicians[58]	The new figures were vastly different from those in an earlier CDC analysis	The main concern regarding the newer CDC analysis is that it did not adequately account for weight loss from serious illnesses such as cancer and heart disease. Including such individuals in the analysis created the false appearance that being overweight protected against death during the follow up.	The report does not mention that the earlier CDC analysis did not account for weight loss from serious illnesses and did not exclude such individuals from the analysis.

were that overweight was associated with slightly but significantly lower mortality than the "normal weight" reference category. An anonymous peer reviewer commented: "[This study] documents the conclusion that I suspect most people who follow the health and obesity literature have concluded but not formalized. In spite of the labeling of BMI 25-<30 with the pejorative title 'overweight,' the data on mortality do not support that this category of body mass index has an increased mortality."

As was clear from our review and from many articles published since, our findings were not unusual. Professor 1 was evidently aware of this, since he was quoted[21] as saying "About every 10 years this idea comes along that says it's better to be overweight. And we have to stomp it out." When I reviewed the literature for our 2013 meta-analysis, I noticed that although almost all the articles, including some from our critics, had found either no increased mortality for the overweight or else slightly decreased mortality, few of them mentioned this in the abstract or gave this finding any prominence. No wonder people thought our findings for the overweight category were unusual; it was not evident how common they actually were.

Apparently, according to some of our critics, new and better scientific results are dangerous and cause confusion if they fail to buttress what you already believe. In 2005, Professor 2 claimed[28] that our findings had "caused a great deal of confusion among the general public." When our 2013 review appeared, Professor 1 fired off an email to my employer in the person of the CDC director, reprising the themes of 'damage' and 'confusion' and saying that he thought a meeting was important to begin to repair the serious damage done by our review article, which, according to Professor 1, had not only caused public confusion over this issue but had also contributed to undermining confidence in science in general.

A second tribunal was convened at PSPH, this time to attack our 2013 literature review. The speaker line-up was almost identical to the symposium in 2005. According to a news report, the panelists "expressed concern that much of the popular journalism and commentary about Flegal's research could undermine the credibility of science".[29] The symposium didn't even pretend to be objective or even-handed – its purpose, as was laid out clearly in an in-house newsletter, was "to elucidate inaccuracies in a recent high-profile JAMA article which claimed that being overweight leads to reduced mortality".[30] According to the in-house PSPH coverage: "Each panelist presented a clear, compelling case as to why the general public should not rely on these flawed study findings, giving attendees numerous reasons to question the validity of the study".

In an interview with the BBC[31] Professor 1 announced, regarding our 2013 review and meta-analysis, "This is an even greater pile of rubbish" than our study in 2005. In a radio interview on NPR,[32] Professor 1 again called our 2013 article "rubbish" (which he described elsewhere as a polite term for the word he really wanted to use) and said that no one should even read it. Hearing him say this aloud made a bad impression on several listeners who wrote to me about it. One woman wrote that Professor 1 sounded like a "bully." His behavior was criticized by the editors of the scientific journal Nature.[33,34]

Although much of the furor has died down, the attacks have continued. For example, in a commentary[35] in 2014 about dietary intakes and a review article[36] in 2015 about dietary intakes, Professors 1 and 2 included gratuitous comments about how misleading and contrary our meta-analysis findings were and cited our meta-analysis as an example of confusing and dangerous conclusions. Neither of these articles about dietary intake had anything to do with our meta-analysis or with obesity and mortality. Professor 2 organized a group to publish his own "Flegal is wrong" paper in the Lancet in 2016,[37] itself with questionable methods and demonstrable flaws.[38–40]

The initial intent of these attacks seemed to be to discredit our work completely. They employed denigrating and insulting remarks ("rubbish," "ludicrous," "complete nonsense," "fatally flawed and widely discredited") implying that our work was not worthy of serious consideration. There were also suggestions that we were unqualified, and my integrity and competence were questioned. Some attacks were surprisingly petty. At one point, Professor 1 posted in a discussion group regarding salt intake that JAMA had shown a track record of poor editorial judgment by publishing "Kathy Flegal's terrible analyses" on overweight and mortality. Similarly, again using a diminutive form of my name, Professor 1 told one reporter: "Kathy Flegal just doesn't get it".[41] It became clear that one of the things that critics found disturbing was that what they called the "lay media" or the "popular press" (which apparently extended to the New York Times, Scientific American and even Nature, a leading scientific journal) had reported on our findings as though they were worthy of serious discussion. One of the effects of the public insults may also have been to deter or intimidate other investigators. An anonymous researcher was quoted[42] elsewhere as saying if character assassination is the price for publishing data that contradicts established beliefs, fewer academics will be willing to stick out their necks and offer up fresh thinking.

Our findings were simply findings, not arguments, explanations, recommendations or statements of personal opinions. However, some apparently had trouble grasping this, referring to our findings as "claims," as though this was a matter of questionable assertions, not of data. For example, a 2017 Facebook post (since deleted) from a senior NCI scientist (and PSPH graduate) referred to our "dangerous (and persistent) claims." Even though their work had little relevance to our estimates, the group from PSPH created a false narrative in which they and I were adversaries, taking sides and duking it out rhetorically. This myth even made its way into a lecture at NIH given by an eminent researcher, who stated incorrectly that some PSPH faculty and I were feuding and refused to appear on the same platform together. When I pointed out that this wasn't true, he graciously apologized and said it was something he had "heard."

Both our 2005 article and our 2013 article were straightforward and transparent. Both are still cited frequently in the scientific literature. We presented our findings objectively and even-handedly, without cloaking them in any spin[43–45] designed to obscure possibly inconvenient results (sometimes called "white hat bias"[45]); indeed, this lack of spin may have been one of the reasons why our findings were considered to be surprising. Our articles drew only on data that were free and readily publicly available and could easily be checked. The controversy was something deliberately manufactured, and the attacks primarily consisted of repeated assertions of preconceived opinions. Nonetheless, these attacks were surprisingly effective. A small number of vocal critics succeeded in raising considerable doubt about our work while concealing major errors in the estimates that they preferred. One result was that unlike other researchers who had published articles on the same topic, we ourselves were sometimes treated as though we were advocates, not scientists striving to be objective.

At first, I was startled, but eventually I came to expect partisan attacks masquerading as scientific concerns. I had expected some modest interest in our findings, pursued through normal channels of scientific discussion. I had not expected an aggressive campaign that included insults, errors, misinformation, behind-the-scenes gossip and maneuvers, social media posts and even complaints to my employer – many more instances than I have space to describe here. It seemed that some felt that our work should be judged not on its merits but rather on whether its findings supported the goals and objectives of the interlocutors. I saw first-hand the antagonism that can be provoked by inconvenient scientific findings.

Guidelines and recommendations should be based on objective and unbiased data. Development of public health policy and clinical recommendations is complex and needs to be evidence-based rather than belief-based.[46–50] This can be challenging when a hot-button topic is involved. Scientific findings should be evaluated on their merits, not on the basis of whether they fit a desired narrative.

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Medical News & Perspectives

Backlash Over Meat Dietary Recommendations Raises Questions About Corporate Ties to Nutrition Scientists

Rita Rubin, MA

It's almost unheard of for medical journals to get blowback for studies before the data are published. But that's what happened to the *Annals of Internal Medicine* last fall as editors were about to post several studies showing that the evidence linking red meat consumption with cardiovascular disease and cancer is too weak to recommend that adults eat less of it.

Annals Editor-in-Chief Christine Laine, MD, MPH, saw her inbox flooded with roughly 2000 emails—most bore the same message, apparently generated by a bot—in a half hour. Laine's inbox had to be shut down, she said. Not only was the volume unprecedented in her decade at the helm of the respected journal, the tone of the emails was particularly caustic.

"We've published a lot on firearm injury prevention," Laine said. "The response from the NRA (National Rifle Association) was less vitriolic than the response from the True Health Initiative."

The True Health Initiative (THI) is a nonprofit founded and headed by David Katz, MD. The group's website describes its work as "fighting fake facts and combating false doubts to create a world free of preventable diseases, using the time-honored, evidence-based, fundamentals of lifestyle and medicine." Walter Willett, MD, DrPH, and Frank Hu, MD, PhD, Harvard nutrition researchers who are among the top names in their field, serve on the THI council of directors.

Katz, Willett, and Hu took the rare step of contacting Laine about retracting the studies prior to their publication, she recalled in an interview with *JAMA*. Perhaps that's not surprising. "Some of the researchers have built their careers on nutrition epidemiology," Laine said. "I can understand it's upsetting when the limitations of your work are uncovered and discussed in the open."

Subsequent news coverage criticized the methodology used in the meat papers and raised the specter that some of the authors had financial ties to the beef industry, representing previously undisclosed conflicts of interest.

But what has for the most part been overlooked is that Katz and THI and many of its council members have numerous industry ties themselves. The difference is that their ties are primarily with companies and organizations that stand to profit if people eat less red meat and a more plant-based diet. Unlike the beef industry, these entities are surrounded by an aura of health and wellness, although that isn't necessarily evidence-based.

State of the Science

The *Annals* published 5 systematic reviews—4 that included results from randomized clinical trials (RCTs) and observational studies examining the relationship between red meat and health, and a fifth that looked at health-related values and preferences about eating meat. Based on the reviews, the authors produced a guideline that concluded adults needn't change their meat-eating habits.

In an accompanying editorial, coauthors Aaron Carroll, MD, and Tiffany Doherty, PhD, wrote that the guideline "is sure to be controversial, but it is based on the most comprehensive review of the evidence to date."

Carroll, a regular *JAMA* contributor who directs the Indiana University School of Medicine's Center for Pediatric and Adolescent Comparative Effectiveness Research, also wrote in the *New York Times* about the difficulties involved in conducting high-quality nutrition research.

"Even observational trials are hard to do well," Carroll wrote. In the short-term, it's difficult to find big differences in death and disease rates, even in large groups of people, he noted. "But quantifying what people are eating over long periods is challenging, too, because people don't remember."

The guideline's lead author, Bradley Johnston, PhD, is a cofounder and director of NutriRECS, an independent group that says it uses its members' expertise in clinical issues, nutrition, public health, and evidence-based medicine to produce nutritional guidelines that aren't hampered by conflicts of interest. Besides systematic reviews about the relationship between dietary patterns, food, and nutrients and health outcomes, NutriRECS said it considers patient and community values, attitudes, and preferences in its guideline recommendations.

In the *Annals* papers, NutriRECS members and their coauthors wrote that they sought to bring scientific rigor to current meat intake guidelines based mostly on observational studies that don't establish cause-and-effect relationships.

Johnston, an associate professor with Texas A&M University's nutrition and food science department, and his coauthors used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach to assess the quality of evidence on which they based their guideline. The GRADE framework considers evidence from randomized controlled trials (RCTs) to be of the highest quality and observational data to be of lower quality because of residual confounding. A panel of 14 individuals from 7 countries voted on the final guideline recommendations, and 3 dissented.

The authors, who noted that their recommendations were "weak" and based on low-certainty evidence, found no statistically significant link between meat consumption and risk of heart disease, diabetes, or cancer in a dozen RCTs that had enrolled about 54 000 participants. They did find a very small disease risk reduction among people who consumed 3 fewer servings of red meat weekly in epidemiological studies that followed millions, but the association was uncertain.

The authors acknowledged that other reasons besides health—namely concerns about the environment and animal welfare—might motivate people to reduce their meat intake, although those factors did not bear on the recommendations.

"That would require a systematic review of the relevant evidence, which was beyond the scope of our work—and indeed, of our expertise," Johnston and his coauthors commented on the *Annals* website in response to criticism for not considering environmental impact.

Katz and other THI members have criticized the authors' use of GRADE because, unlike pharmaceutical research, so much nutrition research is observational and so little involves RCTs. "We can't randomly assign people to diets for decades," Katz told *JAMA*. "Even if we could…we couldn't blind them to what they're eating…everything about nutritional epidemiology cries out for the use of other methods [besides GRADE]."

Katz and coauthors including Willett recently published an article about a tool they constructed that deemphasizes the importance of RCTs in evaluating evidence about what they call lifestyle medicine, including diet. "We're not anti-meat," said Katz, founding director of the US Centers for Disease Control and Prevention–funded Prevention Research Center at Griffin Hospital, a 160-bed acute-care community hospital in Derby, Connecticut, that's affiliated with the Frank H. Netter MD School of Medicine at Quinnipiac University and the Yale School of Medicine. "We're just pro-science."

The problem, said Harvard Medical School obesity specialist David Ludwig, MD, PhD, is that the science is not that good. "The average research study in nutrition is just lower quality."

In a recent *JAMA* Viewpoint, Ludwig and his coauthors wrote that compared with pharmaceutical research, dietary studies are far more challenging in terms of consistency, quality control, confounding, and interpretation, which makes translating those findings into public policy "exceedingly difficult."

Instead of coming up with tools to give more weight to observational studies in guideline development, nutrition scientists need to rethink how they design studies, John Ioannidis, MD, DSc, of the Stanford University School of Medicine, wrote in a 2018 *JAMA* Viewpoint.

"The field needs radical reform," Ioannidis noted.

Word Gets Around

Demands to retract the *Annals* papers before they were published suggest that the journal's embargo policy had been violated. (Embargoes prohibit reporters and press officers at the authors' institutions from circulating articles before they're published. Breaking an embargo is a serious breach.)

An article on the THI website states that the organization had obtained the meat articles 5 days before they were scheduled to be published online. Laine said Katz was on the *Annals*' press release list because he writes a weekly column for the *New Haven Register*, a Connecticut newspaper.

Katz said he circulated only the press release—"that's in the public domain"—but not the embargoed articles, among THI colleagues, telling them that the guideline "looks like it's going to be a serious problem for us."

Actually, embargoes apply to press releases as well as the articles themselves, said Angela Collom, the *Annals* media relations manager. The *Annals* and many other journals post releases to a website run by the American Association for the Advancement of Science that restricts access to members of the media who agree to embargo policies.

"Those channels are not public domain," Collom said. Because Katz shared the press release, she added, the *Annals* dropped him from the list of journalists eligible to receive embargoed releases or articles.

Four days before the articles were published, Katz and 11 THI members sent Laine a letter asking her to "pre-emptively retract publication of these papers pending further review by your office." The signatories included THI council members Hu and Willett; Neil Barnard, MD, president of the Physicians Committee for Responsible Medicine (PCRM); former US Surgeon General Richard Carmona, MD, MPH; David Jenkins, MD, PhD, a nutrition professor at the University of Toronto Faculty of Medicine; and Dariush Mozaffarian, MD, DrPH, dean of the Friedman School of Nutrition Science and Policy at Tufts University.

"It's really frightening that this group, which includes people like Walter Willett and Frank Hu at the Harvard School of Public Health, which happens to be my alma mater, were aware of this and assisting it," Laine said.

What's more, THI member John Sievenpiper, MD, PhD, also signed the letter to Laine even though he coauthored the NutriRECS systematic review about the relationship between meat consumption and all-cause mortality and the risk of cardiovascular disease, heart attack, and type 2 diabetes.

Laine said she contacted Sievenpiper, a nutrition scientist at the University of Toronto, after receiving the letter and pointed out that he had signed a standard form affirming his agreement with his paper's conclusions. That had not changed, he told her, but he did not agree with the guideline paper, of which he was not an author.

Hours before the meat articles were posted and the embargo lifted, Barnard's PCRM went so far as to petition the Federal Trade Commission (FTC) "to correct false statements regarding consumption of red and processed meat released by the *Annals of Internal Medicine*." But the FTC describes its role as protecting consumers and promoting competition in the marketplace, so it's unclear what authority or interest it would have in this case.

Despite PCRM's name, less than 10% of its 175 000 members are physicians, according to its website, which describes the organization's mission as "saving and improving human and animal lives through plant-based diets and ethical and effective scientific research."

"Information Terrorism"

The rebukes continued for weeks after publication of the meat articles, but Katz didn't comment via the typical routes of posting comments on the journal's website or writing a letter to the editor. He said he did neither because he's "able to react much more immediately and generate a much wider awareness with my own blog platforms."

In his October 6 column for the *New Haven Register*, Katz compared the articles, which he called "a great debacle of public health" to "information terrorism" that "can blow to smithereens…the life's work of innumerable careful scientists."

About 3 weeks later, PCRM asked the district attorney for the City of Philadelphia, where the *Annals* editorial office is located, "to investigate potential reckless endangerment" resulting from the publication of the meat papers and recommendations.

Another salvo came during a recent 1-day preventive cardiology conference, where half the presentations were on plant-based diets. During his keynote address, Willett showed a slide entitled "Disinformation" that faulted several organizations and individuals: the "sensationalist media," specifically the *Annals* and long-time *New York Times* science reporter Gina Kolata, who wrote the newspaper's first story about the meat papers; "Big Beef," specifically Texas A&M and nutrition scientist Patrick Stover, PhD, vice chancellor at the school and a coauthor of the NutriRECS meat consumption guideline; and "evidence-based academics," namely NutriRECS and Gordon Guyatt, MD, MSc, chair of the panel that wrote the meat consumption guidelines.

"It was part of my talk addressing the confusion that the public gets from the media about diet and health," Willett said in an email to *JAMA*. "Some of this relates to the triangle of disinformation that is…feeding into this. The same strategy is being used to discredit science on sugar and soda consumption, climate change, air pollution, and other environmental hazards."

Guyatt, a distinguished professor at McMaster University in Hamilton, Ontario, led the development 30 years ago of the concept of evidence-based medicine. In an interview with the Canadian Broadcasting Company a few days after the meat articles were posted, Guyatt called the response to them "completely predictable" and "hysterical."

Tufts University professor Sheldon Krimsky, PhD, described it differently. "It sounds like a political campaign," said Krimsky, who spoke on a panel about corporate influence on public health at the annual meeting of the American Public Health Association. "I've seen Monsanto do the same thing on the other side."

Krimsky, who studies linkages between science and technology, ethics and values, and public policy, said THI is part of a plant-based diet "movement." "If Katz wrote a paper, and it was published in one of the journals, I would assume he would have to disclose his relationship with his organization."

Steven Novella, MD, founder and executive editor of the Science-Based Medicine website and a long-time critic of Katz, was more pointed in his assessment of the THI campaign against the meat articles. "It's a total hit job," Novella, a Yale neurologist, told *JAMA*. "They have a certain number of go-to strategies…in order to dismiss any scientific findings they don't like." One such strategy, he said, is to lodge accusations of "tenuous" conflicts of interest.

"Confluence" or Conflict of Interest?

The *New York Times* was the first organization to raise the issue of potential conflicts of interest among the meat papers' authors. An October 4 article noted that Johnston, who reported having no conflicts of interest in the 3 years prior to publication, coauthored a December 2016 *Annals* study that was funded by the nonprofit International Life Sciences Institute (ILSI), which is primarily supported by the food and agriculture industry.

He and his coauthors of the 2016 article used GRADE to conduct "a separate and independent review of the methodological quality of dietary guidelines that address (added) sugar recommendations," Johnston told *JAMA*. They found that the evidence to support recommendations to cut back on added sugars was low to very low, highlighting "methodological deficiencies in nutritional guidelines," Johnston said. "This paper did not say sugar is okay to consume."

He said he received the ILSI funding in 2015, which was before the 3-year period for which he was required to report competing interests for the meat articles. However, according to a December 31 correction in the *Annals*, Johnston didn't include on his personal disclosure form a grant from Texas A&M AgriLife Research that he received within the 36-month reporting period. The grant funded investigator-driven research about saturated and polyunsatured fats, according to the correction.

Johnston isn't the only one who's had ILSI ties. True Health Initiative member Sievenpiper served as a scientific advisor for ILSI's Carbohydrates Committee and as vice chair of the ILSI North America Scientific Session 2018. And in late 2015, Canada's *National Post* newspaper reported that the Corn Refiners Association retained Sievenpiper as an expert witness to support its case that high-fructose corn syrup is no less healthy than sugar.

Shortly after the meat papers were published, THI Director Jennifer Lutz posted an article entitled "Steak Holder Interests: Industry Funding and Nutrition Reporting."

The article called out Stover, who coauthored the NutriRECS meat guideline, for having an undisclosed conflict of interest because his school receives funding from the beef industry. Stover is vice chancellor and dean for the Texas A&M College of Agriculture and Life Sciences, which is part of Texas A&M AgriLife. Lutz's article noted that 44 Farms, the largest Texas producer of Black Angus cattle, has established an endowment at Stover's school to support the International Beef Cattle Academy.

However, the beef industry provides only about 1.5% of AgriLife's funding, which it posts online, spokeswoman Olga Kuchment said. Federal sources, such as the US Department of Agriculture, account for about half of AgriLife's funding, Kuchment added. Besides animal science, AgriLife research areas include nutrition and food science, horticultural science, and soil and crop sciences. Although he has received AgriLife funding, Johnston said, "I personally have never had ties with the beef industry."

Meanwhile, industry ties and other potential conflicts of interest seem to be common among THI council members and the organization itself.

Among the not-for-profit "partners" listed on the THI website are #NoBeef, the Olive Wellness Institute, which describes itself as a "science repository on the nutrition, health, and wellness benefits of olives and olive products"; and the Plantrician Project, whose mission is "to educate, equip, and empower our physicians, healthcare practitioners and other health influencers with knowledge about the indisputable benefits of plant-based nutrition."

Among THI's for-profit partners are Wholesome Goodness, which sells "better-for-you foods" such as chips, breakfast cereals, and granola bars "developed with guidance from renowned nutrition expert Dr David Katz"; and Quorn, which sells meatless products made of mycoprotein, or fermented fungus made into dough.

Katz, who on his personal website describes himself as an entrepreneur, bristles at the suggestion that he, his organization, or any of his council members might have conflicts of interest.

"We weren't telling people: Buy our kumquats," he said.

Perhaps not kumquats, but Katz, according to his curriculum vitae (CV), and Hu have received funding from the California Walnut Commission. And the T.H. Chan School of Public Health, Hu's and Willett's academic home, has received hundreds of thousands of dollars from the walnut group.

"I don't think there is any basis in the world to accuse Walter Willett of conflict of interest. He and Frank Hu have genuine interest in the health effects of nuts," Katz said. "There's nothing fundamentally wrong [with] industry funding."

And, Katz told *JAMA*, "I think there's a big difference between conflict of interest…vs a confluence of interest. The work you do is what you care about…No one's ever paid me to say anything I don't believe."

Katz is a past president of an organization called the American College of Lifestyle Medicine (ACLM), whose website states that THI was "birthed from under ACLM's wing" in 2015, during his 2-year term. The ACLM established the American Board of Lifestyle Medicine, which isn't recognized by the American Board of Medical Specialties. Among ACLM's corporate "partners" is Plant Strong by Engine 2, which holds retreats "designed to foster and celebrate your plant-based potential," and MamaSezz, which delivers "ready-to-eat whole food plant-based meals with no BS (you know, Bad Stuff)."

Carmona, the THI council member and former surgeon general, serves on the board of Herbalife Nutrition, the dietary supplements company, and as "chief of health innovation" at Canyon Ranch, "the world's recognized leader in…luxury spa vacations."

In a 2018 commentary entitled "Resisting influence from agri-food industries on Canada's new food guide," THI council member Jenkins listed under his "competing interests" dozens of research grants from companies and industry groups, including the Pulse Research Network; the Almond Board of California; the International Nut and Dried Fruit Council; Soy Foods Association of North America; the Peanut Institute; Kellogg's Canada; and Quaker Oats Canada.

Katz's 66-page CV provides much food for thought about industry funding of nutrition research. He lists 2 grants from Hershey Foods totaling $731 000 to study the effects of cocoa on vascular function in people with hypertension and in those with obesity. He received 4 grants totaling $662 000 from the Egg Nutrition Center, the research and education division of the American Egg Board. One of the egg grants was awarded in August 2010, around the same time he published an article entitled "Recent anthropologic and clinical research raises questions about egg/cholesterol relationship–Eggsoneration" in the Egg Nutrition Center's *Nutrition Closeup* newsletter. He also received $249 701 from ISOThrive to study the effects of its eponymous "gastroenterologist recommended microFood" in overweight adults.

Katz also is senior nutrition advisor for Kind Healthy Snacks—a THI partner—and has received $153 000 in research grants from the company. In 2015, the year Katz became an advisor to Kind, it received a warning letter from the US Food and Drug Administration (FDA) for false nutrient claims, including the use of the word "healthy," on its labels.

Consumer Confusion

Do consumers lose when nutrition researchers can't play nice?

Timothy Caulfield, LLM, research director of the University of Alberta's Health Law Institute and a THI council member, gave 3 public lectures in 1 week not long after *Annals* published the meat articles. "This issue came up at all 3," Caulfield said.

"I understand both the concern about conflict of interest, especially in nutrition research, and the value of advocating [for] a more plant-based approach to nutrition," he said. "But there is so much public confusion surrounding diet. I worry about any messaging that might be interpreted as dogmatic."

Caulfield, described in a 2018 profile in Toronto's *Globe and Mail* as "one of North America's most high-profile skeptics, taking on the rising tide of pseudoscience and misinformation," noted that "the [THI] council has many alternative medicine practitioners and embraces 'integrative health.' This can be difficult to square with a science-based approach."

When asked if he planned to step down from the THI council, Caulfield said, "I'll need to put more thought into this. I haven't asked them to remove my name…but I haven't been actively involved."

The cacophony that has erupted over the meat papers is drowning out the valid points they made, Laine said.

"The sad thing is that the important messages have been lost," she said. "Trustworthy guidelines used to depend on who were the organizations or the people they came from." Today, though, "the public should know we don't have great information on diet," Laine said. "We shouldn't make people scared they're going to have a heart attack or colon cancer if they eat red meat." ■

Note: Source references are available through hyperlinks embedded in the article text online.

Bench to Bedside

DNA Prime Editing: A New CRISPR-Based Method to Correct Most Disease-Causing Mutations

Tracy Hampton, PhD

A new genome editing method may overcome critical barriers to correcting disease-causing genetic mutations. The approach draws on the popular clustered regularly interspaced short palindromic repeat (CRISPR)–associated 9 (Cas9) technology but avoids some of its undesired effects on DNA. In principle, the technique—called prime editing—could correct an estimated 89% of genetic variants known to be associated with human diseases.

The strategy, described recently in a study published in *Nature*, relies on prime editors—an altered form of the Cas9 protein and an RNA that together orchestrate a series of DNA targeting, writing, and repair steps that result in an edit. Unlike with typical CRISPR-Cas9 technology, the prime editor Cas9 doesn't make double-stranded cuts in DNA, which can lead to uncontrolled DNA insertions and deletions at the cut site. Instead, the altered Cas9 only snips a single strand of the double helix.

Making double-stranded cuts can be useful for disrupting genes and for moving large segments of DNA, according to the study's senior author, David Liu, PhD, of the Broad Institute of Harvard and MIT. But using double-stranded cuts to make precise DNA changes has proven more difficult.

Liu and his colleagues first overcame this hurdle in 2016, when they developed so-called base editors. Although base editing uses CRISPR's targeting ability, it directly converts one nucleotide base into another instead of cutting the double helix. Base editors can efficiently correct 4 of the most common types of single-base mutations, while avoiding insertion and deletion byproducts, but they can't fix all errors.

Prime editing goes a step further. Not only can it swap single DNA bases, but it can also make both deletions and insertions.

"If CRISPR-Cas9 is like scissors and base editors are like pencils, then prime editors are like word processors, capable of searching for target DNA sequences and precisely replacing them with edited DNA sequences," Liu told *JAMA*. He noted that all 3 technologies have their own strengths and weaknesses and that each will likely have unique and useful roles in applications such as medicine and agriculture.

Liu and his team used prime editing to perform more than 175 edits in various types of human cells, including inserting new DNA segments up to 44 bases long and removing segments up to 80 bases long. Some of the edits hinted at future health applications: using human cells, the researchers successfully corrected the primary genetic causes of sickle cell disease and Tay-Sachs disease. The technique proved to be more efficient than traditional Cas9 editing, with less off-target editing at known Cas9 off-target sites.

A prime editor's protein component fuses an altered form of the Cas9 enzyme, which cuts DNA, and a reverse transcriptase, which generates complementary DNA from an RNA template. The technique's RNA component is a prime editing guide RNA (pegRNA) that specifies the targeted DNA site and encodes the desired edit.

The reverse transcriptase directly copies the part of the pegRNA that encodes the edited DNA sequence into the target site, resulting in a new flap of DNA that contains the edit. When the cell incorporates this edited flap, it replaces the original DNA sequence on both strands of the DNA double helix.

"The key to prime editing's versatility is that the part of the pegRNA that specifies the edited DNA sequence can be virtually any sequence," Liu said. This advantage allows the approach to install all possible point mutations, small insertions, small deletions, and their combinations into target DNA sites. The researchers corrected the Tay-Sachs mutation by removing a 4-base insertion, for example. In another edit, they deleted 2 nucleotide bases at a specific position in the human genome and converted 1 nearby base into another—a G to a T.

"In many respects, this first report of prime editing is the beginning, rather than

Original Research Communications

Associations of unprocessed and processed meat intake with mortality and cardiovascular disease in 21 countries [Prospective Urban Rural Epidemiology (PURE) Study]: a prospective cohort study

Romaina Iqbal,[1] Mahshid Dehghan,[2] Andrew Mente,[2] Sumathy Rangarajan,[2] Andreas Wielgosz,[3] Alvaro Avezum,[4] Pamela Seron,[5] Khalid F AlHabib,[6] Patricio Lopez-Jaramillo,[7] Sumathi Swaminathan,[8] Noushin Mohammadifard,[9] Katarzyna Zatońska,[10] Hu Bo,[11] Ravi Prasad Varma,[12] Omar Rahman,[13] AfzalHussein Yusufali,[14] Yin Lu,[11] Noorhassim Ismail,[15] Annika Rosengren,[16] Neşe Imeryuz,[17] Karen Yeates,[18] Jephat Chifamba,[19] Antonio Dans,[20] Rajesh Kumar,[21] Liu Xiaoyun,[11] Lungi Tsolekile,[22] Rasha Khatib,[23,24] Rafael Diaz,[25] Koon Teo,[2] and Salim Yusuf,[2] on behalf of the PURE study

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ABSTRACT

Background: Dietary guidelines recommend limiting red meat intake because it is a major source of medium- and long-chain SFAs and is presumed to increase the risk of cardiovascular disease (CVD). Evidence of an association between unprocessed red meat intake and CVD is inconsistent.

Objective: The study aimed to assess the association of unprocessed red meat, poultry, and processed meat intake with mortality and major CVD.

Methods: The Prospective Urban Rural Epidemiology (PURE) Study is a cohort of 134,297 individuals enrolled from 21 low-, middle-, and high-income countries. Food intake was recorded using country-specific validated FFQs. The primary outcomes were total mortality and major CVD. HRs were estimated using multivariable Cox frailty models with random intercepts.

Results: In the PURE study, during 9.5 y of follow-up, we recorded 7789 deaths and 6976 CVD events. Higher unprocessed red meat intake (≥250 g/wk vs. <50 g/wk) was not significantly associated with total mortality (HR: 0.93; 95% CI: 0.85, 1.02; *P*-trend = 0.14) or major CVD (HR: 1.01; 95% CI: 0.92, 1.11; *P*-trend = 0.72). Similarly, no association was observed between poultry intake and health outcomes. Higher intake of processed meat (≥150 g/wk vs. 0 g/wk) was associated with higher risk of total mortality (HR: 1.51; 95% CI: 1.08, 2.10; *P*-trend = 0.009) and major CVD (HR: 1.46; 95% CI: 1.08, 1.98; *P*-trend = 0.004).

Conclusions: In a large multinational prospective study, we did not find significant associations between unprocessed red meat and poultry intake and mortality or major CVD. Conversely, a higher intake of processed meat was associated with a higher risk of mortality and major CVD. *Am J Clin Nutr* 2021;00:1–10.

Keywords: unprocessed red meat, poultry, processed meat intake, mortality, cardiovascular disease, cohort study

Introduction

Dietary guidelines recommend limiting the consumption of unprocessed red meat because it is a source of medium- and long-chain SFAs and is presumed to increase the risk of cardiovascular disease (CVD) (1). However, there is mounting evidence that has challenged conventional restrictions on SFA intake for CVD prevention. Several meta-analyses of cohort studies have shown that higher intakes of SFAs were not associated with a higher risk of CVD (1–3) but may be associated with a lower risk of mortality and stroke (4, 5). The uncertainty about SFA intake and its association with CVD is partly due to the variation in its major food sources, heterogeneity in its biological effects, and gene–diet interaction—all of which modulate associations between SFA intake and health outcomes (6).

Cohort studies have consistently found that processed meat, which is modified to improve its taste or to extend its shelf life, has an adverse association with CVD. However, there is uncertainty about the association between unprocessed red meat and CVD. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study, including 448,568 participants across 10 European countries with >26,000 deaths, found no significant association between unprocessed red meat intake and total or cause-specific mortality (7). In contrast, a pooled analysis of 29,682 individuals from 6 US prospective cohort studies found that each additional 2 servings of unprocessed red meat and poultry per week were associated with a 3% and 4% higher risk of mortality, respectively (8). The Nutritional Recommendations (NutriRECS) Consortium has recently recommended that adults do not need to change their meat consumption due to the uncertainty of increased risk associated with higher consumption (9). Most of the evidence on meat intake and health outcomes is from studies conducted in North America, Europe, and Japan, where the amount and type of meat consumed differ from other regions of the world (e.g., South Asia and Africa). Therefore, data from all world regions are essential for making global dietary recommendations.

We aimed to examine the association between different types of processed and unprocessed meat with mortality and CVD using data from the Prospective Urban Rural Epidemiology (PURE) Study.

Methods

Study design and participants

The design of the PURE study has been described previously (10). Briefly, the study is a large-scale prospective cohort study of 164,007 individuals aged 35–70 y from 21 low-, middle-, and high-income countries. The low-income countries included 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; and high-income countries were Canada, Saudi Arabia, Sweden, and the United Arab Emirates. Recruitment began on 1 January 2003 and follow-up visits were conducted every 3 y. During recruitment, the initial response rate was 78% of those eligible, and the first wave had a >96% follow-up rate at 10 y. Details of the follow-up visits overall and by country are provided in **Supplemental Tables 1** and **2**. This analysis is based on the data collected in the first 2 phases of the PURE study. Individuals were enrolled from 21 countries and had completed at least 1 cycle of follow-up visits. Information on vital status was available for 98% of participants, and CVD information was available for 95% of participants. We included all outcome events known to us until 30 June 2019. Details of the sampling and recruitment strategy are described in **Supplemental Figure 1**. For present analysis, we excluded participants with a history of CVD (n = 11,462), history of cancer (n = 1,707), missing information on age and sex, and those with an implausible value of energy intake (<500 or >5000 kcal/d; n = 16,541). All participants provided written informed consent. The ethics committees approved the study protocol at each participating institution (**Supplemental Material**).

The study was coordinated by the Population Health Research Institute, Hamilton Health Sciences, and McMaster University, Hamilton, Ontario, Canada.

Procedures

Standardized questionnaires were used for collecting information about demographic factors, lifestyle, health history, and medication use at baseline and CVD events and mortality information (classified by cause) during follow-up. The disease and mortality information was adjudicated in each country by trained physicians using common definitions. Participants were followed up at 3, 6, and 9 y.

Dietary information

Country-specific (or region-specific in India) validated FFQs were used for collecting information on usual dietary intake from all of the participants at baseline. Where validated FFQs were not available, we developed and validated the FFQs using standard methods (**Supplemental Tables 3** and **4**). The FFQs contained a list of food items commonly consumed over the previous year, and the number of food items in the FFQs varied from 95 to 250. All FFQs contained predefined frequencies of consumption that varied from never to >6 times/d along with local portion sizes. To estimate total energy and nutrient intakes, the USDA food-composition database was used as the base with modifications and adaptations from local databases and collected recipes of some of the food items (11). However, for Canada, China, India, Malaysia, South Africa, Sweden, and Turkey, we used the food-composition database available in that country.

Unprocessed red meat was defined as the consumption of beef, mutton, veal, and pork. Poultry included the flesh of all birds. Processed meat included any types of meat that had been salted, cured, or treated with preservatives and/or food additives. The amount of meat intake was computed by multiplying the daily frequency of consumption by local portion size and then converting to grams per week for further analysis.

The external funders of the study had no role in the design of the study, its implementation at different sites globally for data collection, data analysis, interpretation of the data, or writing of the manuscript. The corresponding author (MD) and co-authors (RI, AM, SR, SY) had access to all the data.

Supplemental Figures 1–5, Supplemental Tables 1–8, and Supplemental Material are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CV, cardiovascular; CVD, cardiovascular disease; MET, metabolic equivalent; MI, myocardial infarction; PURE, Prospective Urban Rural Epidemiology.

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Outcomes

The primary outcomes were total mortality and major cardiovascular events (fatal CVD, nonfatal myocardial infarction, stroke, and heart failure). Secondary outcomes were myocardial infarction (MI), stroke, heart failure, cardiovascular mortality, and noncardiovascular mortality (including cancer mortality). The definitions for these events have been published previously (10).

Statistical analysis

Age, wealth index, and unprocessed red meat, poultry, processed meat, and total energy intakes were reported as continuous variables. The location was categorized as urban or rural. Smoking status was categorized as never, former, or current. Categories of education were none or primary school (first 6 y), secondary school (7–11 y), and college, trade school, or university (>11 y). Physical activity was categorized based on the metabolic equivalent of task (MET) per minute per week into low (<600 MET-min/wk), moderate (600–3000 MET-min/wk), and high (>3000 MET-min/wk) activity. In the PURE study, most participants were from low- and middle-income countries, and meat consumption (an expensive food item) might be more affordable for high-socioeconomic-status individuals than those of low socioeconomic status. To account for socioeconomic factors, we adjusted for both education and wealth index in the multivariable models. Wealth index was developed using information collected on household possessions such as electricity, car, computer, television, phone, etc., and then conducting principal components analysis as a data-reduction technique to create a wealth index.

Due to cultural similarities in the dietary intake, participants were grouped into 7 regions that included North America and Europe, South America, Africa, the Middle East, South Asia, South East Asia, and China.

Daily unprocessed red meat, poultry, and processed meat intakes were adjusted for 1000 kcal/d. For unprocessed red meat and poultry, we grouped participants into those consuming <50 g/wk, 50 to <150 g/wk, 150 to <250 g/wk, and ≥250 g/wk.

For processed meat analysis, since 45% of participants reported "never" consuming processed meat, we restricted our analysis to those countries where median consumption was ≥10 g/d (n = 31,640). The countries included were Argentina, Brazil, Canada, Chile, Poland, South African, and Sweden. Participants were grouped into 0 g/wk, >0 to <50 g/wk, 50 to <150 g/wk, and ≥150 g/wk. Also, we assessed associations between unprocessed red meat, poultry, and processed red meat per 100-g increase per week.

To calculate HRs, we used the Cox frailty models with random intercepts to account for center-level clustering, which took into account region- and country-level clustering effects. Estimates of HRs and 95% CIs are presented for consumption categories using the lowest intakes as the reference group. All models were adjusted for age, sex, location, education, wealth index, smoking status, physical activity, diabetes status, blood pressure–lowering medication, study center, total energy intake, and intakes of fruit, vegetables, dairy, fish, processed foods, refined grains, legumes, and total dietary fiber. We adjusted the analysis of unprocessed red meat intake for poultry intake and vice versa.

In the subgroup analyses, we excluded participants who reported any CVD in the first 2 y after recruitment. We assessed the association in 7 geographic regions separately since the amount of unprocessed red meat and poultry consumption varied across regions. Also, the association between unprocessed red meat and poultry intake was assessed using vegetarians as a reference group. Additionally, we conducted competing risk analyses using the Fine and Gray (12) approach for CVD mortality and major CVD for unprocessed red meat, poultry, and processed meat. In these competing risk regressions, we considered risk of cardiovascular (CV) mortality and major CVD in the absence of non-CV mortality as the competing risk. We also conducted the stratified analysis defining smoking status as never or ever smoker. Further, we examined the association between processed meat and death due to injury as a negative control and computed E-values using the VanderWeele method (13). The potential nonlinear nature of the association of all exposures with outcomes was examined using cubic splines with 3 knots for the exposures. Data were analyzed with the Stata software package, version 15 (StataCorp).

Results

Table 1 shows the characteristics of participants by categories of unprocessed red meat, poultry, and processed meat intake. Participants with higher unprocessed red meat intake consumed more poultry, fruit, vegetables, and dairy, but less starchy foods. A similar pattern was found among poultry consumers. For processed meat intake, compared with nonconsumers, those with higher processed meat intake consumed more unprocessed red meat, poultry, fruit, and vegetables.

During the median follow-up of 9.5 y, we recorded 7789 deaths and 6976 major cardiovascular events (2968 MI, 3335 stroke, and 659 heart failure). **Table 2** shows the association between the consumption of unprocessed red meat and health outcomes. No association was observed between higher consumption of unprocessed red meat (≥250 g/wk vs. <50 g/wk) with total mortality (HR: 0.93; 95% CI: 0.85, 1.02; P-trend = 0.14) or major CVD (HR: 1.01; 95% CI: 0.92, 1.11; P-trend = 0.72). Similarly, we did not observe any significant association between unprocessed red meat intake and risk of CV mortality, non-CV mortality, cancer mortality, MI, stroke, or heart failure.

Higher consumption of poultry was also not significantly associated with total mortality (HR: 0.96; 95% CI: 0.86, 1.06; P-trend = 0.21) or major CVD (HR: 1.02; 95% CI: 0.90, 1.16; P-trend = 0.95) and other health outcomes (**Table 3**).

Higher intake of processed meat (≥150 g/wk vs. 0 g/wk) was associated with higher total mortality (HR: 1.51; 95% CI: 1.08, 2.10; P-trend = 0.009), major CVD (HR: 1.46; 95% CI: 1.08, 1.98; P-trend = 0.004), non-CV mortality (HR: 1.50; 95% CI: 1.03, 2.19; P-trend = 0.02), cancer mortality (HR: 1.84; 95% CI: 1.14, 2.97; P-trend = 0.02), MI (HR: 1.62; 95% CI: 0.98, 2.69; P-trend = 0.03), and stroke (HR: 1.56; 95% CI: 0.94, 2.58; P-trend = 0.04). Further, we found a higher risk of events with each 100-g/wk increase in processed meat intake (**Table 4**).

When individuals with events occurring within 24 mo were excluded in sensitivity analyses, the results were unchanged for both unprocessed red meat and poultry (Tables 2 and 3). Additionally,

TABLE 1 Characteristics of participants by categories of unprocessed red meat and poultry ($n = 134,297$) and processed meat intake ($n = 31,640$)[1]

	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*
Unprocessed red meat intake					
n	38,878	33,644	23,198	38,577	
Age, mean ± SD, y	49.6 ± 10.1	50.4 ± 9.8	50.4 ± 9.6	50.0 ± 9.6	<0.001
Men, *n* (%)	15,611 (40.1)	14,132 (42.0)	9838 (42.4)	16,452 (43.0)	<0.001
Urban, *n* (%)	15,392 (39.6)	18,188 (54.1)	14,106 (60.8)	22,173 (57.5)	<0.001
Current smoker, *n* (%)	7891 (20.4)	7275 (21.8)	4647 (20.2)	8164 (21.3)	<0.001
Trade, college, or university, *n* (%)	4979 (12.9)	6363 (19.0)	5789 (25.0)	8329 (21.6)	<0.001
Highly active, *n* (%)	15,485 (44.7)	13,852 (44.0)	9685 (44.0)	17,015 (46.0)	<0.001
History of diabetes, *n* (%)	3176 (8.2)	2329 (7.0)	1492 (6.4)	2484 (6.5)	<0.001
Taking blood pressure medication, *n* (%)	2970 (7.6)	3992 (12.0)	3267 (14.1)	5647 (14.6)	<0.001
Food intake, mean ± SD, g/d					
Unprocessed red meat	5 ± 6	30 ± 15	62 ± 25	137 ± 76	<0.001
Poultry	16 ± 33	31 ± 40	32 ± 39	33 ± 36	<0.001
Processed meat	3 ± 11	9 ± 18	10 ± 17	9 ± 14	<0.001
Fish	44 ± 99	31 ± 55	30 ± 48	25 ± 40	<0.001
Refined grains	150 ± 211	199 ± 204	179 ± 170	186 ± 169	<0.001
Legumes	83 ± 95	55 ± 68	52 ± 56	47 ± 53	<0.001
Fruit	127 ± 203	214 ± 262	236 ± 255	205 ± 199	<0.001
Vegetables	193 ± 190	258 ± 216	292 ± 207	282 ± 194	<0.001
Dairy	125 ± 191	164 ± 228	214 ± 240	205 ± 216	<0.001
Fiber	16 ± 13	24 ± 16	26 ± 15	24 ± 13	<0.001
Energy intake, mean ± SD, kcal/d	2062 ± 833	2134 ± 818	2209 ± 814	2210 ± 788	<0.001
Poultry intake					
n	69,349	36,793	17,069	11,086	
Age, mean ± SD, y	49.9 ± 10	50.2 ± 10	50.2 ± 10	50.3 ± 9.7	<0.001
Men, *n* (%)	29,182 (42)	15,405 (42)	7012 (41)	4434 (40)	<0.001
Urban, *n* (%)	30,681 (44)	22,180 (60)	10,656 (62)	6342 (57)	<0.001
Current smoker, *n* (%)	15,656 (22)	7190 (20)	3163 (19)	1968 (18)	<0.001
Trade, college, or university, *n* (%)	10,322 (15)	9063 (25)	3835 (23)	2240 (20)	<0.001
Highly active, *n* (%)	29,118 (45)	15,567 (46)	6927 (43)	4425 (42)	<0.001
History of diabetes, *n* (%)	3826 (6)	2822 (8)	1605 (9)	1228 (11)	<0.001
Taking blood pressure medication, *n* (%)	6139 (9)	5010 (14)	2775 (16)	1952 (18)	<0.001
Food intake, mean ± SD, g/d					
Unprocessed red meat	46 ± 60	72 ± 72	79 ± 78	64 ± 66	<0.001
Poultry	5 ± 5	30 ± 16	63 ± 24	107 ± 62	<0.001
Processed meat	5 ± 13	12 ± 19	11 ± 17	8 ± 14	<0.001
Fish	30 ± 73	35 ± 62	38 ± 59	34 ± 54	<0.001
Refined grains	202 ± 234	159 ± 141	154 ± 117	124 ± 91	<0.001
Legumes	64 ± 79	57 ± 66	57 ± 64	53 ± 66	<0.001
Fruit	146 ± 210	233 ± 244	244 ± 230	240 ± 261	<0.001
Vegetables	216 ± 162	286 ± 232	298 ± 234	292 ± 253	<0.001
Dairy	145 ± 200	212 ± 242	204 ± 238	171 ± 202	<0.001
Fiber	21± 15	23 ± 15	23 ± 15	22 ± 15	<0.001
Energy intake, mean ± SD, kcal/d	2076 ± 779	2255 ± 859	2279 ± 807	2043 ± 842	<0.001
Processed meat intake, g/wk	0	<50	50 to <150	≥150	
n	3009	14,597	10,923	3111	
Age, mean ± SD, y	52.2 ± 10.0	52.0 ± 9.5	50.1 ± 9.3	52.0 ± 9.5	<0.001
Men, *n* (%)	936 (31.0)	5516 (38.0)	5224 (48.0)	1267 (41.0)	<0.001
Urban, *n* (%)	1578 (52.4)	9495 (65.0)	6976 (64.0)	1922 (62.0)	<0.001
Current smoker, *n* (%)	786 (26.4)	2806 (19.3)	2436 (22.4)	755 (24.4)	<0.001
Trade, college, or university, *n* (%)	558 (19.0)	5302 (36.5)	3899 (35.8)	1144 (37.0)	<0.001
Highly active, *n* (%)	1156 (52.3)	7418 (56.0)	5552 (57.0)	1590 (57.7)	<0.001
History of diabetes, *n* (%)	180 (6.0)	864 (5.9)	624 (5.7)	179 (5.8)	0.88
Taking blood pressure medication, *n* (%)	654 (10.4)	2960 (46.8)	2095 (33.1)	612 (9.6)	0.01
Food intake, mean ± SD, g/d					
Unprocessed red meat	47 ± 66	92 ± 89	81 ± 73	57 ± 52	<0.001
Poultry	36 ± 39	45 ± 38	40 ± 33	32 ± 30	<0.001
Processed red meat	0	8 ± 5	27 ± 13	67 ± 34	<0.001
Fish	14 ± 24	20 ± 26	22 ± 24	24 ± 23	<0.001
Refined grains	125 ± 102	157 ± 117	137 ± 93	121 ± 74	<0.001
Legumes	33 ± 56	42 ± 56	54 ± 68	36 ± 44	<0.001

(*Continued*)

TABLE 1 (*Continued*)

	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*
Fruit	204 ± 253	256 ± 214	244 ± 214	226 ± 186	<0.001
Vegetables	232 ± 248	351 ± 264	345 ± 231	288 ± 203	<0.001
Dairy	205 ± 260	318 ± 290	308 ± 284	240 ± 231	<0.001
Fiber	23 ± 13	28 ± 15	26 ± 12	24 ± 11	<0.001
Energy intake, mean ± SD, kcal/d	1714 ± 727	2272 ± 822	2194 ± 783	1992 ± 739	<0.001

[1] To test for differences across categories of unprocessed red meat, poultry, and processed meat intake, we used ANOVA test of means and chi-square test for categorical variables. The analysis for processed meat was conducted only among participants from countries with a median consumption of ≥10 g/d (Argentina, Brazil, Canada, Chile, Poland, South African, and Sweden).

we observed a similar association between unprocessed red meat, poultry, and outcomes using vegetarians as the reference group (**Supplemental Table 5**). In the competing risk analyses, the HRs for both CV mortality and major CVD were similar to the conventional estimates from the Cox models (**Supplemental Table 6**).

We further stratified our analysis using smoking status as ever or never smoker. No significant associations were found with smoking status, and the associations between unprocessed red meat and poultry intake with mortality or major CVD were not significant among ever and never smokers (**Supplemental Figure 2**). Higher processed meat intake was associated with higher mortality and the risk of major CVD in both ever and never smokers (**Supplemental Figure 3**). Also, when death due to injury was considered as a negative control, higher consumption of processed meat was not significantly associated with death due to injury (**Supplemental Table 7** and **Supplemental Figure 4**). The E-value suggests that substantial unmeasured confounding would be needed to explain away the observed association between processed meat and events.

Additionally, when we stratified our analyses by geographic regions, for all regions, except for South Asia, no significant differences were found in the associations between unprocessed red meat for total mortality (*P*-interaction for regions and unprocessed red meat = 0.4). Similarly, there was a nonsignificant association between poultry and total mortality in almost all regions. However, a significant positive association was observed for China (*P*-interaction for regions and poultry = 0.6, respectively) (Supplemental Figure 5A, B).

Multivariable cubic splines for unprocessed red meat and poultry showed no significant associations with total mortality. A significant positive linear association was found for processed meat intake and total mortality (**Figure 1**).

Discussion

In a large multinational cohort study of 134,297 participants, including 7789 deaths and 6976 CVD events from 21 countries, we did not find significant associations between unprocessed red meat and poultry intake with mortality or major CVD. In contrast, higher processed meat intake was associated with higher risks of total mortality and major CVD.

Our finding of a nonsignificant association between unprocessed red meat intake and health outcomes is supported by the results of some (but not all) previous studies (14). Unprocessed red meat consumption has generally been associated with increased risks of total mortality and CVD (15). In contrast, a meta-analysis of 6 observational studies involving 1,330,352 individuals, with 137,376 deaths, indicated that unprocessed red meat was not associated with an increased risk of mortality (16). Similarly, in a meta-analysis of 17 prospective cohort studies conducted globally, higher unprocessed red meat consumption was not associated with total mortality (HR: 1.05; 95% CI: 0.93, 1.19; $P = 0.43$) (17). However, recent analyses of US prospective cohort studies reported that higher unprocessed red meat intake was associated with higher risks of mortality and CVD (8, 18). Possible reasons for these differences include differences in the amount of unprocessed red meat intake in different regions of the world [e.g., 100 g/d for the Nurses' Health Study and the Health Professionals Follow-Up Study (18) and ∼57 g/d for the other 6 US cohort studies (8)] compared with the substantially lower intake amounts (37 g/d) among the PURE participants. However, in 1 study where an adverse association was reported between red meat consumption and all-cause and CVD mortality, the reference group was nonconsumers of red meat who may be different in many other behavioral factors that might not have been captured by the study, leading to residual confounding (19). Other factors include differences in cooking methods (e.g., stewed vs. grilled meat preferences) and the background replacement foods (e.g., refined grains vs. animal foods). In addition, most of the studies that have reported adverse associations were from the Western countries, whereas no significant association was observed among studies conducted in Asia (20).

We found an adverse association between processed meat intake and health outcomes, consistent with meta-analyses of observational studies (17, 21, 22). A meta-analysis of 9 observational studies, including 1,330,352 individuals and 137,376 deaths, showed 23% higher mortality among higher processed meat consumers (16). The potential adverse impact of processed meat on health may not be entirely due to its saturated fat or cholesterol content as the amounts of these nutrients are similar in processed and unprocessed meats (23). The amounts of preservative and food additives in processed and unprocessed meats differ markedly, which may partly explain their different effects on health (24). In a large cohort study conducted in 6 states and 2 metropolitan areas of the United States, processed meat's nitrate content explained a large proportion of the increased risk of CVD mortality (25). Similarly, in a European study, adverse associations with CV mortality and respiratory mortality were observed only for processed meat consumption due to high nitrite content (26).

TABLE 2 Association of unprocessed red meat intake and outcome events[1]

	Intake					
	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*-trend[2]	Per 100-g/wk increase
N	38,878	33,644	23,198	38,577		
Total mortality						
No. of events	3433	1938	930	1488		0.98 (0.97, 1.00)
Age, sex, and center adjusted	1.00 (ref)	0.96 (0.90, 1.03)	0.88 (0.81, 0.96)	0.84 (0.78, 0.92)	0.001	
Multivariable	1.00 (ref)	1.01 (0.94, 1.09)	0.99 (0.90, 1.08)	0.93 (0.85, 1.02)	0.14	
Excluding those with event in first 24 mo	1.00 (ref)	1.03 (0.96, 1.11)	0.99 (0.89, 1.10)	0.96 (0.87, 1.07)	0.43	
CV mortality						
No. of events	1287	642	305	561		0.99 (0.96, 1.02)
Age, sex, and center adjusted	1.0 (ref)	0.92 (0.83, 1.03)	0.83 (0.71, 0.96)	0.88 (0.77, 1.02)	0.04	
Multivariable	1.0 (ref)	0.91 (0.83, 1.06)	0.90 (0.76, 1.05)	0.97 (0.84, 1.14)	0.68	
Excluding those with event in first 24 mo	1.0 (ref)	0.99 (0.86, 1.13)	0.88 (0.74, 1.05)	1.02 (0.86, 1.21)	0.95	
Non-CV mortality						
No. of events	2326	1388	664	980		
Age, sex, and center adjusted	1.0 (ref)	0.96 (0.89, 1.04)	0.89 (0.80, 0.99)	0.81 (0.73, 0.89)	0.001	0.98 (0.96, 1.00)
Multivariable	1.0 (ref)	1.02 (0.94, 1.11)	1.02 (0.91, 1.14)	0.89 (0.79, 1.00)	0.10	
Excluding those with event in first 24 mo	1.0 (ref)	1.03 (0.94, 1.12)	1.03 (0.91, 1.15)	0.91 (0.81, 1.03)	0.21	
Cancer mortality						
No. of events	578	518	311	486		0.98 (0.95, 1.01)
Age, sex, and center adjusted	1.0 (ref)	0.98 (0.86, 1.12)	0.87 (0.74, 1.01)	0.81 (0.69, 0.94)	0.002	
Multivariable	1.0 (ref)	1,04 (0.90, 1.20)	0.98 (0.83, 1.16)	0.90 (0.76, 1.05)	0.10	
Excluding those with event in first 24 mo	1.0 (ref)	1.03 (0.90, 1.20)	0.98 (0.82, 1.17)	0.92 (0.78, 1.09)	0.25	
Major CVD						
No. of events	2449	1673	1027	1827		
Age, sex, and center adjusted	1.0 (ref)	0.95 (0.88, 1.02)	0.91 (0.84, 1.00)	0.95 (0.87, 1.03)	0.22	1.00 (0.98, 1.01)
Multivariable	1.0 (ref)	0.98 (0.91, 1.06)	1.00 (0.91, 1.10)	1.01 (0.92, 1.11)	0.72	
Excluding those with event in first 24 mo	1.0 (ref)	0.98 (0.90, 1.07)	0.98 (0.90, 1.09)	1.04 (0.94, 1.15)	0.35	
Myocardial infarction						
No. of events	1255	621	374	718		
Age, sex, and center adjusted	1.0 (ref)	0.92 (0.82, 1.03)	0.87 (0.76, 1.01)	0.99 (0.86, 1.13)	0.87	
Multivariable	1.0 (ref)	0.91 (0.81, 1.03)	0.90 (0.77, 1.05)	0.98 (0.85, 1.13)	0.89	1.00 (0.97, 1.03)
Excluding those with event in first 24 mo	1.0 (ref)	0.91 (0.80, 1.04)	0.85 (0.72, 1.00)	0.99 (0.84, 1.15)	0.89	
Stroke						
No. of events	971	870	556	938		
Age, sex, and center adjusted	1.0 (ref)	1.02 (0.92, 1.13)	1.00 (0.88, 1.12)	0.96 (0.85, 1.07)	0.34	
Multivariable	1.0 (ref)	1.09 (0.98, 1.22)	1.15 (1.01, 1.31)	1.10 (0.97, 1.25)	0.18	1.00 (0.97, 1.02)
Excluding those with event in first 24 mo	1.0 (ref)	1.10 (0.97, 1.23)	1.17 (1.02, 1.35)	1.15 (1.00, 1.32)	0.04	
Heart failure						
No. of events	208	166	115	167		
Age, sex, and center adjusted	1.0 (ref)	0.77 (0.61, 0.97)	0.87 (0.67, 1.13)	0.78 (0.60, 1.01)	0.15	
Multivariable	1.0 (ref)	0.82 (0.63, 1.06)	0.98 (0.73, 1.31)	0.80 (0.59, 1.07)	0.28	0.97 (0.92, 1.03)
Excluding those with event in first 24 mo	1.0 (ref)	0.81 (0.62, 1.07)	0.85 (0.62, 1.18)	0.79 (0.58, 1.09)	0.23	

[1] n = 134,297. Values are HRs (95% CIs) unless otherwise indicated. Multivariable models adjusted for age, sex, location, education, wealth index, smoking status, physical activity, diabetes status, blood pressure–lowering medications, fruits, vegetable, dairy, poultry, fish, refined grains, processed foods, legumes, total dietary fiber, total energy intake, and center as a random effect. CV, cardiovascular; CVD, cardiovascular disease; ref, reference.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous value.

Our study has several strengths. First, the PURE study is one of the largest multinational studies that has examined the association between different types of meat and health outcomes in different regions of the world and the only cohort study to cover 5 continents. Second, a large number of fatal and nonfatal events were recorded in this study, making our findings robust. Third, country-specific validated FFQs were used for the collection of the dietary data by well-trained staff. The PURE study covers substantially more diverse populations and broad patterns of diet. The sampling strategy used in PURE ensures representation from urban and rural communities from different geographic areas (27).

Furthermore, our results were robust in different populations with varying meat intake levels, which suggests that the findings are widely applicable. In the current study, the sample comprised 134,297 participants with a completed FFQ and without a history of CVD or cancer at baseline. Baseline characteristics were generally similar between people who were included or excluded from the current analysis. The follow-up rates in the PURE study were high (96% at 9 y), so loss to follow-up was unlikely to significantly impact our findings.

Nonetheless, our study also has some potential limitations. First, dietary intake was self-reported and variations in reporting might lead to random errors that could distort the associations.

TABLE 3 Association of poultry intake and outcome events[1]

	Intake					
	<50 g/wk	50 to <150 g/wk	150 to <250 g/wk	≥250 g/wk	*P*-trend[2]	Per 100-g/wk increase
n	69,349	36,793	17,069	11,086		
Total mortality						
No. of events	4570	1805	868	546		
Age, sex, and center adjusted	1.00 (ref)	0.96 (0.89, 1.02)	0.80 (0.74, 0.87)	0.80 (0.73, 0.87)	<0.001	
Multivariable	1.00 (ref)	0.93 (0.87, 1.00)	0.88 (0.81, 0.97)	0.96 (0.86, 1.06)	0.21	1.00 (0.97, 1.03)
Excluding those with event in first 24 mo	1.00 (ref)	0.98 (0.91, 1.06)	1.07 (0.96, 1.19)	1.03 (0.91, 1.16)	0.64	
CV mortality						
No. of events	1670	634	300	191		
Age, sex, and center adjusted	1.00 (ref)	0.90 (0.81, 1.01)	0.88 (0.76, 1.02)	0.85 (0.71, 1.01)	0.03	
Multivariable	1.00 (ref)	0.93 (0.82, 1.06)	1.03 (0.87, 1.22)	0.91 (0.75, 1.11)	0.56	1.00 (0.95, 1.05)
Excluding those with event in first 24 mo	1.00 (ref)	0.98 (0.86, 1.12)	1.07 (0.89, 1.29)	1.00 (0.80, 1.24)	0.81	
Non-CV mortality						
No. of events	3068	1281	622	387		
Age, sex, and center adjusted	1.00 (ref)	0.87 (0.80, 0.94)	0.89 (0.80, 0.99)	0.88 (0.77, 0.99)	0.01	
Multivariable	1.00 (ref)	0.96 (0.88, 1.05)	1.08 (0.96, 1.21)	1.01 (0.88, 1.16)	0.56	1.00 (0.97, 1.04)
Excluding those with event in first 24 mo	1.00 (ref)	0.98 (0.89, 1.07)	1.06 (0.94, 1.20)	1.02 (0.89, 1.19)	0.54	
Cancer mortality						
No. of events	1,075	458	217	143		
Age, sex, and center adjusted	1.00 (ref)	0.82 (0.73, 0.93)	0.90 (0.76, 1.06)	0.93 (0.76, 1.14)	0.17	
Multivariable	1.00 (ref)	0.91 (0.80, 1.04)	1.00 (0.83, 1.21)	1.05 (0.85, 1.30)	0.79	1.00 (0.95, 1.06)
Excluding those with event in first 24 mo	1.00 (ref)	0.92 (0.80, 1.06)	0.94 (0.77, 1.15)	1.05 (0.84, 1.31)	0.98	
Major CVD						
No. of events	4248	1642	656	430		
Age, sex, and center adjusted	1.00 (ref)	0.93 (0.87, 1.00)	0.91 (0.83, 1.01)	0.98 (0.87, 1.10)	0.19	
Multivariable	1.00 (ref)	0.98 (0.91, 1.05)	0.98 (0.88, 1.09)	1.02 (0.90, 1.16)	0.95	1.00 (0.97, 1.04)
Excluding those with event in first 24 mo	1.00 (ref)	1.01 (0.93, 1.09)	0.98 (0.87, 1.10)	1.03 (0.90, 1.19)	0.86	
Myocardial infarction						
No. of events	1725	699	321	223		
Age, sex, and center adjusted	1.00 (ref)	0.96 (0.87, 1.07)	1.01 (0.87, 1.17)	1.13 (0.95, 1.34)	0.33	
Multivariable	1.00 (ref)	1.00 (0.89, 1.11)	1.07 (0.92, 1.25)	1.15 (0.95, 1.39)	0.16	1.04 (0.98, 1.08)
Excluding those with event in first 24 mo	1.00 (ref)	1.06 (0.94, 1.19)	1.09 (0.92, 1.30)	1.23 (1.00, 1.50)	0.05	
Stroke						
No. of events	2222	734	248	131		
Age, sex, and center adjusted	1.00 (ref)	0.92 (0.84, 1.02)	0.87 (0.75, 1.02)	0.79 (0.65, 0.97)	0.01	
Multivariable	1.00 (ref)	0.98 (0.88, 1.09)	0.90 (0.76, 1.07)	0.84 (0.67, 1.04)	0.10	0.96 (0.91, 1.02)
Excluding those with event in first 24 mo	1.00 (ref)	1.01 (0.91, 1.13)	0.88 (0.74, 1.06)	0.77 (0.60, 0.98)	0.06	
Heart failure						
No. of events	306	198	77	75		
Age, sex, and center adjusted	1.00 (ref)	0.91 (0.74, 1.12)	0.73 (0.54, 0.97)	1.10 (0.81, 1.49)	0.77	
Multivariable	1.00 (ref)	0.93 (0.74, 1.18)	0.80 (0.58, 1.10)	1.16 (0.83, 1.61)	0.83	1.02 (0.94, 1.11)
Excluding those with event in first 24 mo	1.00 (ref)	0.95 (0.74, 1.22)	0.77 (0.54, 1.09)	1.25 (0.88, 1.78)	0.62	

[1] $n = 134{,}297$. Values are HRs (95% CIs) unless otherwise indicated. Multivariable models adjusted for age, sex, location, education, wealth index, smoking status, physical activity, diabetes status, blood pressure–lowering medications, fruits, vegetable, dairy, unprocessed red meat, fish, refined grains, processed foods, legumes, total dietary fiber, total energy intake, and center as a random effect. CV, cardiovascular; CVD, cardiovascular disease; ref, reference.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous value.

However, given the large sample size of the study it is less likely that the findings of the study would be affected by random error. We did not measure diet after the baseline assessment, and some individuals might have changed their diet over time. However, in large observational studies with 4 different approaches for assessing the association of dietary fats with risk of CHD using repeated dietary measurements (baseline diet only, the most recent diet, and 2 different algorithms for calculating cumulative average diets) similar results were reported (28). Therefore, we are confident that, with a relatively short follow-up (<10 y), our estimates would not differ with repeated measures. A further limitation was that we were unable to include method of cooking for each country. We acknowledge that this limitation might attenuate the association between unprocessed red meat and poultry and health outcomes. Moreover, dietary data obtained from FFQs are generally not considered a measure of absolute intake, and are usually used to rank individuals into categories of intake. As with any observational study, there is a chance of residual confounding in our analysis. However, extensive established and potential risk factors were considered during

TABLE 4 Association of processed meat intake and outcome events[1]

	Intake					
	0 g/wk	<50 g/wk	50 to <150 g/wk	≥150 g/wk	*P*-trend[2]	Per 100-g/wk increase
n	3009	14,597	10,923	3111		
Total mortality						
No. of events	222	688	506	159		
Age, sex, and center adjusted	1.00 (ref)	1.08 (0.92, 1.27)	1.16 (0.98, 1.37)	1.30 (1.03, 1.62)	0.01	
Multivariable	1.00 (ref)	1.21 (0.96, 1.52)	1.34 (1.05, 1.71)	1.51 (1.08, 2.10)	0.009	1.16 (1.04, 1.28)
Excluding those with event in first 24 mo	1.00 (ref)	1.23 (0.97, 1.57)	1.40 (1.08, 1.82)	1.64 (1.16, 2.33)	0.003	
CV mortality						
No. of events	80	178	145	50		
Age, sex, and center adjusted	1.00 (ref)	0.90 (0.68, 1.20)	1.05 (0.79, 1.41)	1.43 (0.97, 2.10)	0.07	
Multivariable	1.00 (ref)	0.90 (0.60, 1.35)	0.98 (0.63, 1.53)	1.39 (0.73, 2.63)	0.42	1.06 (0.84, 1.33)
Excluding those with event in first 24 mo	1.00 (ref)	0.93 (0.59, 1.48)	1.15 (0.69, 1.89)	1.83 (0.90, 3.70)	0.10	
Non-CV mortality						
No. of events	178	543	383	125		
Age, sex, and center adjusted	1.00 (ref)	1.06 (0.89, 1.28)	1.08 (0.89, 1.31)	1.16 (0.90, 1.49)	0.29	
Multivariable	1.00 (ref)	1.29 (1.00, 1.68)	1.42 (1.06, 1.88)	1.50 (1.03, 2.19)	0.02	1.18 (1.05, 1.32)
Excluding those with event in first 24 mo	1.00 (ref)	1.27 (0.96, 1.67)	1.41 (1.04, 1.89)	1.53 (1.04, 2.27)	0.02	
Fatal cancer						
No. of events	38	260	187	58		
Age, sex, and center adjusted	1.00 (ref)	1.46 (1.03, 2.07)	1.52 (1.06, 2.19)	1.58 (1.02, 2.44)	0.06	1.18 (1.03, 1.34)
Multivariable	1.00 (ref)	1.44 (0.98, 2.11)	1.55 (1.03, 2.31)	1.84 (1.14, 2.97)	0.02	
Excluding those with event in first 24 mo[3]						
Major CVD						
No. of events	104	489	447	166		
Age, sex, and center adjusted	1.00 (ref)	1.12 (0.90, 1.40)	1.37 (1.09, 1.71)	1.77 (1.35, 2.32)	<0.001	
Multivariable	1.00 (ref)	0.98 (0.77, 1.26)	1.15 (0.89, 1.48)	1.46 (1.08, 1.98)	0.004	1.16 (1.05, 1.29)
Excluding those with event in first 24 mo	1.00 (ref)	0.95 (0.73, 1.25)	1.14 (0.87, 1.51)	1.46 (1.04, 2.03)	0.003	
Myocardial infarction						
No. of events	39	217	202	73		
Age, sex, and center adjusted	1.00 (ref)	1.01 (0.71, 1.44)	1.20 (0.84, 1.72)	1.65 (1.08, 2.51)	0.003	
Multivariable	1.00 (ref)	1.05 (0.70, 1.57)	1.21 (0.80, 1.84)	1.62 (0.98, 2.69)	0.03	1.14 (0.98, 1.32)
Excluding those with event in first 24 mo	1.00 (ref)	0.97 (0.64, 1.49)	1.16 (0.75, 1.81)	1.70 (0.99, 2.91)	0.02	
Stroke						
No. of events	41	195	177	62		
Age, sex, and center adjusted	1.00 (ref)	1.14 (0.81, 1.62)	1.42 (1.00, 2.03)	1.70 (1.11, 2.61)	0.002	
Multivariable	1.00 (ref)	0.95 (0.64, 1.40)	1.13 (0.74, 1.71)	1.56 (0.94, 2.58)	0.04	1.23 (1.07, 1.43)
Excluding those with event in first 24 mo	1.00 (ref)	0.97 (0.62, 1.50)	1.28 (0.81, 2.03)	1.68 (0.96, 2.92)	0.01	
Heart failure						
No. of events	17	62	70	28		
Age, sex, and center adjusted	1.00 (ref)	1.10 (0.63, 1.93)	1.65 (0.94, 2.87)	1.84 (0.96, 3.55)	0.009	
Multivariable	1.00 (ref)	1.13 (0.53, 2.44)	1.55 (0.71, 3.42)	1.55 (0.60, 4.00)	0.14	1.19 (0.93, 1.52)
Excluding those with event in first 24 mo	1.00 (ref)	1.21 (0.53, 2.76)	1.50 (0.64, 3.50)	1.54 (0.55, 4.30)	0.27	

[1] $n = 31{,}640$. Values are HRs (95% CIs) unless otherwise indicated. Multivariable model adjusted for age; sex; location; education; wealth index; smoking status; physical activity; diabetes status; blood pressure–lowering medication; fruit; vegetables; legumes; unprocessed meats; starchy foods; % of energy from SFAs, MUFAs, and PUFAs; total energy intake; and center as a random effect. The analysis for processed meat was conducted only among participants from countries with a median consumption of ≥10 g/d (Argentina, Brazil, Canada, Chile, Poland, South African, and Sweden). CV, cardiovascular; CVD, cardiovascular disease; ref, reference.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous value.

[3] Due to the limited number of events, the model did not converge.

analysis of mortality and CVD and other dietary variables. We measured risk factors (e.g., education, smoking, etc.) using standardized questionnaires adopted from 2 large international case-control studies of INTERHEART and INTERSTROKE (29, 30), and there is less chance that residual confounders diverted the associations. Furthermore, the consistency of results across different regions with markedly different lifestyles and unprocessed red meat and poultry intakes makes it less likely that confounders, which might have varied in different regions, explained our observations.

In conclusion, we observed no significant association between the consumption of unprocessed red meat and poultry intake and health outcomes, and higher intake of processed meat was associated with higher risks of mortality and CVD. These findings may indicate that limiting the intake of processed meat should be encouraged.

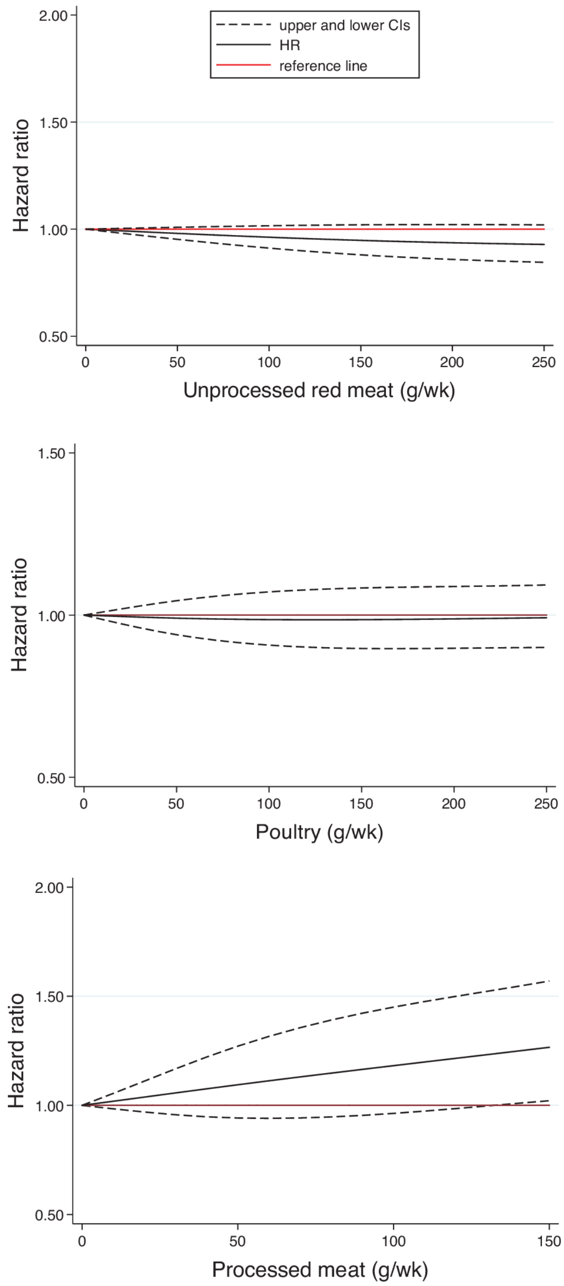

FIGURE 1 Association between unprocessed red meat, poultry, and processed meat intake and total mortality: cubic spline analysis. The multivariable model adjusted for age; sex; education; wealth index; smoking; location; physical activity; history of diabetes; blood pressure–lowering medication; daily intakes of fruits, vegetables, dairy, refined grains, processed foods, legumes, total dietary fiber, total daily energy; and center as a random effect. Models for unprocessed red meat are adjusted for poultry and vice versa.

The authors' responsibilities were as follows—SY: conceived and initiated the PURE study, supervised its conduct, and reviewed and commented on the draft; RI, MD, AM, and SY: had primary responsibility for writing of the manuscript; SR: coordinated the worldwide study and reviewed and commented on drafts; MD: coordinated the entire nutrition component of the PURE study and performed all data analyses; all other authors: coordinated the study in their respective countries and provided comments on drafts of the manuscript; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, codebook, and analytic code will not be made available for the PURE study because the PURE study is an ongoing study and during the conduct only the investigators who have participated/contributed to the study can have access to the data. Select summary data may be shared with policy makers for specific purposes. The study executive will consider specific requests for data analyses by noncontributing individuals 3 y after the study has been completed (i.e., complete recruitment and a minimum of 10 y follow-up in all) and the participating investigators have had an opportunity to explore questions that they are interested in. Costs related to data curating and related efforts will be contributing to the conduct of the study and requested analyses.

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