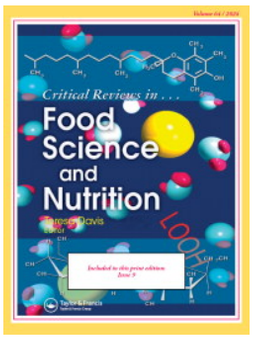

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SYSTEMATIC REVIEW

Red and processed meat intakes and cardiovascular disease and type 2 diabetes mellitus: An umbrella systematic review and assessment of causal relations using Bradford Hill's criteria

Erica R. Hill[a], Lauren E. O'Connor[a,b], Yu Wang[a], Caroline M. Clark[a], Bethany S. McGowan[c], Michele R. Forman[a] and Wayne W. Campbell[a]

[a]Department of Nutrition Science, Purdue University, West Lafayette, Indiana, USA; [b]Agricultural Research Service, United States Department of Agriculture, Beltsville, Maryland, USA; [c]Purdue University Libraries and School of Information Studies, Purdue University, West Lafayette, Indiana, USA

ABSTRACT

Observational research suggests higher red and processed meat intakes predict greater risks of developing or dying from cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM), but this research limits causal inference. This systematic review of reviews utilizes both observational and experimental research findings to infer causality of these relations. Reviews from four databases were screened by two researchers. Reviews included unprocessed red meat (URM), processed meat (PM), or mixed URM + PM intake, and reported CVD or T2DM outcomes. Twenty-nine reviews were included, and causality was inferred using Bradford Hill's Criteria. Observational assessments of CVD outcomes and all meat types consistently reported weak associations while, T2DM outcomes and PM and Mixed URM + PM assessments consistently reported strong associations. Experimental assessments of Mixed URM + PM on CVD and T2DM risk factors were predominately not significant which lacked coherence with observational findings. For all meat types and outcomes, temporality and plausible mechanisms were established, but specificity and analogous relationships do not support causality. Evidence was insufficient for URM and T2DM. More experimental research is needed to strengthen these inferences. These results suggest that red and processed meat intakes are not likely causally related to CVD but there is potential for a causal relationship with T2DM.

KEYWORDS

Causation; human adults; nutrition; morbidity; mortality; randomized controlled trial; relative risk

Introduction

The 2020–2025 Dietary Guidelines for Americans recommends eating patterns that are low in "red and processed meat intake" with the caveat that "lean meats" can be part of a healthy eating pattern (as mainly fresh, frozen or canned versus further processed) when recommendations for sodium and saturated fat intakes are met (DGA 2020). These recommendations are consistent with others made by the American Heart Association (Lichtenstein et al. 2021) and American Diabetes Association (Evert et al. 2019). Yet, these recommendations are based largely on observational research (i.e., prospective cohorts) that show inconsistent associations and often do not include evidence from short term experimental studies (i.e., randomized controlled trials (RCT), including controlled feeding) (DGA 2015; O'Connor and Campbell 2017; DGA 2020). Observational studies are well suited to assess associations of self-reported dietary intake with incidence and related mortality of cardiometabolic diseases (CMD) such as cardiovascular disease (CVD) or type 2 diabetes mellitus (T2DM) over time. However, residual and unmeasured confounding, as well as documented biases in self-reported dietary data hinder capacity for determining causality (Shim, Oh, and Kim 2014; Subar et al. 2015). Alternatively, randomized controlled feeding trials can assess causality between a specific exposure and disease risk factors despite typically having smaller sample sizes and shorter durations (Weaver and Miller 2017). Assessing the relation between red and processed meat intake on CMD using evidence from both observational and randomized controlled feeding trials would advance our understanding of whether these relationships are likely causal or not (Beyerbach et al. 2022).

The Bradford Hill Causality Criteria were developed to infer the potential for causal relations of public health concern, such as smoking and lung cancer, by interpreting findings from observational research in conjunction with experimental evidence if available (Hill 1965). These criteria can be operationalized by researchers and public health professionals to elicit an inference, which is a conclusion reached based on evidence and critical thinking. These long-established criteria are adapted to inform

CONTACT Wayne W. Campbell campbellw@purdue.edu
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nutrition-related public health recommendations (WCRF 2018). Independent researchers have also applied modified versions of Bradford Hill's Causality Criteria to infer causality between several dietary factors and disease endpoints, encompassing individual nutrients, whole foods, eating patterns, or other dietary exposures (Mente et al. 2009; Micha et al. 2017; Livesey and Livesey 2019; Livesey et al. 2019). Such an approach could be applied to the body of literature about red and processed meat intakes and risk for cardiometabolic disease to provide further clarity for future recommendations. There is a plethora of long-term observational studies assessing red and processed meat intake and clinical endpoints (e.g., stroke, myocardial infarctions) as well as shorter-term randomized controlled feeding trials assessing established clinical risk factors (e.g., blood pressure, low-density lipoproteins). Yet, it is uncommon that both types of study designs are considered together in evidence reviews for dietary recommendations (DGA 2015; USDA 2015; DGA 2020; USDA 2020).

The objective of this umbrella (Aromataris et al. 2015) systematic review is to apply the Bradford Hill Causality Criteria (Hill 1965) to infer the potential for causal relations between intakes of red and processed meat and CVD or T2DM using systematic reviews and meta-analyses of both observational and experimental research, including randomized controlled feeding trials, on the topic. In addition, AMSTAR 2, a systematic review appraisal tool (Shea et al. 2017), is used to assess the quality of evidence.

Methods

Search strategy

A preliminary search strategy and database selection (Supplemental Table S1) were developed prior to conducting the search. The databases searched were: (1) PubMed, (2) Scopus, (3) Cochrane Database of Systematic Reviews, and (4) Cumulative Index of Nursing and Allied Health Literature (CINAHL). Searches were conducted without filters or restrictions and the reference lists of the included articles were reviewed for additional eligible articles. Grey literature was included in our search, but only peer-reviewed systematic reviews or meta-analyses were of interest. A health sciences research librarian (BM) coordinated the development of the search strategy. The protocol and methods were designed following the PRISMA reporting checklist (Moher et al. 2009) and registered at PROSPERO (PROSPERO 2011), the International Prospective Registrar of Systematic Reviews (the review protocol can be accessed at https://www.crd.york.ac.uk/prospero/ using ID number: CRD42020127976). Before registration, preliminary searches and pilot testing was conducted, but the formal screening process did not begin until after registration. The search was conducted up to July 2021 and there were no significant deviations from our approved PROSPERO protocol.

Search criteria

Our research question aimed to address whether intakes of red and processed meat are causally related to CVD or T2DM in generally healthy adults. The PICOS (Population, Intervention/Exposure, Comparator, Outcome, and Study Design) (Aslam and Emmanuel 2010) criteria applied to the research question are outlined in Table 1. We conducted an "umbrella systematic review," i.e., a systematic review of systematic reviews or meta-analyses of observational and/or experimental literature (Aromataris et al. 2015). Throughout this manuscript we use the abbreviation "OBS" to identify outcomes from observational studies, which are mostly prospective longitudinal cohort studies reporting relative risks (RRs). We use the abbreviation "RCT" to identify outcomes from experimental studies, which are mostly randomized controlled feeding trials reporting mean differences or change values.

Inclusion criteria were determined *a priori* and were: (1) systematic reviews or systematically searched meta-analyses of cohort, experimental, and/or cross-sectional design; (2) red meat consumption as an *a priori* independent exposure or variable as listed in the search terms, objectives, or methods sections of the reviews; (3) report of CVD and/or T2DM risk factors (RF), incidence, or mortality outcomes, as described in the next section; (4) populations without a diagnosis of cardiometabolic disease of interest at enrollment; and (5) a participant group mean age ≥19 years old. Exclusion criteria were: (1) narrative reviews or individual primary research studies; (2) systematic reviews that did not include red meat consumption as an *a priori* independent exposure or variable; (3) systematic reviews of specific clinical or diseased populations; (4) population with a mean age < 19 years old; (5) animal or in vitro models; (6) reviews not published in English; and (7) meta-analytical approaches that lacked systematic assessment of included studies. The references and rationales for excluding articles after full text review are presented in Supplemental Table S2.

Table 1. Description of PICOS criteria for an umbrella review assessing causal relations between red and processed meat intake and cardiometabolic disease.

Variable	Description
Population	Human adults with a mean age ≥ 19 years who are free of the cardiometabolic disease outcome of interest at enrollment
Intervention/Exposure	Red or processed meat consumption listed as an *a priori*[a] independent exposure or variable of interest
Comparator	No or lower red meat intake with no restrictions on alternative food sources
Outcome	Report of any CVD and/or T2DM risk factors, incidence or mortality outcomes[b]
Study Design	Systematic reviews or systematically searched meta-analyses of observational and experimental human studies

PICOS (Population, Intervention/Exposure, Comparator, Outcome, Study Design); CVD (Cardiovascular Disease; T2DM (Type 2 Diabetes Mellitus).
[a]Red or processed meat consumption was determined to be an *a priori* independent exposure or variable if listed in the search terms, objectives, or methods sections of the review.
[b]See Supplemental Table S3 for list of outcomes.

Screening and data abstraction

Two researchers (ERH and YW) independently screened and crosschecked each article from the literature search, and a third researcher (CMC) was consulted to settle any discrepancies. Two researchers (ERH and YW) independently abstracted and crosschecked the following data from each included review: (1) author names, (2) publication year, (3) detailed outcome, (4) type of meat reported/consumed, (5) definition of meat type, (6) summary estimates, (7) 95% confidence intervals (CI), (8) heterogeneity measures (I^2 value), (9) details of a dose-response analyses when available, (10) number and type of primary research studies in the systematic review or meta-analysis articles, (11) participant characteristics, and (12) funding source. Authors were not contacted because additional information was not needed.

Definitions for the meat type categories

Due to inconsistent use and description of meat terminology in chronic disease research (Gifford, O'Connor et al. 2017; O'Connor et al. 2020), we re-categorized meat exposures (i.e., consumption of skeletal muscle and associated tissue of mammal, avian, or aquatic species)(Seman et al. 2018) that were reported in the systematic reviews and meta-analyses. We used the following categories: Unprocessed Red Meat (URM), Processed Meat (PM), and Mixed Unprocessed Red Meat and Processed Meat (Mixed URM + PM) based on the 2015–2020 Dietary Guidelines for Americans (DGA) definitions (DGA 2015), as this was the current DGA version at study inception. These descriptions are consistent with those used for the 2020–2025 DGA as well (DGA 2020). The 2015–2020 DGA defined red meat as "all forms of beef, pork, lamb, veal, goat, and non-bird game (e.g., venison, bison, elk)" (DGA 2015). Processed meat was defined as red meat or poultry that is "preserved by smoking, curing, salting, and/or the addition of chemical preservatives" (DGA 2015). By default, we defined unprocessed red meat as all forms of beef, pork, lamb, veal, goat, and non-bird game (e.g., venison, bison, elk) *not* preserved by smoking, curing, salting, and/or the addition of chemical preservatives. Most of the included reviews did not disaggregate processed meat into independent processed poultry and processed red meat intake categories. About 30% of the processed meat consumed in the US is processed poultry (O'Connor, Wambogo, et al. 2021) therefore, we assume that the PM category in our review includes both processed red meat and processed poultry. Unprocessed poultry fell outside of the scope of our umbrella review. If included reviews used terms such as "red meat," "red and processed meat," or "total red meat" without providing detailed descriptions to determine degree of processing, then these reviews were categorized into the Mixed URM + PM category due to ambiguity. Therefore, the Mixed URM + PM category is mutually exclusive from the URM and PM categories and is *not* a combination of the two. See Supplemental Table S3 which includes the meat terminology and accompanied descriptions provided in the included reviews and how those were then re-categorized for our analysis into URM, PM, or Mixed URM + PM.

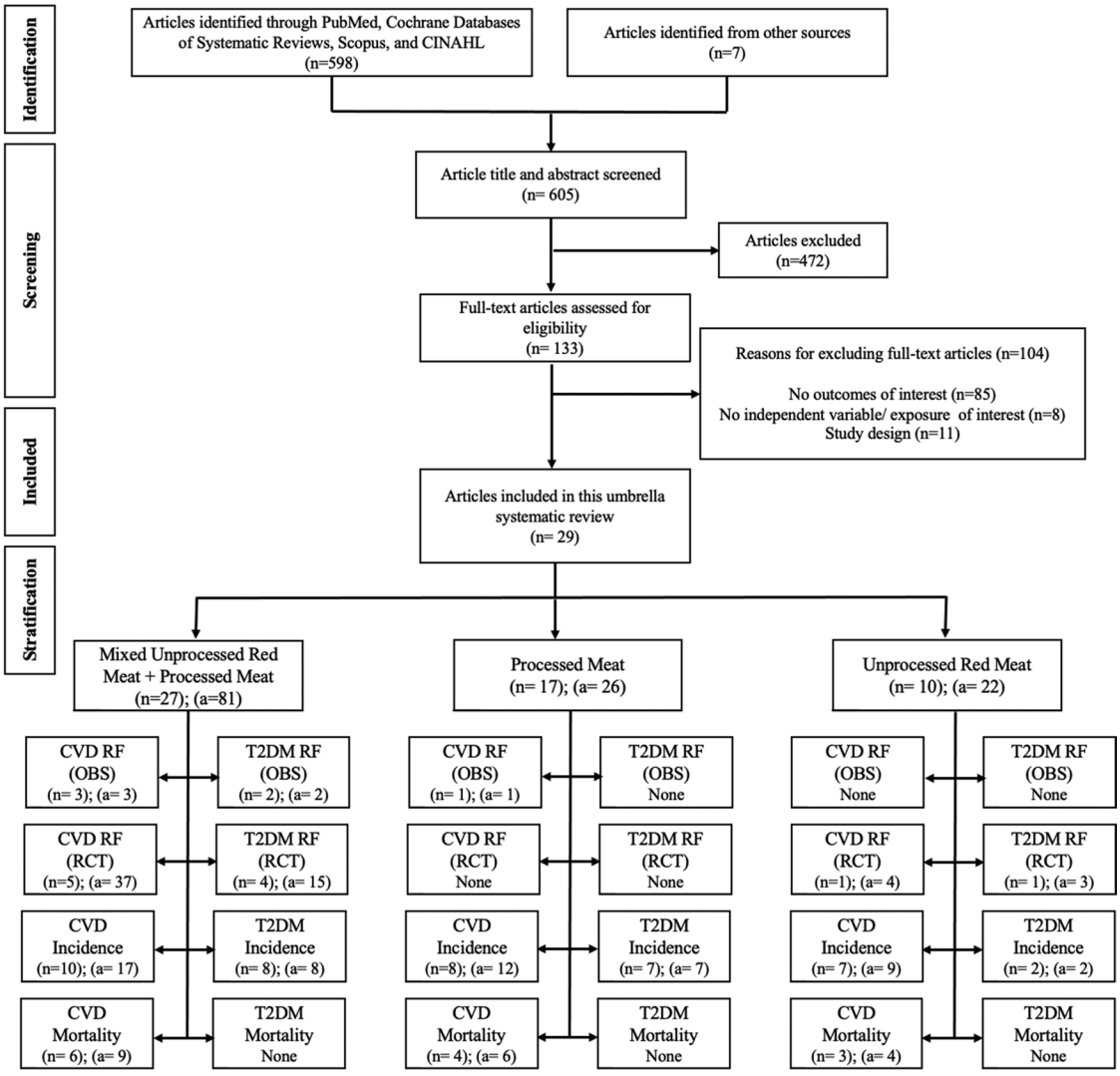
Exposure and outcome stratification

In this review, exposures and outcomes were stratified by meat type: Mixed URM + PM, PM, and URM, and then further categorized by outcome (see Supplemental Table S3): CVD RF (OBS), CVD RF (RCT), CVD Incidence, CVD Mortality, T2DM RF (OBS), T2DM RF (RCT), T2DM Incidence and, T2DM Mortality. We are mindful that CVD encompasses more specific diagnoses (i.e., myocardial infarction, stroke, ischemic heart disease, etc.), however there were insufficient reviews to meaningfully assess theses outcomes individually.

The following is an example of how we categorized and stratified exposures and outcomes. Bechthold et al conducted independent analyses for "red meat" and "processed meat" intake and CVD Incidence (specific outcomes included: CHD, heart failure (HF), and stroke) totaling six different analyses (Supplemental Table S4) (Bechthold et al. 2019). We categorized the "red meat" exposure into the Mixed URM + PM category because no explicit definition was provided for red meat (i.e., no mention of degree of processing) and we categorized the "processed meat" exposure into the PM category. Each analysis was treated as a separate point estimate and stratified by type of meat exposure and type of outcome. We refer to each of these point estimates as independent "assessments" throughout this manuscript. We refer to the entirety of each systematic review or meta-analysis included in our analysis as a "review." See Figure 1 for a full breakdown of the number of reviews and assessments by meat type and outcome category.

Causal inference assessment

The Bradford Hill Causality Criteria were described in 1965 to help infer the likely causal association between smoking and lung cancer (Hill 1965). These criteria have since been adapted by researchers and policymakers to develop guidelines of causal inference for public health purposes (Mente et al. 2009; Micha et al. 2017; WCRF 2018; Livesey and Livesey 2019; Livesey et al. 2019). The criteria are used to develop an inference, which is a conclusion reached based on evidence and reasoning (Rothman and Greenland 2005). Long term randomized controlled feeding trials assessing effects of red and processed meat intake on chronic disease outcomes (e.g., stroke, myocardial infarction) would be preferred to infer causality but this study design is infeasible and often unethical (Todt and Luján 2017). Therefore, observational studies are relied upon for dietary guidance purposes (DGA 2015; DGA 2020). It is practical to assess effects of red and processed meat intake via a randomized controlled feeding trial with shorter-term risk factors as outcomes. However, due to the short-term nature of the approach, this study design is not often included in evidence reviews for dietary guidelines development (DGA 2015; DGA 2020). Thus, the Bradford Hill Causality Criteria are well suited to infer causal relations among both longer-term observational studies and shorter-term randomized controlled feeding trials. The Causality Criteria include (1) Strength, (2) Consistency, (3) Specificity, (4) Temporality, (5) Biological Gradient, (6) Plausibility, (7) Experiment, (8) Coherence, and (9) Analogy (Table 2) (Hill 1965). The



CVD (cardiovascular disease); T2DM (Type 2 Diabetes Mellitus); RF (Risk Factors); OBS (Observational studies); RCT (Randomized controlled feeding trials); n (number of reviews); a (number of assessments)

Reviews (i.e., systematic reviews and meta-analyses) were stratified by type of meat and then further categorized by outcome. Each analysis was treated as a separate entity and we refer to these independent analyses, or point estimates, as independent "assessments" throughout this manuscript.
Overlap occurred with some included reviews assessing multiple types of meat and/or outcomes. Certain risk factor assessments were considered both CVD and T2DM outcomes (i.e., bodyweight).

Figure 1. Article screening process flow chart for an umbrella review assessing red and processed meat intake and cardiometabolic disease.

Table 2. The Bradford Hill causality criteria descriptions (Hill 1965) for an umbrella review assessing red and processed meat intake and cardiometabolic disease.

Bradford Hill criteria	General description
Strength	A large association is more likely to be causal but a small association does not mean that there is no causal effect
Consistency	Consistent findings observed for different populations, in different places, at different times, under different circumstances strengthens the likelihood of causality
Specificity	If the exposure is not related to other diseases or causes of death, then this strengthens the likelihood of causality
Temporality	The exposure must occur before the outcome
Biological Gradient	Greater exposure leads to either increased or decreased incidence of the outcome
Plausibility	A plausible biological mechanism exists to explain the relation between the exposure and outcome
Experiment	When available, experimental evidence can provide insights into direct cause and effect relationships
Coherence	Agreement between the observational and experimental findings increase the likelihood for causality
Analogy	The effect of similar exposures on the outcomes of interest may be considered to infer causality

Causality Criteria were dichotomized as "Supported" or "Not supported" based on how the evidence met each of the criteria. However, all nine Causality Criteria were considered collectively to infer potential causal relations between each meat type and outcome category.

In this umbrella review, we are including systematic reviews and meta-analyses of observational and experimental studies. Observational studies typically assess risk by conducting analyses comparing the highest percentile vs. lowest percentile of intake or via dose-response continuous intake analyses. To consider each type of evidence under the appropriate criterion, the point estimates for high vs. low assessments are summarized in the Strength Criterion and the point estimates for dose-response assessments are summarized in the Biological Gradient Criterion. Reviews of experimental studies, i.e., randomized controlled feeding trials, reporting on risk factor outcomes are summarized in the Experiment Criterion.

Strength

As previously stated, this criterion includes point estimates that are comparing the high vs. low percentiles of intake from reviews of observational studies. In the included reviews, statistical significance (95% confidence interval does not cross 1.0) is reported for these assessments. However, with regards to inferring causality, statistical significance is not necessarily indicative of a strong association (Sorkin et al. 2021). Therefore, we used an *a priori* cut off: RR ≥1.2 to indicate a strong association. A 20% increased risk is biologically meaningful at the population level and considers potential attenuation of associations due to biases or poor control of confounding factors (Byers and Lyle 1999; NCEP 2001).

Consistency

We included high vs. low assessments from reviews of observational studies which included different prospective cohort populations from varying geographic locations and time periods. We considered associations to be consistent if ≥ 67% of reported high vs. low assessments had a RR ≥ 1.2 (Mente et al. 2009).

Biological gradient

This criterion includes dose-response or trend assessments from reviews of observational studies. We documented the percentage of assessments that reported a significant dose-response curve and if the shape of the relationship (i.e., linear, non-linear, J-shape, etc.) was reported then it was described in Supplemental Material.

Experiment

This criterion includes assessments on risk factor outcomes from reviews of experimental studies, i.e., randomized controlled feeding trials. We reported the percentage of assessments that the 95% CI of the mean differences did not include 0.0 between higher and lower meat intakes.

Coherence

We compared the results from the Strength Criterion and Experiment Criterion to infer the presence of coherence across study designs.

Plausibility

We qualitatively describe various proposed biological mechanisms between the three meat categories and CVD or T2DM outcomes.

Temporality

Only reviews of prospective observational and experimental studies were included to meet this criterion.

Specificity

We qualitatively describe notable relationships between red meat and processed meat intake and other health outcomes.

Analogy

We qualitatively described associations between other animal-based protein sources (white meat, dairy, seafood, and eggs) and CVD and T2DM outcomes, then cross-compared those associations with our results from red and processed meat.

Risk of bias and quality analysis

AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) was applied to assess study quality and risk of bias of the included systematic reviews and meta-analyses as well as our own umbrella review. AMSTAR 2 is used to assess systematic reviews and meta-analyses of both randomized and non-randomized trials through a series of 16 questions (Shea et al. 2007; Shea et al. 2017). Per AMSTAR 2 protocol, reviews were given quality ratings of either High, Moderate, Low, or Critically Low based on the presence of critical or non-critical biases. This tool assesses the quality of the reviews but not the quality of the included primary research studies. Two researchers (ERH and YW) independently entered and crosschecked data for the AMSTAR 2 assessment and a third researcher (CMC) was consulted to settle disputes. The appropriateness of using AMSTAR 2 as a tool to assess quality of evidence in nutrition research is supported by its use by the 2015 Dietary Guidelines Advisory Committee (USDA 2015).

Publication bias assessment

Publication bias of the included reviews was assessed for each meat type and outcome category. Natural log-transformed 95% CI for pooled Relative Risk (RR) and 95% CI for mean differences from each review were used to determine the standard error of summary risk estimates using the delta method (Feiveson, University 2017). Funnel plots and Egger's tests were computed to assess publication bias using STATA SE software (version 17.0) with statistical significance level set at 5%. This is

a commonly used method to assess publication bias among meta-analyses but these funnel plots are subject to certain limitations and results may be explained by other types of biases other than publication bias (Terrin, Schmid, and Lau 2005). Publication bias was assessed for all quantifiable assessments but was done separately for the highest vs. lowest, dose-response, and risk factor assessments. Assessment of publication bias is a criterion of the AMSTAR 2 assessment to be considered a High quality review.

Results

Of the 605 articles screened, 133 full text articles were assessed for eligibility and 29 systematic reviews and meta-analyses (each referred to as a "review") were included in this umbrella systematic review. The references and rationales for excluding articles after full text review are presented in Supplemental Table S2. Figure 1 presents a flow chart of the number of reviews and assessments. "Assessments" are referred to as individual point estimates between a meat exposure and type of outcome. Twenty-two reviews included only observational studies (Aune, Ursin, and Veierød 2009; Micha, Wallace, and Mozaffarian 2010; Kaluza, Wolk, and Larsson 2012; Akesson et al. 2013; Chen et al. 2013; O'Sullivan et al. 2013; Abete et al. 2014; Lippi, Mattiuzzi, and Sanchis-Gomar 2015; Wang et al. 2016; Yang et al. 2016; Kim et al. 2017; Schwingshackl, Hoffmann, et al. 2017; Schwingshackl, Schwedhelm, et al. 2017; Tian et al. 2017; Kim and Je 2018; Bechthold et al. 2019; Fan et al. 2019; Schlesinger et al. 2019; Vernooij et al. 2019; Zeraatkar, Han, et al. 2019; Yang et al. 2020; Papier et al. 2021) and seven reviews included only experimental studies (Maki et al. 2012; O'Connor, Kim et al. 2017; Schwingshackl et al. 2018; Guasch-Ferré et al. 2019; Zeraatkar, Johnston et al. 2019; An, Liu, and Liu 2020; O'Connor, Kim, et al. 2021). Notably, no review assessed observational and experimental studies together. Of the 29 included reviews, the following outcomes were examined: 15 with only CVD (Kaluza, Wolk, and Larsson 2012; Maki et al. 2012; Akesson et al. 2013; Chen et al. 2013; O'Sullivan et al. 2013; Abete et al. 2014; Lippi, Mattiuzzi, and Sanchis-Gomar 2015; Wang et al. 2016; Yang et al. 2016; Kim et al. 2017; O'Connor, Kim et al. 2017; Schwingshackl, Schwedhelm, et al. 2017; Bechthold et al. 2019; Guasch-Ferré et al. 2019; Papier et al. 2021), six with only T2DM (Aune, Ursin, and Veierød 2009; Schwingshackl, Hoffmann, et al. 2017; Tian et al. 2017; Fan et al. 2019; Yang et al. 2020; O'Connor, Kim, et al. 2021), and eight with both CVD and T2DM (Micha, Wallace, and Mozaffarian 2010; Kim and Je 2018; Schwingshackl et al. 2018; Schlesinger et al. 2019; Vernooij et al. 2019; Zeraatkar, Han, et al. 2019; Zeraatkar, Johnston et al. 2019; An, Liu, and Liu 2020). Three reviews were strictly systematic reviews without a meta-analysis (Akesson et al. 2013; Lippi, Mattiuzzi, and Sanchis-Gomar 2015; Schwingshackl et al. 2018).

Presentation of results and synthesis of quality assessment

We first present Strength, Consistency, Biological Gradient, Experiment, Coherence, and AMSTAR 2 results for each meat type and outcome stratum for CVD. We then describe *post- hoc* how inferences change when including only reviews that had AMSTAR 2 ratings of High and Moderate quality to see if inferences would change based on the quality of the reviews included. Plausibility is then described globally for all meat types and CVD. This same format is followed for T2DM. Lastly, we present results for the Temporality, Specificity, and Analogy Criteria for CVD and T2DM combined because qualitative operationalization of these is not specific to either disease or type of meat. We summarize whether each Bradford Hill Causality criterion was supported or not supported for each meat/outcome stratum in Table 3, and compile conclusions of causal inference in Table 10. Tables 4–9 show the findings from the Strength, Consistency, Biological Gradient, Experiment, Coherence and AMSTAR 2 quality analyses. Supplemental Table S4 presents population characteristics, meat terminology and description, and outcomes of each review. Supplemental Table S5 presents the AMSTAR 2 assessment and ratings for each included review. Additionally, our review meets the AMSTAR 2 criteria for a High quality review (Shea et al. 2017; Supplemental

Table 3. Bradford Hill causality criteria summary for all meat type categories and CVD and T2DM outcomes.

Bradford Hill causality criteria	Cardiovascular disease outcomes			Type 2 diabetes mellitus outcomes		
	Mixed URM + PM	PM	URM	Mixed URM + PM	PM	URM
Strength	X	X	X	✓	✓	Could not assess
Consistency	X	X	X	✓	✓	Could not assess
Specificity	X	X	X	X	X	X
Temporality	✓	✓	✓	✓	✓	✓
Biological Gradient	✓ [a]	✓	✓[a]	✓[a]	✓	X
Plausibility	✓	✓	✓	✓	✓	✓
Experiment	X	Could not assess	X[b]	X	Could not assess	X
Coherence	X	Could not assess	X[b]	X	Could not assess	Could not assess
Analogy	X	X	X	X	X	X

CVD (Cardiovascular Disease); T2DM (Type 2 Diabetes Mellitus); URM (Unprocessed Red Meat); PM (Processed Meat). ✓ = criteria are supported; X = criteria are not supported; Could not assess = criteria could not be assessed due to lack of reviews.

This summary table is representative of all reviews included into this umbrella review and is supported by the secondary analysis of High and Moderate quality reviews unless otherwise noted.

[a]There was not support for the causal criterion in the *post hoc* secondary analysis of High and Moderate quality reviews.

[b]This criterion could not be assessed in the *post hoc* secondary analysis because there was no experimental evidence from High and Moderate quality reviews.

Table S5.1). Supplemental Tables S6–S20 present the individual assessments used for the Strength, Biological Gradient, and Experiment Criteria and include indication of statistical significance, I^2 heterogeneity metric, AMSTAR 2 quality of each assessment, and the shape of the dose-response assessments, if available.

Cardiovascular disease: strength, consistency, biological gradient, experiment, coherence, and quality

Mixed unprocessed red meat + processed meat

Table 4 shows the Mixed URM + PM and CVD findings from the Strength, Consistency, Biological Gradient, Experiment, Coherence and AMSTAR 2 quality analyses. ***Strength and Consistency*:** Twenty high vs. low assessments from 10 reviews of observational studies were reported. Eleven of the 20 assessments (55%) were statistically significant, yet only two of the 20 assessments (10%) had an effect size ≥1.2 (Supplemental Table S6). ***Biological Gradient:*** Seventeen dose-response assessments from 11 reviews of observational studies were reported. Fourteen of the 17 assessments (~82%) were statistically significant but the shape of this relationship was not consistently reported (Supplemental Table S7). Four of the 11 reviews reported a visual representation of the relationship shape with two reviews reporting a linear and two reviews reporting a non-linear relationship (Supplemental Table S7). ***Experiment:*** Thirty-one assessments from four reviews of experimental studies were reported. Only eight of the 31 assessments (~26%) were statistically significant, suggesting experimental evidence does not support a relationship between intakes of Mixed URM + PM and CVD risk factors (Supplemental Table S8). ***Coherence*:** There is a lack of coherence between the observational findings and experimental evidence, i.e., observational findings reported statistically significant and positive associations between Mixed URM + PM and CVD outcomes, whereas experimental evidence showed mostly non-significant effects on CVD risk factors. These findings are supported by two additional systematic reviews of observational studies identified in our search that lacked quantifiable analyses. These reviews reported that inconsistent evidence, or an overall lack of evidence contributed to an unclear relationship between mixed unprocessed red meat and processed meat intake and CVD incidence and mortality (Akesson et al. 2013; Lippi, Mattiuzzi, and Sanchis-Gomar 2015).

AMSTAR 2 quality

Among 17 total reviews assessing observational CVD outcomes, four reviews (~24%) were rated as High or Moderate quality and contributed five assessments, while 13 reviews (~76%) were rated as Low or Critically Low quality and contributed 22 assessments (Supplemental Tables S6, S7). Among four reviews that assessed experimental CVD risk factors, two (50%) were rated as High or Moderate quality and had 13 assessments, while the other two reviews (50%) were rated as Critically Low quality and contributed 18 assessments (Supplemental Table S8). Restricting to only Moderate and High quality reviews further supported the ***Strength and Consistency*** Criteria but the ***Biological Gradient*** Criterion was not supported (Supplemental Tables S6–S8).

Processed meat

Table 5 shows the PM and CVD findings from the Strength, Consistency, Biological Gradient, Experiment, Coherence and AMSTAR 2 quality analyses. ***Strength and Consistency:*** Eleven high vs. low assessments from eight reviews of observational studies were reported. Nine of the 11 total

Table 4. Mixed unprocessed red meat + processed meat and CVD outcomes: Bradford Hill causality criteria and AMSTAR 2 quality findings.

Bradford Hill causality criteria*						
		Outcome	Total reviews	Total assessments	Statistically significant assessments	ES ≥1.2 assessments
Strength and Consistency	Not Supported	CVD RF (OBS)	3	3	2	1†
		CVD Incidence	5	11	7	1‡
		CVD Mortality	4	6	2	0
Biological Gradient	Supported	CVD RF (OBS)	2	2	2	–
		CVD Incidence	6	9	8	–
		CVD Mortality	4	6	4	–
Experiment	Not Supported	CVD RF (RCT)	4	31	8	–
Coherence	Not Supported	Lack of coherence between observational findings and experimental evidence				

AMSTAR 2 quality of assessments						
Outcome	Total reviews	Total assessments	Quality of assessments:			
			High	Moderate	Low	Critically low
CVD RF (OBS)	3	3	0	0	1	2
CVD Incidence	8	15	2	1	10	2
CVD Mortality	6	9	1	1	5	2
CVD RF (RCT)	4	31	7	6	0	18

CVD (Cardiovascular Disease); RF (Risk Factors); OBS (outcomes from Observational studies); RCT (outcomes from Randomized experimental studies); ES (Effect Size); AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews).

*Refer to Table 2 for Bradford Hill Causality Criteria descriptions.

†Assessment is not statistically significant (RR: 1.31 95% CI: 0.91, 1.89) (Kim and Je 2018).

‡Assessment is not statistically significant (RR: 1.33 95% CI: 0.95, 1.89(Vernooij et al. 2019).

Table 5. Processed meat and CVD outcomes: Bradford Hill causality criteria and AMSTAR 2 quality findings.

Bradford Hill causality criteria*						
		Outcome	Total articles	Total assessments	Statistically significant assessments	ES >1.2 assessments
Strength and Consistency	Not Supported	CVD RF (OBS)	1	1	1	0
		CVD Incidence	5	7	6	1
		CVD Mortality	2	3	2	1[†]
Biological Gradient	Supported	CVD RF (OBS)	1	1	1	–
		CVD Incidence	7	11	9	–
		CVD Mortality	4	6	5	–
Experiment	Could Not Assess	CVD RF (RCT)	0	0	0	–
Coherence	Could Not Assess	Could not assess due to lack of experimental data				

AMSTAR 2 quality of assessments						
Outcome	Total articles	Total assessments	Quality of assessments:			
			High	Moderate	Low	Critically low
CVD RF (OBS)	1	1	0	0	0	1
CVD Incidence	8	12	2	2	6	2
CVD Mortality	4	6	1	0	3	2
CVD RF (RCT)	0	0	0	0	0	0

CVD (Cardiovascular Disease); RF (Risk Factors); OBS (outcomes from Observational studies); RCT (outcomes from Randomized experimental studies); ES (Effect Size); AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews).
*Refer to Table 2 for Bradford Hill Causality Criteria descriptions.
[†]Assessment is not statistically significant (RR: 1.52 95% CI: 0.52, 4.66) (Abete et al. 2014).

Table 6. Unprocessed meat and CVD outcomes: Bradford Hill causality criteria and AMSTAR 2 quality findings.

Bradford Hill causality criteria*						
		Outcome	Total articles	Total assessments	Statistically significant assessments	ES >1.2 assessments
Strength and Consistency		CVD RF (OBS)	0	0	0	0
	Not Supported	CVD Incidence	4	4	4	0
		CVD Mortality	2	2	0	0
Biological Gradient	Supported	CVD RF (OBS)	0	0	0	–
		CVD Incidence	6	8	5	–
		CVD Mortality	2	3	3	–
Experiment	Not Supported	CVD RF (RCT)	1	4	0	–
Coherence	Not Supported	Lack of coherence between observational findings and experimental evidence				

AMSTAR 2 quality of assessments						
Outcome	Total articles	Total assessments	Quality of assessments:			
			High	Moderate	Low	Critically low
CVD RF (OBS)	0	0	0	0	0	0
CVD Incidence	7	9	2	2	3	2
CVD Mortality	3	4	0	1	3	0
CVD RF (RCT)	1	4	0	0	0	4

CVD (Cardiovascular Disease); RF (Risk Factors); OBS (outcomes from Observational studies); RCT (outcomes from Randomized experimental studies); ES (Effect Size); AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews).
*Refer to Table 2 for Bradford Hill Causality Criteria descriptions.

assessments (~82%) reported a statistically significant association but only two of the 11 total assessments (~18%) had an effect size ≥1.2 (Supplemental Table S9). ***Biological Gradient:*** Eighteen dose-response assessments from 11 reviews of observational studies were reported. Among those 18 assessments, 15 (~83%) were statistically significant (Supplemental Table S10). Three of the 11 reviews reported a visual representation of the relationship shape with one review reporting a linear and two reviews reporting a non-linear relationship (Supplemental Table S10). ***Experiment and Coherence:*** No review reported findings from experimental studies on processed meat and CVD risk factors so the Experimental and Coherence Criteria could not be assessed.

AMSTAR 2 quality

Among 13 reviews with observational CVD outcomes, four (~30%) were rated as High or Moderate quality and contributed five assessments. The remaining nine reviews (~70%) were rated as Low or Critically Low quality and contributed 14 assessments (Supplemental Tables S9, S10). Restricting to only High and Moderate quality reviews did not change results (Supplemental Tables S9, S10).

Unprocessed red meat

Table 6 shows the URM and CVD findings from the Strength, Consistency, Biological Gradient, Experiment, Coherence and AMSTAR 2 quality analyses. ***Strength and***

Consistency: Six high vs. low assessments from four reviews of observational studies were reported. Four of the six assessments (~67%) reported statistically significant associations but of the total assessments, none had an effect size ≥1.2 (Supplemental Table S11). ***Biological Gradient:*** Eleven dose-response assessments from seven reviews of observational studies were statistically significant. Only one review reported a visual representation of the relationship shape, and it was nonlinear (Supplemental Tables S12). ***Experiment*:** One review of experimental studies reported four assessments, but none were statistically significant, suggesting that the available experimental evidence does not support a relationship between intakes of URM and CVD (Supplemental Table S13). ***Coherence*:** There is a lack of coherence between the observational findings and experimental evidence, i.e., observational findings reported statistically significant positive associations between URM and CVD outcomes, whereas experimental evidence showed non-significant effects on CVD risk factors.

AMSTAR 2 quality

Among 10 reviews with observational CVD outcomes, four (40%) were rated as High or Moderate quality and contributed five assessments, while six (60%) were rated as Low or Critically Low quality and contributed eight assessments (Supplemental Tables S11, S12). One review assessed experimental CVD risk factors and was rated as Critically Low quality and contributed four assessments (Supplemental Table S13). Restricting to only Moderate and High quality reviews further supported the ***Strength and Consistency*** Criteria but the ***Biological Gradient*** Criterion was not supported and there were no High or Moderate quality reviews from experimental studies, so ***Experiment*** and ***Coherence*** could not be assessed (Supplemental Tables S11–S13).

Plausibility

Several plausible biological mechanisms have been proposed to explain associations between red meat intake and CVD outcomes. Dietary saturated fat and cholesterol (which is in relatively high concentrations in some red and processed meat products) may increase the risk of cardiovascular disease by raising serum low-density lipoprotein cholesterol concentrations (Bergeron et al. 2019), which in turn could contribute to the development of atherscerosis (Wolmarans et al. 1991; Gascon et al. 1996; Hodson, Skeaff, and Chisholm 2001). Despite red meat containing these nutrients of concern for overconsumption, a systematically searched meta-analysis of RCTs included in our results, did not show significant effects of unprocessed red meat with any blood lipids or lipoprotein markers (O'Connor, Kim et al. 2017). Heme iron in red meat may contribute to oxidative stress, and DNA damage, thought to increase the risk of stroke (Cross, Pollock, and Bingham 2003; Kaluza, Wolk, and Larsson 2013), however this proposed mechanism has yet to be thoroughly investigated or confirmed by experimental research (O'Connor, Kim, et al. 2021). Increased consumption of sodium, which is commonly found in processed meats, was associated with risk of hypertension (Sacks et al. 2001; He and MacGregor 2002), vascular stiffness (Sanders 2009), and stroke (Strazzullo et al. 2009). Additionally, processed meats likely contain greater amounts of nitrates and nitrites than unprocessed meats, which may contribute to vascular and endothelial dysfunction (Kleinbongard et al. 2006; Förstermann 2008). Higher red meat intake is also associated with elevated circulating trimethylamine-N-oxide through gut bacterial and hepatic flavin monooxygenase activities on components such as choline and carnitine (Naghipour et al. 2021). While observational evidence suggests inconsistent associations between trimethylamine-N-oxide and CVD risk (Naghipour et al. 2021), limited experimental research with randomized-controlled feeding indicates a link between red meat intake, trimethylamine-N-oxide, and homeostatic model assessment of insulin resistance, but not other lipids or lipoproteins (e.g., triglycerides, total cholesterol, HDL-C, or LDL-C) (Krishnan et al. 2021). Even though there is a lack of experimental confirmation for some of these mechanisms, all are biologically plausible to support the Plausibility Criterion.

Type 2 diabetes mellitus: strength, consistency, biological gradient, experiment, coherence, and quality

Mixed unprocessed red meat + processed meat

Table 7 shows the Mixed URM + PM and T2DM findings from the Strength, Consistency, Biological Gradient, Experiment, Coherence and AMSTAR 2 quality analyses. ***Strength and Consistency:*** Eight high vs. low assessments from eight reviews of observational studies were reported. Most assessments (~88%) reported statistically significant associations and seven of the eight total assessments (~88%) had an effect size ≥1.2 (Supplemental Table S14). No review reported an outcome for T2DM-related mortality likely because T2DM is not often the immediate cause of death, but generally an underlying condition that may contribute to the primary cause of death. ***Biological Gradient:*** Seven dose-response assessments from seven reviews of observational studies were reported. Six of the seven total assessments (~86%) were statistically significant, but the shape of this relationship was not consistently reported (Supplemental Table S15). ***Experiment:*** Twelve assessments from three reviews of experimental studies were reported. Half of the assessments were statistically significant (50%), thus precluding a conclusion regarding the relationship between Mixed URM + PM intake and T2DM risk factors (Supplemental Table S16). ***Coherence:*** There was a lack of coherence between the observational findings and experimental evidence, i.e., observational findings reported a majority of statistically significant and positive associations between Mixed URM + PM and T2DM outcomes, but reviews of experimental evidence were too inconsistent to draw conclusions. An additional systematic review of experimental studies (Schwingshackl et al. 2018) was identified in our search but lacked quantifiable analyses. This review reported that when compared to other

Table 7. Mixed unprocessed red meat + processed meat and T2DM outcomes: Bradford Hill causality criteria and AMSTAR 2 quality findings.

Bradford Hill Causality Criteria*						
		Outcome	Total reviews	Total assessments	Statistically significant assessments	ES ≥1.2 assessments
Strength and Consistency	Supported	T2DM RF (OBS)	2	2	1	1†
		T2DM Incidence	6	6	6	6
Biological Gradient	Supported	T2DM RF (OBS)	1	1	1	–
		T2DM Incidence	6	6	5	–
Experiment	Not Supported	T2DM RF (RCT)	3	12	6	–
Coherence	Not Supported	Lack of coherence between observational findings and experimental evidence				

AMSTAR 2 quality of assessments						
Outcome	Total reviews	Total assessments	Quality of assessments:			
			High	Moderate	Low	Critically low
T2DM RF (OBS)	2	2	0	0	1	1
T2DM Incidence	8	8	1	1	4	2
T2DM RF (RCT)	3	12	6	6	0	0

T2DM (Type 2 Diabetes Mellitus); RF (Risk Factors); OBS (outcomes from Observational studies); RCT (outcomes from Randomized experimental studies); ES (Effect Size); AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews).
*Refer to Table 2 for Bradford Hill Causality Criteria descriptions.
†Assessment is not statistically significant (RR: 1.31 95% CI: 0.91, 1.89) (Kim and Je 2018).

Table 8. Processed meat and T2DM outcomes: quantitative Bradford Hill causality criteria and AMSTAR 2 quality findings.

Bradford Hill causality criteria*						
		Outcome	Total reviews	Total assessments	Statistically significant assessments	ES ≥1.2 assessments
Strength and Consistency	Supported	T2DM RF (OBS)	0	0	0	0
		T2DM Incidence	5	5	5	5
Biological Gradient	Supported	T2DM RF (OBS)	0	0	0	–
		T2DM Incidence	6	6	6	–
Experiment	Could Not Assess	T2DM RF (RCT)	0	0	0	–
Coherence	Could Not Assess	Could not assess due to lack of experimental data				

AMSTAR 2 quality of assessments						
Outcome	Total reviews	Total assessments	Quality of assessments:			
			High	Moderate	Low	Critically low
T2DM RF (OBS)	0	0	0	0	0	0
T2DM Incidence	7	7	1	1	3	2
T2DM RF (RCT)	0	0	0	0	0	0

T2DM (Type 2 Diabetes Mellitus); RF (Risk Factors); OBS (outcomes from Observational studies); RCT (outcomes from Randomized experimental studies); ES (Effect Size); AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews).
*Refer to Table 2 for Bradford Hill Causality Criteria descriptions.

food groups, Mixed URM + PM was one of the least effective at reducing HbA1c and fasting glucose, which may suggest coherence with the observational findings (Schwingshackl et al. 2018).

AMSTAR 2 quality

Among 10 reviews assessed with observational T2DM outcomes, two reviews (20%) were rated High or Moderate quality and contributed two assessments, while the remaining eight reviews (80%) were rated Low or Critically Low quality and contributed eight assessments (Supplemental Tables S14, S15). All three reviews of experimental T2DM risk factor outcomes were rated High or Moderate quality and contributed 12 assessments (Supplemental Table S16). Restricting to only Moderate and High quality reviews further supported the ***Strength, Consistency, Experiment***, and ***Coherence*** Criteria but the ***Biological Gradient*** Criterion was not supported (Supplemental Tables S14–S16).

Processed meat

Table 8 shows the PM and T2DM findings from the Strength, Consistency, Biological Gradient, Experiment, Coherence and AMSTAR 2 quality analyses. ***Strength and Consistency:*** Five high vs. low assessments from five reviews of observational studies were reported. All the PM and T2DM incidence assessments reported were statistically significant and all five assessments (100%) had effect sizes ≥1.2 (Supplemental Table S17). ***Biological Gradient:*** Six dose-response assessments from six reviews of observational studies were reported. All the assessments (100%) were statistically significant, but the shape of the relationship was not consistently reported (Supplemental Table S18). Three of the six reviews reported a visual representation of the relationship shape with two reviews reporting a linear and

Table 9. Unprocessed red meat and T2DM outcomes: quantitative Bradford Hill causality criteria and AMSTAR 2 quality findings.

Bradford Hill causality criteria*						
		Outcome	Total reviews	Total assessments	Statistically significant assessments	ES ≥1.2 assessments
Strength and Consistency	Could Not Assess	T2DM RF (OBS)	0	0	0	0
		T2DM Incidence	0	0	0	0
Biological Gradient	Not Supported	T2DM RF (OBS)	0	0	0	–
		T2DM Incidence	2	2	1	–
Experiment	Not Supported	T2DM RF (RCT)	1	3	0	–
Coherence	Could Not Assess	Could not assess due to lack of observational data				

AMSTAR 2 quality of assessments						
Outcome	Total reviews	Total assessments	Quality of assessments:			
			High	Moderate	Low	Critically low
T2DM RF (OBS)	0	0	0	0	0	0
T2DM Incidence	2	2	1	0	1	0
T2DM RF (RCT)	1	3	3	0	0	0

T2DM (Type 2 Diabetes Mellitus); RF (Risk Factors); OBS (outcomes from Observational studies); RCT (outcomes from Randomized experimental studies); ES (Effect Size); AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews).
*Refer to Table 2 for Bradford Hill Causality Criteria descriptions.

Table 10. Bradford Hill causality inference summary table for an umbrella review assessing red and processed meat intake and cardiometabolic disease.

Outcome	Meat type	Causal inference summary
Cardiovascular Disease	Mixed Unprocessed Red Meat + Processed Meat	We infer that a causal relationship is not likely due to consistently weak associations among observational studies, which are coherent with non-significant experimental evidence, despite a temporal relationship and plausible biological mechanisms.
	Processed Meat	We infer that a causal relationship is not likely due to consistently weak associations among observational studies, despite the potential for a dose-response relationship and plausible biological mechanisms. No reviews of experimental evidence were found; thus, coherence could not be assessed and contribute to this inference.
	Unprocessed Red Meat	We infer that a causal relationship is not likely due to consistently weak associations among observational studies, which were coherent with non-significant experimental evidence, despite a temporal relationship and plausible biological mechanisms.
Type 2 Diabetes Mellitus	Mixed Unprocessed Red Meat + Processed Meat	We infer a potential for a causal relationship due to consistently strong associations among observational studies, plausible mechanisms, and a potential for a dose-response relationship. Yet, coherence is lacking with the experimental evidence reporting non-significant findings.
	Processed Meat	We infer a potential for a causal relationship due to consistently strong associations among observational studies, plausible mechanisms, and a potential for a dose-response relationship. No reviews of experimental evidence were reported; thus, coherence could not be assessed and contribute to this inference.
	Unprocessed Red Meat	Insufficient evidence precluded evaluation.

one review reporting a nonlinear relationship (Supplemental Table S18). ***Experiment and Coherence:*** No review reported experimental findings between processed meat and T2DM risk factors, so the Experimental and Coherence Criteria could not be assessed due to lack of evidence.

AMSTAR 2 quality

Seven reviews assessed observational T2DM outcome assessments and two reviews (~29%) were rated as High or Moderate quality and contributed two assessments. The remaining five reviews (~71%) were rated as Low or Critically Low quality and contributed five assessments (Supplemental Tables S17, S18). Restricting to only High and Moderate quality reviews did not change results (Supplemental Tables S17, S18).

Unprocessed red meat

Table 9 shows the URM and T2DM findings from the Strength, Consistency, Biological Gradient, Experiment, Coherence and AMSTAR 2 quality analyses. ***Strength and Consistency:*** No review of observational studies provided high vs. low intake assessments, so these criteria could not be assessed. ***Biological Gradient:*** Two dose-response assessments from two reviews of observational studies were included. Only one assessment (50%) was statistically significant; neither review provided a visual representation of the shape of the relationship (Supplemental Table S19). ***Experiment***: One review of experimental studies reported three assessments, and none were statistically significant. (Supplemental Table S20). ***Coherence*:** This criterion could not be assessed due to lack of evidence.

AMSTAR 2 quality

Among two reviews of observational T2DM outcomes, one (50%) was rated as High quality and contributed one assessment and the other review was rated as Low quality and contributed one assessment. Only one review assessed experimental T2DM risk factors and was rated as High quality

and contributed three assessments (Supplemental Tables S19, S20). Restricting to only High and Moderate quality reviews did not change results (Supplemental Tables S19, S20).

Plausibility

Similar to the plausible biological mechanisms as CVD, dietary saturated fat and cholesterol from red meat or processed meat may increase the risk of type 2 diabetes mellitus through increased serum low-density lipoprotein cholesterol concentration (Bergeron et al. 2019), which could contribute to insulin resistance (Bendinelli et al. 2013). However, a meta-analysis of RCTs included in our results did not show that higher compared to lower meat intakes affected T2DM risk factors, including fasting glucose, insulin, and HOMA-IR (O'Connor, Kim, et al. 2021). Heme iron in red meat may contribute to oxidative stress, and DNA damage which may increase risk for T2DM (Cross, Pollock, and Bingham 2003; Zhao et al. 2012). Processed meats likely contain greater amounts of nitrates and nitrites, which may contribute to a decrease in insulin secretion (Portha et al. 1980; McGrowder, Ragoobirsingh, and Dasgupta 2001). Cooking preparation methods such as open flame or high-temperature cooking has also been associated with an increased risk of T2DM (Liu et al. 2018). Even though there is a lack of experimental confirmation for some of these mechanisms, all are biologically plausible to support the Plausibility Criterion.

Cardiovascular disease and type 2 diabetes mellitus: temporality, specificity, and analogy

Temporality

After the search was completed, only one review used a cross-sectional design (Rouhani et al. 2014) which violated the Temporality Criterion; therefore, this review was excluded *post hoc*. Thus, all systematic reviews and meta-analyses included only prospective observational and experimental studies within populations who were free of the cardiometabolic disease of interest at baseline (Thiese 2014). Including only prospective study designs ensures documentation of red and processed meat intakes prior to ascertainment of outcomes of interest, thus supporting the Temporality Criterion for all meat type and outcome categories.

Specificity

"Total red meat" intake was reported to increase risk for all-cause mortality, accidental deaths, and all other causes of death which have no plausible biological mechanism related to meat intake (Sinha et al. 2009; Klurfeld 2015). Intake of "red and processed meat" is associated with several different types of cancers such as gastric, colorectal, and breast (Chan et al. 2011; Farvid et al. 2018; Kim, Kim et al. 2019) as well as end stage renal disease (Lew et al. 2017). While it is plausible that there may be a common underlying mechanism relating red and processed meat intake to CVD, T2DM, and some cancers, there is no plausible explanation for the association with all-cause mortality and accidental deaths. Intakes of red and processed meats are linked to a wide range of adverse outcomes; therefore, this evidence does *not* support the Specificity Criterion for any meat type and outcome categories.

Analogy

We describe parallels between red and processed meat and other animal-based protein sources (white meat, fish/seafood, dairy, and eggs) and their relations to CVD and T2DM in Supplemental Table S21. Briefly, white meat intake was not associated with an increased risk in CVD and T2DM incidence or mortality; fish and seafood intake had non-significant associations with risk of CVD and T2DM with the caveat that fish be lean; dairy intake had inverse or non-significant associations with CVD and T2DM risk factors, incidence, and mortality outcomes, particularly with low or reduced fat products; eggs were inconsistently associated with an increased risk of CVD and T2DM in observational studies but experimental studies reported non-significant findings with risk factors. The patterns that we observed in white meat, fish/seafood, dairy, and egg literature were analogous to the literature on the red and processed meat intake, but since the findings did not suggest causality, the Analogy Criterion was *not* supported.

Publication bias

Potential publication bias was detected for four comparisons: PM and CVD Mortality (using the high vs. low RRs; $p = 0.016$; Supplemental Figure S5), Mixed URM + PM and T2DM Incidence (using the dose-response RRs; $p = 0.017$; Supplemental Figure S12), PM and CVD Mortality (using the dose-response RRs; $p = 0.0378$; Supplemental Figure S14), PM and T2DM Incidence (using the dose-response RRs; $p < 0.001$; Supplemental Figure S15). The Cochrane Handbook recommends inclusion of at least 10 assessments to adequately power test for publication bias (Sterne, Egger, and Moher 2011), but none of these significant comparisons met this criterion, so these findings should be interpreted with this in mind. See Supplemental Figures S1–24 for visuals of all funnel plots and Egger's test results.

Discussion

Observational research is the predominant evidence underlying dietary recommendations regarding red and processed meat intakes and cardiometabolic disease-related outcomes in the US (DGA 2015; DGA 2020). Our umbrella systematic review builds upon this evidence by using long-established criteria (Hill 1965) for causal inference in which we additionally incorporated experimental evidence from short-term randomized controlled feeding trials of relevant clinical risk factors. We infer that a causal relationship is not likely present between red and processed meat intakes and CVD risk. This is largely because reviews

with observational studies report consistently weak associations (four of the 26 (~15%) total high vs. low intake assessments from all meat type categories and CVD outcomes reported RR's ≥1.2) which was coherent with reviews of experimental studies reporting a lack of significant effects on CVD risk factors. However, we infer a potential for a causal relationship between PM and Mixed URM + PM and T2DM. This statement is largely supported by consistently strong associations (12 of the 13 (~90%) total high vs. low intake assessments from all meat type categories and T2DM outcomes reported RR's ≥1.2), but additional experimental evidence is needed to corroborate coherence across study designs. Conducting more observational studies will not further advance our understanding of this topic, but rigorous randomized controlled feeding trials may help fill causal gaps (Brown, Bohan Brown, and Allison 2013; Brown et al. 2021). Overall, our results suggest the inclusion of experimental evidence and consideration of how meat variables are operationalized are prudent in conclusions regarding red and processed meat intake and cardiometabolic health.

Our results exemplify how the original nine Bradford Hill Causality Criteria (Hill 1965) may be adapted to review a broad scope of human nutrition research instead of relying solely on observational evidence to infer diet-disease causal relationships. This is important because long-term direct causal evidence is often not ethically, financially, or otherwise feasible to obtain in nutrition research (Weaver and Miller 2017). We modeled our approach based on previous Bradford Hill assessments of other nutrition topics (Mente et al. 2009; Micha et al. 2017; Livesey and Livesey 2019; Livesey et al. 2019). Consistent with those assessments, we considered an *a priori* RR ≥1.2 to indicate a strong association. Some consider a 10% increased risk (RR cutoff of 1.10) to indicate higher risk of disease (Neuhouser 2020), while a 50% increased risk (RR cutoff of 1.5)(Willett 2012; Klurfeld 2015) is considered appropriate by others. A 20% increased risk is biologically meaningful at the population level and considers potential attenuation of associations due to biases or poor control of confounding factors (Byers and Lyle 1999; NCEP 2001). Some prior Bradford Hill assessments developed scoring systems to tally the criteria, or provide a grade based on weighting each criterion equally (Dyda et al. 2018; Fundora et al. 2020). We avoided this approach as it was advised against by Bradford Hill himself, who encouraged critical inquisition to interpret findings and infer causation rather than depend on a numbered score (Hill 1965; Potischman and Weed 1999). Instead, our review collectively considered all nine Bradford Hill Criteria to infer causation, with emphasis on the Strength, Consistency, Coherence, and Experimental Criteria, as well as the quality of evidence and the potential for publication bias. A more standardized approach for future nutrition applications would be beneficial, akin to the standardized methodology developed by the American Institute for Cancer Research's Continuous Update Project (WCRF 2018).

Our review focused on meat as a whole food (Mixed URM + PM, URM, or PM) rather than specific nutritive components of meat, such as sodium or saturated fat. Reducing or limiting these nutrients is recommended for prevention of CVD (Arnett et al. 2019). Educating omnivorous consumers to choose lean red meats and/or unprocessed red meats could help meet daily sodium and saturated fat intake recommendations. However, our findings suggest that high intakes of red and processed meats as independent whole foods likely do not directly increase CVD risk. Simply reducing red and processed meat intake may not reduce risk for CVD, particularly depending on what is being consumed in place of it. It is also important to inform meat consumers about overall diet quality. High intakes of red and processed meats are a hallmark of a Western-style eating pattern, as are high intakes of sugar sweetened beverages, refined grains, and non-meat foods high in sodium, added sugar, and saturated fat (Shan et al. 2019). Often, red and processed meat intakes are associated with an increased CVD risk in Westernized countries (Iqbal et al. 2021). This pattern of eating is also associated with other unhealthy lifestyle behaviors such as low physical activity, high alcohol intake, and tobacco use which may also increase CVD risk (Pérez-Martínez et al. 2017; Chudasama et al. 2020). Bradford Hill stated that "one-to-one relationships are not frequent [and] multi-causation is generally more likely than single causation"(Hill 1965). Our results suggest that it is unlikely that consuming higher amounts of red and processed meats are one-to-one causes of CVD, but instead likely depend on the entirety of the dietary and behavioral patterns of individuals.

Our results suggest a potential for a causal relationship between PM and Mixed URM + PM intakes and T2DM. Most T2DM assessments had RR's ≥1.2, some as large as 1.41 (95%CI: 1.25, 1.60) (Aune, Ursin, and Veierød 2009) for processed meat and T2DM incidence. These consistently large effect sizes that reach statistical significance are not commonly seen in nutrition epidemiology (Potischman and Weed 1999). In fact, this is more than double the risk associated between processed meat intake and colorectal cancer (WCRF 2018). Further, 13 of the 15 total (~87%) dose-response analyses of T2DM assessments were statistically significant. High quality experimental evidence, particularly of processed meat intake, on T2DM risk factors is lacking to corroborate these notably strong and consistent associations. Publication bias also could not be ruled out for some T2DM assessments (Supplemental Figures S12, S14, and S15), meaning that there may be non-significant or weak associations that were not published. An inference for URM and T2DM was not made due to a lack of reviews with observational studies. More experimental research is needed between PM and Mixed URM + PM on T2DM risk factors to reach stronger conclusions of causality.

We used AMSTAR 2 to assess the quality of included systematic reviews or meta-analyses (Shea et al. 2017) as well as a guide to ensure that our review was of high quality (Supplement Table S5.1). Our findings using AMSTAR 2 indicated that most of the reviews rated as High or Moderate quality were reviews of experimental evidence while most of the reviews rated Low or Critically Low quality were

reviews of observational evidence. The Low or Critically Low quality reviews were frequently rated as such for a lack of one or more of the following critical items: (1) explicit statement of *a priori* methods, (2) assessment of risk of bias, (3) discussion of risk of bias when interpreting findings, and (4) assessment of publication bias. A *post-hoc* assessment of the High and Moderate quality reviews only largely supported our original findings from when all reviews were combined. A limitation with our approach and the use of AMSTAR 2 is that one review may have multiple assessments. Therefore, one review could contribute a high number of assessments and affect the total number of High, Moderate, Low, or Critically Low quality assessments, depending on the quality of the review. Further, AMSTAR 2 rates the quality of the systematic review methods, not the quality or internal validity of the included empirical studies. Our results should be interpreted with this in mind, because a High quality systematic review included in our review could have potentially included low quality empirical studies.

A noted limitation of synthesizing meat-related human research is variability in meat terminology, a lack of standardized composition of meat-containing foods, and a lack of consensus of meat definitions (Gifford, O'Connor et al. 2017; O'Connor et al. 2020). Research shows that variability among the terms used to describe meat-containing foods can result in meaningful differences in population-level intake estimates. For example, the decision to include vs. exclude processed meat as part of an exposure assessment (akin to the difference between Mixed URM + PM vs. URM in our analysis) can result in intake estimates that differ by up to 9 oz-eq/week (O'Connor, Herrick, et al. 2021). A strength of our approach is that we re-categorized included reviews into three mutually exclusive and explicit meat categories (URM, PM and Mixed URM + PM) based on the 2015–2020 Dietary Guidelines for Americans definitions (DGA 2015). We relied on the descriptions provided in the reviews, and if the descriptions were unclear the reviews were categorized into the Mixed URM + PM category. This helped ensure that reviews were being compared appropriately based on meat category and allowed for a more granular assessment of meat intake and CVD and T2DM. That said, our review focused largely on relative consumption (e.g., high vs. low intake) of red and processed meats. The review did not take into consideration the leanness or absolute quantities of meat consumed, which are other important factors to consider for public health recommendations. Further, the common practice of using food frequency questionnaires or dietary recalls to assess dietary intakes with observational studies are prone to recall error, measurement error, and have a potential for inaccurate nutrient and food group estimation (Satija et al. 2015). Collectively, we consider that assessing observational studies in conjunction with randomized controlled feeding trials, as we did in this review, improves understanding of diet-disease associations (Beyerbach et al. 2022).

Our objective for this review was to systematically assess reviews of both observational and experimental research and infer causality between intakes of red and processed meats and risk for CVD and T2DM. This approach is different from the series of systematic reviews released by the NutriRECS Consortium panel in 2019, which had the aim to provide dietary recommendations regarding red and processed meat intake (Johnston et al. 2018; Johnston et al. 2019; Valli et al. 2019; Vernooij et al. 2019; Zeraatkar, Han, et al. 2019). We are not making recommendations for public consumption, but rather hope that our inferences can aid in interpretation of future evidence reviews for public guidance on this topic.

We are mindful that multiple reviews may have included the same empirical research studies which may disproportionately influence our collective findings. A majority of assessments within the included reviews were deemed to have high heterogeneity, indicating significant variability among the empirical research. Some reviews had multiple summary estimates, which contributed greater weight to our findings. We only used reviews written in English, eliciting potential language or cultural biases. The majority of included reviews were primarily of Caucasian cohorts (Stern and Kleijnen 2020). Our inferences between CVD and T2DM are discordant despite commonalities among some of their risk factors. We recognize that T2DM is considered a risk factor for CVD (Einarson, Acs et al. 2018), however our a *priori* objective was to assess these two diseases independently. Among the strengths of this review, our search strategy was inclusive in that we did not restrict our search based on populations or eating patterns, increasing external validity of our findings (Higgins and Green 2011). As widely used in public health research (Mente et al. 2009; Micha et al. 2017; WCRF 2018; Livesey and Livesey 2019; Livesey et al. 2019), this review operationalized classic causality criteria (Hill 1965) to reviews that included both observational and experimental studies to infer causal relations.

Conclusion

We infer red and processed meat intakes are not causally related to cardiovascular disease outcomes due to consistently weak associations and a lack of coherence with experimental evidence. However, we infer processed meat and mixed red and processed meat intakes are potentially causally related to type 2 diabetes mellitus due to consistently strong associations. More randomized controlled feeding trials are needed, specifically for processed meat, to support or refute these inferences. These results emphasize the importance of integrating longer-term observational studies of clinical endpoints and shorter-term randomized controlled feeding trials of clinical risk factors when developing future public dietary guidance.

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access to all the data in the review and take primary responsibility for final content. Hill, Wang, and Drs O'Connor, Campbell and Forman made critical revisions and provided intellectual content. All authors read and approved the final manuscript. This work was supported by The Beef Checkoff.

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ORCID

Erica R. Hill http://orcid.org/0000-0002-9294-1056
Lauren E. O'Connor http://orcid.org/0000-0002-4142-5756
Yu Wang http://orcid.org/0000-0001-8146-0559
Bethany S. McGowan http://orcid.org/0000-0002-4797-4836
Michele R. Forman http://orcid.org/0000-0002-3060-6068
Wayne W. Campbell http://orcid.org/0000-0002-7847-7242

Data availability statement

All results described in the manuscript are provided in the Supplemental Material.

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