Evidence Synthesis and Evaluation in Nutrition

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## Abstract

Chronic non-communicable diseases affect a large proportion of the population and are associated with significant morbidity, mortality, and social and economic impact. Large cohort and modelling studies estimate that a substantial proportion of these conditions can be attributed to dietary habits. Clinicians, guideline developers, policymakers, and researchers use systematic reviews that address the relationship between dietary exposures and health outcomes to advise the public on optimal dietary habits, formulate recommendations and policies, and plan future research. A growing body of evidence, however, suggests that there are serious problems with current methods for evidence synthesis and evaluation in nutrition, examples of which include overreliance on expert opinion and consensus, failure to follow standard systematic review methods, and the application of inconsistent criteria for the assessment of the certainty of evidence. These issues have led to ineffective (at best) or harmful (at worst) dietary recommendations and policies and the proliferation of research that cannot be confidently applied to guide dietary decisions. The objective of this thesis is to advance methods for evidence synthesis and evaluation in nutrition. The thesis begins by reviewing contemporary challenges in evidence synthesis and evaluation for dietary guideline development and offering novel insight on opportunities for future improvement. The thesis subsequently provides a descriptive analysis of limitations of recently published systematic reviews and meta-analyses of nutritional epidemiology studies. This thesis then presents two systematic reviews and meta-analyses addressing the health effects of red and processed meat consumption that serve as examples of the application of rigorous systematic review methods in nutrition. This thesis ends by describing opportunities and challenges for future evidence synthesis and evaluation in nutrition.

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None

## DECLARATION OF ACADEMIC ACHIEVEMENT

This is a "sandwich thesis" comprised of six chapters.

Chapter 1 is unpublished. DZ is the sole author

Chapter 2 is published in *Annual Reviews of Nutrition*. DZ, BCJ, and GHG conceived the idea; DZ compiled the content and drafted the first version of the article; DZ, BCJ, and GHG revised for important intellectual content. All authors approved the final version of the article.

Chapter 3 is under review at the *American Journal of Clinical Nutrition.* DZ, JLS, JB, and RJdS conceived the idea; DZ, AB, REM, IC, AG, DOL, AM, ES, KA, and DM collected data; DZ analyzed the data; DZ, JLS, JB, and RJdS interpreted the results; DZ drafted the first version of the article; DZ, TAK, VH, JLS, SEH, JB, and RJdS revised for important intellectual content. All authors approved the final version of the article.

Chapter 4 is published in *Annals of Internal Medicine.* DZ, GHG, MMB, PAC, and BCJ conceived the idea; DZ, MAH, RWMV, RED, KC, KM, MZ, JJB, CV, MR, YL, JZ, APD, CL, and MMB collected data; DZ analyzed the data; DZ, GHG, MMB, PAC, SEH, and BCJ interpreted the results; DZ drafted the first version of the article; DZ, GHG, MMB, PAC, SEH, and BCJ revised for important intellectual content. All authors approved the final version of the article.

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Chapter 6 is unpublished. DZ is the sole author.

# CHAPTER 1: INTRODUCTION TO THE THESIS

Chronic non-communicable diseases affect a large proportion of the population and are associated with significant morbidity, mortality, and social and economic impact (1). Large cohort and modelling studies estimate that a substantial proportion of these conditions can be attributed to dietary habits (1, 2). Clinicians, guideline developers, policymakers, and researchers use systematic reviews that address the relationship between dietary exposures and health outcomes to advise the public on optimal dietary habits, formulate recommendations and policies, and plan future research (3-5). A growing body of evidence, however, suggests that there are serious problems in current methods for evidence synthesis and evaluation in nutrition (6-10). These issues include the failure to conduct comprehensive literature reviews, overreliance on non-randomized evidence and expert opinion, disregard of important biases (e.g. biases due to confounding, measurement of the exposure, and selective reporting), and the application of inconsistent criteria to evaluate the certainty of evidence. These issues have produced conflicting, and often controversial, dietary recommendations—many of which have likely been inefficacious—and have led to the proliferation of research that is too low certainty to be confidently applied to guide dietary recommendations and policies (8, 11-15).

The objective of this thesis is to advance methods for evidence synthesis and evaluation in nutrition to better inform dietary guidance, policy decisions, and nutrition research.

**Chapter 2** of this thesis addresses contemporary challenges in evidence synthesis and evaluation for the purpose of dietary guideline development. It highlights limitations of current practices—issues that have led to the development of conflicting and ineffective recommendations and policies—and offers valuable insight on opportunities for future improvement.

**Chapter 3** is a cross-sectional descriptive analysis of the characteristics and quality of a sample of recently published systematic reviews and meta-analyses of nutritional epidemiology studies. We show that reviews of nutritional epidemiology studies often have serious limitations that compromise their credibility.

**Chapters 4 and 5** are two systematic reviews that were used to inform dietary guidelines on red and processed meat consumption (16). The first of these reviews summarizes the evidence from 55 cohort studies, including over four million participants, addressing the relationship between red and processed meat and all-cause mortality and adverse cardiometabolic outcomes. The second review summarizes the evidence from 70 cohort studies, including over six million participants, addressing the relationship between patterns of red and processed meat consumption and the risk of adverse health outcomes. These reviews serve as examples of the application of rigorous systematic review methods in nutrition and overcome the common limitations of reviews of nutritional epidemiology studies that we describe in chapter 3.

**Chapter 6** summarizes key insights and implications from chapters 2 to 4, highlights strengths and limitations, and reflects on opportunities and challenges for future research in nutrition.

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# CHAPTER 2: EVIDENCE COLLECTION AND EVALUATION FOR THE DEVELOPMENT OF DIETARY GUIDELINES AND PUBLIC POLICY ON NUTRITION

ANNUAL REVIEWS

*Annual Review of Nutrition*

# Evidence Collection and Evaluation for the Development of Dietary Guidelines and Public Policy on Nutrition

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nutrition public policy, dietary guidelines, GRADE, consumer engagement, conflicts of interest, risk of bias

**Abstract**

Dietary guidelines and recommendations, usually developed by government bodies or large authoritative organizations, have major downstream effects on public policy. A growing body of evidence supports the notion that there are serious deficiencies in the methods used to develop dietary guidelines. Such deficiencies include the failure to access or conduct comprehensive systematic reviews, a lack of systematic or rigorous evaluation of the quality of the evidence, a failure to acknowledge the limitations of the evidence base underlying recommendations, and insufficiently stringent management of conflicts of interest. These issues may be addressed by adhering to international standards for guideline development, including adopting systematic review methodology and using rigorous systems to evaluate the certainty of the evidence and to move from evidence to recommendations, of which the GRADE approach (Grading of Recommendations Assessment,

Development and Evaluation) is the most rigorous and fully developed. Improving the methods by which dietary guidelines are produced has considerable potential to substantially improve public policy decision-making.

## Contents





## INTRODUCTION

Decision-making about public policy on nutrition should be based on the best evidence and be aligned with public values and preferences. One of the primary ways in which public policy decision-making about nutrition occurs is through the development of dietary guidelines and recommendations by government bodies and authoritative organizations. These guidelines have major downstream effects and are used to inform policies on agriculture, food assistance programs, and nutrition in schools, prisons, hospitals, and nursing homes, in addition to influencing recommendations from health-care professionals and health messaging in the media (100). Evidence indicates that there are inconsistencies and limitations in the methods used to develop dietary guidelines, with subsequent adverse impacts on nutrition public policy (16, 27, 65, 87, 100). This paper addresses issues and challenges in developing dietary guidelines and discusses the implications of these issues for public policy on nutrition. We begin by describing how governments and organizations develop and use dietary guidelines to make public policy decisions about nutrition. We then discuss important issues in developing dietary guidelines, including the merits and limitations of the most common types of evidence used to inform dietary guidelines; issues related to evaluating the certainty of evidence and moving from evidence to recommendations; additional considerations such as equity, environmental impact, and feasibility that may need to be examined when developing recommendations; the engagement of consumers and stakeholders;

and the management of conflicts of interest. Finally, we describe how limitations in dietary guidelines and recommendations can lead to ineffective and harmful public policy on nutrition.

## HOW DO GOVERNMENTS AND ORGANIZATIONS DEVELOP DIETARY GUIDELINES AND TO WHAT EXTENT DO GUIDELINES AFFECT PUBLIC POLICY ON NUTRITION?

**DGA:** Dietary Guidelines for Americans

**DGAC:** Dietary Guidelines Advisory Committee

**WIC:** Women, Infants, and Children program

**IARC:** International Agency for Research on Cancer

In most settings, dietary guidelines are produced by governments and authoritative organizations. These guidelines subsequently have major downstream policy effects (100). In the United States, legislation mandates that the United States Department of Agriculture (USDA) and the Department of Health and Human Services (DHHS) publish a new version of dietary guidelines every 5 years (Pub. L. No. 101-445, 101 U.S.C.). The most recent version of the guidelines was published in 2015 (109). The development of the United States Dietary Guidelines for Americans (DGA) is done in three stages: (*i*) review of the evidence; (*ii*) development of recommendations; and (*iii*) implementation of the guidelines. In the first stage, nominations from the public inform the selection of a Dietary Guidelines Advisory Committee (DGAC). The offices of the USDA and DHHS review the nominations and select the DGAC members. The 15 members of the 2015 DGAC were prominent researchers in the fields of nutrition, health, and medicine. The role of the DGAC is to provide advice and recommendations to the federal government regarding the current state of scientific evidence on nutrition and health. The committee formulates research questions and either uses existing reviews and reports or commissions additional reviews to address the questions. The evidence compiled by the DGAC is used in the second stage by the DHHS and USDA to develop recommendations. These recommendations are developed independently of the DGAC. A consequence of this is that recommendations may be more political and may not be completely aligned with the conclusions drawn in the DGAC's report. The public is subsequently invited to review and comment on drafts of the DGAC's report and the recommendations. The DGA and DGAC's report are revised based on feedback and, in the third stage, the recommendations are implemented through policies and programs and the distribution of nutrition education materials for the public. The DGA is endorsed by many government programs, including, among others, MyPlate (a nutrition guide depicting recommendations for the ratio in which different food groups should be consumed), the Women, Infants, and Children (WIC) program (a federal nutrition assistance program for pregnant women and mothers of young children that offers vouchers that can be used to purchase preapproved foods), and the National School Lunch Program (a federally assisted meal program operating in public schools).

Other countries typically follow a similar process to develop dietary recommendations. Unlike in the United States, the periodic review of research evidence and revision of dietary guidelines are not legislated in most other countries (30). For example, Canada's national dietary guidelines, *Eating Well with Canada's Food Guide*, are updated only if there is an identified need to revise guidelines (23, 40). In almost all countries, recommendations are formulated through a consensus process led by working groups or committees after a review of the evidence, which is completed with variable rigor (16). Unlike the United States, most countries do not develop de novo reviews of the evidence, instead relying on published reviews and reports (16). A minority of countries involve consumers through consultations or workshops to further discuss recommendations (16). Irrespective of the process, dietary guidelines have downstream effects on government policies and programs and on health messaging (100). However, the extent of the impact of these guidelines on various policies can vary based on the setting.

The World Health Organization's International Agency for Research on Cancer (IARC) is an example of an authoritative organization that provides guidance for governments in making





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decisions about public policy. The mandate of the IARC is to provide government authorities with scientific opinions on carcinogens. It does this by publishing monographs on the association between various agents and cancers. While the IARC does not specifically focus on diet, it has investigated dietary factors (45, 46, 63), and its most striking and controversial opinion was its classification in 2015 of red meat as probably carcinogenic and processed meat as carcinogenic (33, 110).

To lead the development of its monographs, the IARC assembles a working group composed of scientific experts, who are reportedly without conflicts of interest, to provide an overview of the relevant research evidence. After reviewing the evidence, the working group meets and makes decisions through a consensus-based approach. A summary of the decision and process is published shortly after the meeting, and the full monograph is usually published within 6 months. The monograph on red meat and processed meat, however, remained unpublished until 3 years after the meeting (46).

**Observational studies:** studies that do not involve the random allocation of participants to interventions by an investigator

**Systematic review:** a search for and summary of the evidence that addresses a research question using a transparent and reproducible method

**Randomized controlled trials (RCTs):** RCTs assign participants at random to alternative interventions and thus produce balance between trial arms in both known and unknown prognostic factors

## WHAT EVIDENCE IS USED IN DEVELOPING DIETARY GUIDELINES?

Evidence informing dietary guidelines and recommendations most often comes from randomized trials and observational studies that attempt to establish causal relationships between dietary exposures and health outcomes. Guideline developers may also consider evidence from experimental animal and mechanistic studies, as does the IARC. However, this evidence is severely limited in establishing causal relationships between dietary exposures and health outcomes and, hence, is usually used only to support evidence from randomized trials and observational studies. We now look in detail at the merits and limitations of randomized trials and observational studies and describe considerations in assessing their overall quality and ability to provide evidence supporting a causal relationship between nutritional exposures and health outcomes. We also review the importance of basing dietary guidelines and recommendations and public policy decisions on systematic reviews of the evidence.

### Randomized Controlled Trials

Randomized controlled trials (RCTs) assign participants at random to alternative interventions and thus produce balance between trial arms in both known and unknown prognostic factors. Because they safeguard against potential imbalances in prognostic factors, RCTs have the potential to provide higher-certainty evidence of causation. Unfortunately, however, conducting rigorous RCTs with high applicability in nutrition poses enormous challenges (41, 91, 105). Trials of nutritional supplements typically pose the same challenges as trials of most pharmacological interventions. Hence, in this article we primarily focus on trials of dietary interventions.

Typically, rigorous dietary trials must possess the same characteristics as rigorous trials in other fields. To ensure prognostic balance between arms, all RCTs, including dietary RCTs, must conceal randomization—that is, prior to randomization, the person enrolling participants must be unaware of the arm to which each participant will be allocated. This is best operationalized by using central allocation through a computer or telephone. However, dietary trials are also subject to additional challenges in controlling bias, particularly in relation to blinding, which is achieved when study participants, clinicians, data collectors, and those adjudicating outcomes are all unaware of the arm to which participants are assigned in the trial. Blinding safeguards against vulnerability to placebo effects (those assigned to an intervention may do better not because of the biological effects of the intervention, but because of their belief in its merits), cointerventions (those exposed to the target intervention receive other beneficial treatments that control groups do not or vice versa), and bias in the measurement and adjudication of outcomes (personnel measuring and adjudicating

outcomes may favor one intervention over another). Blinding of study participants in dietary RCTs is, of course, not possible. People will always be aware of what they are eating. Blinding of those collecting health outcome data and adjudicating outcomes is, however, almost always possible. By contrast, and similar to most pharmacological trials, blinding of study participants, data collectors, and outcome adjudicators is almost always possible for trials of nutritional supplements.

We may be misled not only by bias in dietary trials but also by random error resulting from small sample sizes and small numbers of outcome events. This is a particular problem in studies of nutritional exposures in which effect sizes may be smaller than those of pharmacological or surgical interventions, thus increasing the number of participants required (99). Furthermore, one would anticipate that the effects of most nutritional exposures on important health outcomes will occur only after prolonged exposure, necessitating studies of long duration to ensure adequate exposure. Such long trials impose a significant burden on participants, are costly to conduct, and are subject to another serious source of bias: the loss of participants to follow-up (i.e., missing outcome data) (55). To address the need for long follow-up, RCTs may choose to focus on surrogate outcomes (see, e.g., 28). Unfortunately, there are a myriad of examples of interventions with apparently salutary effects on surrogates but no effect—or even detrimental effects—on outcomes important to patients and the public (11, 20). Hence, dietary RCTs focusing on surrogate outcomes usually provide only poor-quality evidence on outcomes of critical importance, such as mortality and major morbidity.

A final challenge for dietary RCTs is that participants often do not adhere closely to the diet to which they are assigned, and adherence may diminish over time (91, 101). This reduces differences in diet between trial arms, further reducing the size of a possible effect and increasing the number of participants required and, to the extent that one is interested in a comparison of the diets as prescribed, reducing the applicability of the results. While a lack of compliance with the intervention may be a sign that the intervention is not tolerable, it does not necessarily mean that the intervention will be completely ineffective if implemented. Although participants may not adhere to a dietary pattern within a trial, they may adhere to the dietary pattern if widely promoted by physicians, governments, the food industry, and the media, as was the case with the low-fat diet that became widespread in much of the latter half of the twentieth century (64). Additionally, even low levels of adherence across many individuals can have a large impact on health outcomes across a population.

Despite these formidable obstacles, there is reason to persist with the conduct of dietary RCTs, the most compelling of which may be (as we will show) that observational studies are unlikely to provide high-quality evidence regarding dietary impact on outcomes important to patients. Trialists may be able to ultimately offer high-quality evidence regarding the health effects of various dietary patterns if they ensure concealed randomization and blind adjudication of outcomes, implement strategies to optimize adherence to assigned diets, minimize loss to follow-up, and enroll large numbers of participants and follow them for a long enough duration so that it can be reasonably expected that the outcome will be impacted by the intervention (usually a decade or longer for outcomes important to the population, such as all-cause mortality and cardiovascular and cancer events). Although the cost of such RCTs will be high, one might argue—as some have—that they will nevertheless prove cost effective in comparison to the hundreds of conflicting and misleading observational studies published every year (48, 105).

## Observational Studies

Unlike RCTs, observational studies provide evidence on the health effects of dietary exposures when they are self-selected. Hence, adherence, which is a major difficulty with conducting RCTs

in nutrition, is not an issue. Unfortunately, observational studies have other problems, which we enumerate, making strong causal inferences unlikely.

**FFQ:** food frequency questionnaire

**NHANES:** National Health and Nutrition Examination Survey

**Confounding:** confounding occurs when the estimated effect of an exposure on an outcome is biased due to differences in risk factors between exposure groups

The first limitation of observational studies in nutrition, and perhaps the most important, is dietary measurement. Typically, nutritional epidemiology studies measure diet by using a food frequency questionnaire (FFQ). FFQs query participants' usual frequency and quantity of consumption of a list of foods and beverages. Memory-based dietary assessments are prone to both random and systematic error because people are not good at recalling or quantifying their diet (5). For example, the National Health and Nutrition Examination Survey (NHANES) used the 24-hour recall method to measure diet, which requires participants to recall their diets during a 24-hour period. However, two out of three participants in the NHANES reported an amount of energy intake incompatible with life (5, 47). Authors of such observational studies often argue that their memory-based dietary assessments, be they based on FFQs or 24-hour recall, have been adequately validated. Typically, however, these memory-based dietary assessments are tested against other methods that also have important limitations. For example, FFQs are often validated against 24-hour recall, which is also prone to error, as the NHANES experience illustrates (see, e.g., 17, 98). Furthermore, methods for validation are diverse, and no consistent criteria are used in the literature to assess whether dietary assessment methods are adequately valid and reliable, and investigators have yet to reach a consensus on a gold standard for dietary measurement. An additional issue in dietary measurement is its timing. Even if dietary measurement is accurate at one point in time, if measured years before the onset of the disease under study (as is often the case), the measure may not capture participants' eating patterns through the key period of exposure (see, e.g., 56, 58, 102). Thus, without periodic dietary assessment, changes in diet over time may inaccurately depict diet–disease associations.

The next threat to trustworthy causal inference from observational studies is one that is not at all specific to the field of nutrition. RCTs provide stronger evidence than observational studies because if they are sufficiently large, they ensure that prognostic factors such as age, sex, and comorbidities—whether known or unknown, measured or unmeasured—are similarly distributed between trial arms. Observational studies offer no such assurance. Indeed, when, as in dietary observational studies, participants' preferences or food availability and access are the primary determinants of exposure, prognosis will almost certainly differ substantially among groups, a situation we refer to as confounding. Confounding occurs when the estimated effect of an exposure on an outcome is biased due to differences in risk factors of the outcome between exposure groups. Investigators deal with this issue by conducting adjusted analyses, primarily through regression models, which, in principle, create prognostically homogeneous groups (1). The problem that remains, however, is that adjusted analyses will yield unbiased results only if all important prognostic factors are known and measured accurately; when that is not the case, prognostic imbalance will persist. The risk of disease associated with a particular dietary exposure may also be influenced by the presence of other risk factors, many of which might be unknown and, hence, uncontrolled in studies of free-living populations.

Were residual confounding not a problem, RCTs and optimally conducted observational studies would yield similar results, and some have argued that in most instances, at least in nutrition, they do (4, 91). That may be the case, but the problem remains that in any instance, prior to evidence from RCTs, we do not know whether we are dealing with one of the majority of situations in which results from an RCT will confirm those of observational studies or the minority in which they will not. Indeed, many examples exist of the failure of RCTs to replicate the results of observational studies (38, 60, 111, 112).

A final problem with evidence from observational studies is the potential for selective reporting and publication bias. Publication bias in nutrition is likely common, primarily due to

the overabundance of data that can be used to correlate many exposures with many outcomes and so dredge the data for interesting findings (47). Safeguards against such practices, such as registration of observational studies, do not exist. Even when there are published protocols of observational studies, authors rarely prespecify exposure–outcome relationships of interest.

**Meta-analysis:** a statistical technique to pool results from separate studies investigating the same or similar research questions; it provides a quantitative summary across studies

Despite the myriad of limitations of observational studies, we may be more certain of their findings in three uncommon situations (36). First, when observed effect sizes are large, we can be more confident that the effect can be attributed to the intervention or exposure of interest. In such cases, residual confounding is less likely to explain the association. However, if the large effect size comes from a study with methodological limitations (i.e., those that do not comprehensively or accurately and periodically measure prognostic factors and the exposure of interest, accurately measure the target outcomes, minimize missing outcome data, and conduct appropriate adjusted analyses according to a prespecified and publicly accessible protocol), the large effect size may represent a large overestimate. Typically, our confidence in the findings of observational studies is increased when the effect estimate on the relative risk scale is less than 0.5 or greater than 2 (36).

Second, the presence of a dose–response gradient has long been recognized as an important criterion for supporting a causal relationship (93). Although dose–response relationships may increase our certainty about the findings of observational studies, they will mislead us when dose-dependent confounding exists. For instance, an apparent dose–response relationship between an exposure of interest (e.g., processed meat) and a health outcome (e.g., mortality from cardiovascular disease) may be confounded with another variable that is also correlated with the exposure (e.g., salt). Due to dense correlation networks among nutritional exposures, dose–response relationships may strengthen causal inferences to a lesser extent in nutrition than in in other fields.

Finally, occasionally all plausible confounders and biases from observational studies will result in an underestimation of an apparent effect. This situation is unlikely to occur in nutritional epidemiology because all plausible confounders and their directions of bias are only rarely understood with a high degree of confidence (83). Since we almost never see strong associations in nutritional studies, dose–response relationships provide only modest additional reassurance, and because we are rarely aware of all of the important confounding factors with certainty, seldom will we be able to make causal inferences from observational studies with high certainty.

Unfortunately, dietary guidelines have placed too heavy of an emphasis on the findings of observational studies without appropriately acknowledging their limitations, as we will show (39, 100). While observational evidence may also be supported by other lines of evidence, such as in vitro biochemical studies and animal experiments, the certainty of evidence from such sources is also severely limited and cannot be used to surmount the inherent limitations of observational studies (49, 84, 85).

## Systematic Reviews

Standards for developing trustworthy guideline recommendations suggest the need for comprehensive systematic reviews of the evidence (7, 19, 54, 80). A systematic review is a search for and summary of the evidence that addresses a research question using a transparent and reproducible method. It is often, but not always, accompanied by a meta-analysis, which is a statistical method for pooling results from different studies to provide a single effect estimate for each outcome of interest. Systematic reviews have several advantages compared with single studies. Single studies, as well as reviews of the evidence without a systematic search and objective eligibility criteria, are liable to be unrepresentative of the total body of evidence and, thus, can be misleading. Also, single studies may not be adequately powered to detect important effects. This is especially true in

## CRITERIA FOR RIGOROUS SYSTEMATIC REVIEWS AND META-ANALYSES

Rigorous systematic reviews and meta-analyses should:

- explicitly address a sensible research question
- conduct an exhaustive and reproducible search to select relevant studies
- assess the risk of bias using appropriate criteria
- use appropriate statistical methods to pool results from primary studies
- conduct an evaluation of the overall quality of evidence



nutrition, where effect sizes are usually small (99). Compared with single studies, systematic reviews include a greater range of study participants and so have greater external validity. The sidebar Criteria for Rigorous Systematic Reviews and Meta-Analyses presents the relevant criteria (74).

Unfortunately, many dietary recommendations are not based on systematic reviews or are based on systematic reviews that are not methodologically rigorous. In a review of guidelines on sugar intake, Erickson and colleagues (27) found that in four of nine guidelines, systematic searches for relevant studies to inform recommendations had not been conducted. Blake and colleagues (16) found that less than 20% of national dietary guidelines were based on systematic reviews. The US National Academies of Sciences, Engineering, and Medicine (NAS) has published two reports critiquing the process used to develop the DGA (77, 78). The reports identified important deficiencies in the systematic review processes and called for increased adherence to standardized processes and methods for evidence synthesis. The 2015 DGAC did not use systematic reviews for approximately half of its research questions, instead choosing to rely on unsystematic reports prepared by third-party organizations and ad hoc examinations of the evidence by experts (25). For example, the DGAC based recommendations for low-carbohydrate diets on what they referred to as "exploratory searches" rather than systematic reviews (25, p. 186). Furthermore, the DGAC undertook very few meta-analyses, instead choosing to use what they referred to as "qualitative synthesis" in order to identify "Key Trends" in the evidence (25, p. 35). Such an approach does not consider the magnitude of effect (important because very small effects may not warrant changes in dietary behavior), the precision of estimates, or the extent of inconsistency in the results of primary studies. Both imprecision and inconsistency represent important considerations in determining the certainty of evidence (37).

Although the IARC states that it conducts a review of the evidence, details of the search strategy and eligibility criteria are not reported in its monographs, raising concerns that rather than conducting a systematic search, the working group identifies relevant studies based on their experience and prior knowledge of the field. The apparent failure to conduct a comprehensive review may explain why the IARC report on red and processed meats did not include two key studies: the Women's Health Initiative Dietary Modification (WHI-DM) trial and the Polyp Prevention Trial (14, 92). The WHI-DM trial randomized nearly 49,000 participants to either a low-fat diet or their usual diet. The low-fat dietary intervention arm reduced the intake of red meat by 20% (14). The Polyp Prevention Trial tested a similar low-fat, high-fiber dietary intervention in more than 2,000 participants and found a statistically significant decreased intake of red and processed meats in the intervention group (92). Furthermore, although the IARC states that it critically reviews the evidence, it does not provide explicit judgments regarding the risk of bias in each study (46). Without an appropriate assessment of the risk of bias, conflicting results from studies of varying quality may be inappropriately given equal weight.

**NAS:** US National Academies of Sciences, Engineering, and Medicine

## HOW IS THE CERTAINTY OF EVIDENCE EVALUATED TO INFORM DIETARY GUIDELINES?

**GRADE:** Grading of Recommendations Assessment, Development and Evaluation

To move from evidence to recommendations, decision-makers must consider criteria regarding the overall certainty of the body of evidence in addition to the magnitude of desirable and undesirable consequences and the values and preferences of the target population (37). The expression values and preferences refers to the importance people place on each of the outcomes associated with a decision, and it is crucial to balancing desirable and undesirable consequences. There are various systems for rating the certainty of evidence and moving from evidence to recommendations (see, e.g., 25, 26, 37, 43). Of the systems available, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is by far the most rigorously developed and widely used (37). GRADE was developed to address the limitations of previous systems for rating the certainty of evidence (8, 9). Unlike many of its predecessors, GRADE yields clear and understandable recommendations and is simple to apply (having undergone extensive user testing) and, hence, is the focus of this review (8, 9, 21, 62, 76, 90). The GRADE system uses four categories to rate the certainty of evidence: high, moderate, low, or very low (see the sidebar Certainty of Evidence and Definitions). Lower levels of certainty indicate a greater likelihood that the underlying true effect is substantially different from the observed effect.

Rating the certainty of evidence begins by considering study design. A body of evidence based on RCTs is initially assigned high certainty, and observational studies are assigned low certainty due to concerns about confounding. The certainty may be reduced if reviewers note limitations regarding the risk of bias, inconsistency, imprecision, indirectness, or publication bias (12). For each criterion, certainty may be reduced by one or two levels depending on the seriousness of concerns. An increase in certainty may occur when observational studies produce large effect sizes or a dose–response gradient or when all plausible confounders or biases would reduce a demonstrated effect or suggest a spurious effect when results show no effect. As we described in the previous section, it is rare to have high-certainty evidence from observational studies of nutrition because effect sizes are usually small; dose–response gradients are not as reassuring against confounding bias as they are in other fields; and we seldom ever have knowledge of all plausible confounders.

According to the GRADE system, recommendations can be either strong or weak. The direction and strength of a recommendation is determined by the balance between desirable and undesirable consequences and our certainty about the effect estimates (37). The balance between desirable and undesirable consequences is, in turn, determined by the magnitude of effect estimates for each outcome of interest and the values and preferences of the target population. The larger the gradient between the desirable and undesirable effects—based on the values and preferences of the target population—the higher the likelihood that a strong recommendation is warranted. Another determinant of the strength of recommendations is our certainty of the effect estimates. Typically, a strong recommendation is associated with high, or at least moderate, certainty about

### CERTAINTY OF EVIDENCE AND DEFINITIONS

- **High certainty**: The true effect is most likely very close to the effect estimate.
- **Moderate certainty**: The true effect is likely to be close to the effect estimate, but there is a possibility that it is different.
- **Low certainty**: The true effect may be substantially different from the effect estimate.
- **Very low certainty**: The true effect is likely to be substantially different from the effect estimate.

the effect estimates for critical outcomes. The more closely balanced the trade-offs between desirable and undesirable outcomes, the more likely that low-certainty evidence underlying any critical outcome will result in a weak recommendation. A final concern that may decrease the strength of recommendations is uncertainty about or variability in the values and preferences of the target population. Uncertainty in values and preferences means that we do not confidently know whether undesirable outcomes are outweighed by desirable outcomes, according to the perspective of the target population. Variability in values and preferences means that a single recommendation would not apply uniformly across the target population. In such situations, weak recommendations are warranted. In general, making strong recommendations based on low-certainty evidence is discouraged, apart from a few paradigmatic situations (3). An alternative way of defining strong recommendations is that they indicate high- or at least moderate-certainty evidence that the benefits of a course of action clearly outweigh harms, or vice versa, according to the majority of the target population, whereas weak recommendations indicate that we are uncertain whether benefits are clearly outweighed by harms, or vice versa, for the majority of the target population.

The GRADE Evidence to Decision frameworks were developed to facilitate the process of moving from evidence to recommendations (2). They build on the GRADE method and provide a structured process through which decision-makers can be informed about the relative benefits and harms of the options being considered, provide decision-makers with a rating of the certainty of the evidence about benefits and harms, and ensure that all important factors are considered in the decision-making process. The Evidence to Decision frameworks can also support stakeholders in understanding the judgments made by decision-makers and the evidence supporting those judgments.

It must be noted that there is by necessity a considerable amount of subjectivity involved in rating the certainty of evidence and grading recommendations and that two persons evaluating the same body of evidence might reasonably come to different conclusions (75). However, the advantage of GRADE is that it provides a transparent framework through which these subjective judgments can be documented and communicated to stakeholders.

The GRADE system has been criticized by nutrition researchers for rating evidence from observational studies as having low certainty (see, e.g., 95). Such criticism is usually centered on the challenges of conducting RCTs in nutrition, challenges which our prior discussion has made clear. Picture, however, two bodies of observational studies that are identical in the rating of their certainty of evidence, but one addresses a question for which RCTs are feasible and the other does not. Should a higher rating of certainty in the context of unfeasible RCTs be provided (in other words, does the unfeasibility of RCTs increase one's certainty in the evidence)? We would argue that it should not.

There are compelling reasons for maintaining similar criteria for evaluating certainty across disciplines. Clinicians, patients, and other policy-makers must weigh the benefits and harms of many different kinds of interventions—including pharmacological, surgical, and nutritional—for a clinical or public health problem. For example, to choose between bariatric surgery or lifestyle interventions for obesity, patients and clinicians must weigh the potential benefits and harms associated with a surgical intervention and a lifestyle intervention. Using modified criteria to assess the certainty of evidence for some interventions and not others would be misleading. We have highlighted the formidable limitations of both RCTs and observational studies in nutrition. Acknowledging these limitations is preferable to pretending they do not exist.

Some have suggested that in situations in which the certainty of evidence is low or very low, guideline panels should refrain from making recommendations (18). This situation is common in nutrition. However, ultimately the public, clinicians, and policy-makers will be faced with situations in which they must make decisions. Refraining from making a recommendation is not

helpful to stakeholders. In such situations, making a weak recommendation or a recommendation to consider the values and preferences of the target population when deciding between alternative courses of action is preferable to not making a recommendation.

Turning our attention to how the certainty of evidence is evaluated and recommendations are formulated in existing dietary guidelines, there is great variability in whether decision-making bodies rate the certainty of the evidence and the methods by which they do so. In one investigation, only 5 of 32 national dietary guidelines committees explicitly evaluated the certainty of the evidence underpinning their recommendations (16). Among those committees that did, the appropriateness of the criteria used was questionable. For example, the technical advisory group for the development of New Zealand's national dietary guidelines evaluates the certainty of evidence through discussion using unspecified criteria (16). The DGAC used the USDA Nutrition Evidence Library system to rate the certainty of evidence as strong, moderate, limited, or not assignable, based on the risk of bias, numbers of studies and study participants, consistency across studies, impact, and generalizability, criteria that, although they appear reasonable and have close correspondence to GRADE criteria, still have limitations (25). For example, the criterion "impact" considers the magnitude of effect and the directness with which studies evaluate the association between the exposure and the outcomes of interest: two seemingly unrelated concepts. If the effect size is small and not clinically important or the evidence does not address the outcomes of interest, the certainty of the evidence is rated as limited. If the effect size is large with evidence directly addressing the outcomes of interest, the certainty of evidence is rated as strong, given that there are no limitations in the other domains. The framework does not, however, consider the situation in which there is high-certainty evidence that an effect is very small and of marginal importance. Moreover, the DGAC does not present explicit judgments for each of the five Nutrition Evidence Library criteria, instead presenting only the overall rating, the validity of which remains in question due to the lack of transparency in the ratings for each of the five criteria.

In their reports critiquing the development of the DGA, NAS also identified a lack of transparency in how evidence is translated into recommendations and important inconsistencies between the 2015 DGAC report and the subsequent recommendations (77, 78). Notable inconsistencies include the 2015 DGA stance on healthy dietary patterns and sodium restriction. Despite the limitations of the evidence regarding the health effects of vegetarian dietary patterns highlighted in the DGAC report, the guidelines recommend a vegetarian dietary pattern as one of three healthy dietary patterns for Americans (109). The DGA also recommends limiting daily sodium intake (to <2,300 mg) for all adults (109). The DGAC report, however, notes that evidence regarding the effects of sodium on cardiovascular outcomes is inconsistent and insufficient to conclude that lowering sodium intake to below 2,300 milligrams per day either increases or decreases the risk of cardiovascular events in the general population (25). Such inconsistencies between the evidence and the recommendations raise concerns regarding the extent to which the DGA recommendations are evidence based.

## WHAT ADDITIONAL CONSIDERATIONS ARE NEEDED WHEN DEVELOPING DIETARY GUIDELINES?

In addition to the health effects associated with diet, dietary guidelines may also choose to consider issues such as resource use, equity, environmental impact, feasibility, and acceptability. **Table 1** presents these additional considerations and their relations to dietary guidelines. Whether guideline developers address these additional considerations largely depends on the perspective they assume. For example, dietary guidelines targeted at health professionals are less likely to consider costs and environmental impact compared with guidelines that take a societal perspective.

**Table 1 Additional considerations for those developing guidelines in nutrition**

| Consideration | Details |
|---|---|
| Resource use | Healthy dietary patterns may be costly. Evaluating the cost effectiveness of programs that promote healthy dietary patterns may be important. Evaluations of cost effectiveness should ideally be specific to each setting in which the guidelines will be implemented as costs will vary between regions. |
| Equity | There may be reasons for anticipating differences in the relative effectiveness of dietary recommendations for disadvantaged groups. For example, recommended foods and beverages may be less accessible to disadvantaged groups. Therefore, the implementation of recommendations may result in an increase in health disparities. Recommendations may include strategies to reduce anticipated inequity. |
| Environmental impact | Although certain dietary patterns may optimize health outcomes, they may not be environmentally sustainable in the long term. For example, meat production requires large amounts of land and water to grow grain to feed livestock. It also contributes to methane emissions. |
| Feasibility | There may be important barriers to implementing dietary recommendations. For example, global and national food suppliers may not be prepared to deal with the shift in a population's dietary patterns that may follow the implementation of a new dietary guideline. The food industry may not be adequately prepared to respond to changes in demand with new or alternative products. |
| Acceptability | Some dietary interventions may not be acceptable to stakeholders. Stakeholders are broadly defined as individuals, groups, or organizations that may be directly affected by or interested in a proposed policy. Cultural and religious considerations may make some dietary patterns unacceptable to some groups of people. Certain dietary interventions may be burdensome and unacceptable to the general public. |



If guideline developers choose to address additional considerations, they should make explicit the weight of each consideration in their decision-making process.

Ideally, additional considerations should be accompanied by a comprehensive search for and synthesis of the related evidence, conducted with a rigor similar to that used in systematic reviews addressing health outcomes. It is perhaps unsurprising that guideline panels do not always achieve this degree of rigor. For example, the Nordic Nutrition Recommendations describe the characteristics of environmentally sustainable diets without undertaking a systematic review of the relevant evidence (82). The magnitude of consideration given to environmental sustainability in relation to health effects is also not specified, raising questions about how decision-makers might balance situations in which environmentally sustainable dietary patterns are at odds with those that optimize health outcomes.

Most national dietary guidelines limit their scope to considering only health outcomes (30). Some countries, such as the Netherlands, Sweden, and Brazil, also consider environmental sustainability. The 2015 DGAC recommended considering environmental sustainability in its report to the USDA and DHHS. The DGAC conducted a systematic review of modeling studies to identify the most environmentally sustainable dietary patterns. This sparked an intense debate regarding whether environmental sustainability is within the scope of national dietary guidelines (10). Ultimately, the guidelines were published without reflecting sustainability considerations. It is possible that the recommendations in the 2015 DGA would have been different had environmental sustainability been considered. For instance, nuts (particularly almonds), which the guideline recommends, require many liters of water to produce a very small quantity (10). The production of seafood, another recommended food group, is in the midst of rapid expansion to meet growing worldwide demand, but the collapse of some fisheries due to overfishing in past decades raises concerns about sustainability (29). It remains controversial whether the consideration of environmental sustainability has a place in national dietary guidelines.

## HOW SHOULD CONSUMERS BE ENGAGED IN DEVELOPING DIETARY GUIDELINES?

Consumer engagement is now internationally recognized as an important component of guideline development (19, 80, 86, 94). Involving consumers recognizes individuals as having valuable input about their health, respects the rights of citizens to participate in health policy development, and improves the implementability and uptake of guidelines. Within the GRADE framework, consumers can provide input regarding the relative importance placed on the outcomes of interest and, in turn, decide whether the benefits of a course of action are outweighed by its harms. In dietary guidelines, consumers are predominantly members of the general public. Other consumers may include health professionals and policy-makers.

While the value of consumer engagement is well recognized, there is great variability in how consumers are engaged in the development of both medical and dietary guidelines, with no accepted gold standard approach (6). Ideally, consumers should be engaged throughout the entire process of guideline development (6). A comprehensive framework on consumer engagement that we find helpful was published by Armstrong and colleagues in 2017 (6). The framework summarizes strategies for ensuring meaningful consumer engagement at various steps of the guideline development process. These strategies include, but are not limited to, soliciting priority topics from the public, including consumers on guideline development panels, surveying consumers regarding the importance of proposed outcomes for guideline questions, consulting consumers on decisions related to the analysis and presentation of data, involving consumers in drafting recommendations or reviewing drafts of recommendations, and querying consumers regarding expected barriers to the dissemination and implementation of guidelines. Additionally, consumers can be engaged in two ways: passively (whereby consumers are solicited for their ideas or views through public forums) and actively (whereby consumers are involved in meetings and focus groups and a dialogue between guideline developers and consumers is established), with active engagement being preferred to passive engagement. Barriers to consumer engagement include ensuring recruitment of a representative spectrum of consumers, determining how to facilitate meaningful engagement with consumers who have insufficient understanding of the relevant content or guideline development process, and handling situations in which consumers may hold scientifically indefensible views.

Unfortunately, current dietary guidelines fall short of ensuring adequate consumer engagement (27, 87). In most cases, consumer engagement is passive and restricted to one or two steps within the guideline development process or completely overlooked. For example, while the DGA process engages the public through nominations of members to the DGAC, the ultimate selection process for members of the DGAC is a black box (77). Furthermore, members of the public do not directly participate in the development of DGA recommendations. Rather, they are restricted to opportunities for public comment on the DGA and DGAC report. It is unclear the extent to which and how public comments subsequently shape recommendations. Similarly, the 2012 Nordic Nutrition Recommendations included a period of public comment without any detail regarding how recommendations were modified based on public comments (82).

## HOW SHOULD CONFLICTS OF INTEREST BE ADDRESSED?

Interpreting a body of evidence involves a level of subjectivity that may lead to discordant conclusions by different individuals (97). This can be problematic when conflicts of interest influence the interpretation of the evidence and the resulting recommendations. Financial conflicts of interest and industry sponsorships have received substantial attention in nutrition (81). Financial conflicts include ownership of stocks or shares, paid employment, or receipt of research grants.

Nonfinancial conflicts, including intellectual and personal conflicts, may, however, also be important (35, 50). Intellectual conflicts include previous involvement in research that bears on the recommendation. Personal conflicts can include previous advocacy, personal preferences, and culture and religion.

To date, the most common strategies proposed to limit the influence of conflicts of interest on recommendations have been to exclude individuals with conflicts from the guideline group or limit the number of individuals with conflicts to a minority of the group (35, 69, 70). It has also been proposed that important conflicts of interest should prohibit panelists from leadership roles and active participation in the final decision-making process for the recommendations for which they have conflicts (35). Some guideline groups have used an external standing committee to screen candidates by reviewing their conflicts of interest and evaluating the likelihood of their conflicts influencing recommendations (69, 70). Additionally, it has been suggested that information on conflicts in guideline groups should be monitored and periodically updated, given that guideline development is a lengthy process with some guidelines taking many years to produce (54).

A previous report suggests that less than 15% of national dietary guidelines disclose the conflicts of interest of working members, and less than 10% have a policy for managing conflicts (16). In 2017, Erickson and colleagues (27) found problems in the reporting and handling of conflicts of interest in most published guidelines on sugar consumption. Among dietary guidelines that have a policy regarding the handling of conflicts of interest, simple disclosure is the most common (16, 27). Most dietary guidelines do not have policies for dealing with intellectual or personal conflicts or managing conflicts beyond disclosure.

The 2015 DGA also fell short on appropriately managing conflicts of interest. Relevant conflicts were not disclosed in either the DGAC report or the accompanying guideline document (25, 109). Yet the research history of DGAC members reveals many relevant conflicts (104), including the receipt of funding from the California Walnut Commission, the International Tree Nut Council, and various food companies, including Bunge, Unilever, General Mills, and PepsiCo (13, 42, 61, 72, 96). Some members of the DGAC have also been closely involved with large cohort studies that have been used to support the guideline's recommendations (24, 32, 89). The DGAC relied heavily on nonsystematic reports produced by third-party organizations, such as the American Heart Association and the American College of Cardiology, that receive substantial funding from the vegetable oil industry (104). Although the report recommends a high consumption of vegetable oils and nuts and places undue emphasis on findings from particular observational studies with a high potential for confounding, the extent to which conflicts influenced recommendations remains uncertain.

In contrast to the DGA, the IARC reports that it bars experts with conflicts of interest from participating in the working group. The panel may consult experts with conflicts as invited specialists who may contribute expertise to noninfluential issues but who cannot serve in leadership positions, draft texts that pertain to the interpretation of data, or participate in deliberations. Whether the IARC takes a comprehensive approach and also includes intellectual and personal conflicts in its policy is not explicitly reported: It is most likely that the IARC's definition of conflicts of interest is restricted to financial conflicts.

Organizations producing guidelines, in addition to considering conflicts of interest among guideline developers, might also consider the extent to which primary studies being used to guide recommendations are industry sponsored. Evidence regarding the extent to which industry sponsorships can bias the results of studies in nutrition is mixed. A systematic review found there was no statistically significant difference between conclusions from industry-sponsored studies and nonindustry-sponsored studies in nutrition (22). Other research has found evidence for substantial bias in industry-sponsored systematic reviews of sugar-sweetened beverages and artificial

sweeteners (15, 66). If partnerships between researchers and the food industry are transparent and provide open access to protocols and verifiable data, records indicating the intent to publish results, and the eventual publication of results, methodologists participating in guideline development should be able to use the results of industry-sponsored studies to guide recommendations without being affected by potentially misleading reporting (68).

## WHAT ARE THE CONSEQUENCES OF USING POOR EVIDENCE TO GUIDE PUBLIC POLICY DECISIONS ABOUT NUTRITION?

Starting in the 1970s, the US government, along with other authoritative organizations, recommended a shift to a low-fat diet. In 1980, the first DGA was published with the recommendations to "avoid too much fat, saturated fat, and cholesterol" (103; 107, p. 11). The 1985 DGA went further and recommended that fats be restricted to less than 30% of total caloric intake (108). Other governments shortly followed with their own dietary recommendations for low-fat diets. For example, in 1983, the United Kingdom's National Advisory Committee on Nutritional Education published dietary guidance echoing the 1980 DGA (79). The food industry responded to increased consumer demand for low-fat foods by developing thousands of new products that were lower in fat. In an effort to maintain palatability, fat-replacement strategies often required increasing the carbohydrate content, and fat was replaced by a combination of sugars and starches (65). In the following years, the intake of dietary fats decreased from approximately 36% of total caloric intake in the late 1970s to approximately 33% in 2000, and carbohydrate intake increased by approximately 10% (67).

Recent research suggests that the focus on reducing dietary fat may have directly contributed to the growing burden of chronic diseases. Increased rates of obesity and heart disease have been found to coincide with the introduction of recommendations to consume a low-fat diet (44). Although a causal relation cannot be concluded—given the many limitations of observational research already discussed—the temporal association is striking between reduced fat intake and increased carbohydrate intake and the rise in the prevalence of overweight, obesity, and cardiometabolic conditions (73). At the very least, dietary recommendations to reduce fat intake did not reduce the prevalence of cardiometabolic diseases as they were intended to. The health effects of low-fat dietary patterns remain a contentious issue and, given the magnitude of scientific uncertainty that exists even today, further highlight that past recommendations to consume a low-fat diet were largely inappropriate (31, 34, 88, 103).

The case of dietary fats illustrates the importance of using strong evidence to guide recommendations. In general, the evidence used to guide recommendations is now considered to be poor quality and potentially misleading (59, 71, 106). Much of the evidence came from ecological studies with a high potential for confounding. Other studies addressed the effects of short dietary interventions on surrogate outcomes. At the time, data from RCTs addressing patient-important outcomes did not support the effectiveness of low-fat diets, but observational evidence was viewed as sufficient to implicate dietary fats in the pathogenesis of heart disease (39). At the time of the inception of the recommendations to consume low-fat diets, the techniques of epidemiology and causal inference were much different from today (53). The RCT had not yet attained its hegemonic gold standard status, and the hazards of observational evidence had not yet been widely recognized (53). It has also been argued that recommendations to consume low-fat diets were advanced by the sugar industry, which reportedly employed various spin tactics to implicate fats and not sugar in the pathogenesis of cardiovascular disease (57). In 2018, Johns & Oppenheimer (53) presented an alternative and equally compelling account of how both the sugar and fat industries engaged in attempts to influence dietary recommendations. However, the hypothesis implicating

dietary fats in heart disease was supported by more evidence, albeit very weak, compared with the antisugar hypothesis, and, hence, gained more endorsement and traction (53). The example of dietary fats illustrates that failure to acknowledge the limitations of the evidence base may lead to recommendations that are ineffective, at best, or harmful, at worst.

IOM: Institute of Medicine

Turning to another issue, nutrition as a field is more susceptible to influence from industry and those with conflicts of interest because the evidence is usually of low certainty. This is illustrated by the controversy surrounding the WIC program in the United States and its stance on white potatoes. In 2014, WIC removed white potatoes from its list of approved foods, based on a report from the Institute of Medicine (IOM) that concluded that low-income families already consumed large quantities of white potatoes and that potatoes have low nutritional value (51). Potato lobbyists, spearheaded by the National Potato Council, worked to overturn this change, arguing that potatoes are just as nutritious as other fruits and vegetables. Recently, WIC added white potatoes back to the list of approved foods, based on a more recent report from the IOM that concluded white potatoes are a cost-effective source of fiber and potassium and are nutritionally valuable (52). While the reversal of the decision may be attributed to scientific developments in potato research, in our opinion, that is unlikely. Rather, low-certainty evidence is generally more open to undue influence from those with conflicts of interest. Inconsistent and alternating dietary recommendations are arguably more likely when the evidence is of low certainty, given that uncertain evidence is generally more open to interpretation.

Inaccurate and conflicting dietary guidance is detrimental to the public's understanding of nutrition and people's ability to build healthy diets. Nutritional guidance, once adopted, appears frequently in the media. At a time when consumers are already subjected to an overabundance of nutrition and health information, governments and organizations should be held accountable for developing policies that are rooted in strong science and free from influence by those with conflicts of interest (54).

## HOW CAN DECISION-MAKING ABOUT PUBLIC POLICY ON NUTRITION BE IMPROVED?

Although current dietary guidelines suffer from shortcomings, they have a large impact on public policy. Improving the methods for developing dietary guidelines has the potential to improve public policy decision-making about nutrition. To make this improvement, we must base all recommendations on methodologically rigorous systematic reviews and should primarily rely on higher quality evidence to guide recommendations. If only low-certainty evidence is available, guideline panels must acknowledge the limitations of the evidence base and refrain from making strong recommendations.

All decision-making is complex. Decision-makers may not have clear criteria, may sometimes neglect important criteria, or may give inappropriate importance to select criteria. Hence, we recommend the use of a transparent and structured system to evaluate the certainty of the evidence and to move from evidence to recommendations, such as the GRADE system, which is the most widely used system and an improvement over its predecessors (8, 9, 21, 62, 76, 90).

Norms for handling conflicts of interest in developing dietary guidelines are inadequate. While disclosure is an important step, further measures should be taken to protect recommendations from undue influence. Such measures should include prohibiting those with conflicts of interest from participating in the final decision-making process for the recommendation for which they have conflicts and excluding those with conflicts of interest from leadership positions.

Most dietary guidelines do not meet standards for adequate stakeholder engagement (87). Current dietary guidelines would benefit from further stakeholder engagement, including

engagement of the general public, academic researchers, and members of professional organizations. While broad participation in the process should be proactively sought, participation needs to be incorporated thoughtfully. Ideally, such engagement should occur throughout the entire process of developing recommendations and should include some active components, such as involving consumers as part of guideline panels.

Finally, decision-makers can make use of several resources that set standards for the development of guidelines. While many of these resources target the development of medical guidelines, most, if not all, are relevant to nutrition. Such resources include the IOM's standards for developing trustworthy guidelines (80); guidance from the GRADE working group, which sets the gold standard for grading the certainty of evidence and strength of recommendations (**http://www.gradeworkinggroup.org/**); the Guidelines International Network–McMaster Guideline Development Checklist (94); tools for measuring the quality of guidelines, such as the AGREE (Appraisal of Guidelines, Research and Evaluation) tool (19); and a recent initiative to adhere to the best international standards in the development of nutritional recommendations (54; **https://nutrirecs.com**).

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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# CHAPTER 3: SYSTEMATIC REVIEWS AND META-ANALYSES OF OBSERVATIONAL NUTRITIONAL EPIDEMIOLOGY STUDIES OFTEN HAVE SERIOUS METHODOLOGICAL LIMITATIONS—A CROSS-SECTIONAL STUDY

This chapter is under review at *American Journal of Clinical Nutrition*.

**Systematic reviews and meta-analyses of observational nutritional epidemiology studies often have serious methodological limitations: A cross-sectional study**

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**Running head:** Reviews of nutritional epidemiology studies

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**Abstract**

***Background:*** Dietary recommendations and policies should be guided by rigorous systematic reviews. Reviews that are of poor methodological quality may be ineffective or misleading. Most of the evidence in nutrition comes from non-randomized studies of nutritional exposures (usually referred to as nutritional epidemiology studies), but to date there has been no evaluation of the quality of systematic reviews of such studies.

***Objective:*** To investigate the quality of recently published systematic reviews and meta-analyses of nutritional epidemiology studies and to propose guidance addressing major limitations.

***Design:*** We searched MEDLINE (Jan 2018 to Aug 2019), EMBASE (Jan 2018 to Aug 2019), and the Cochrane Database of Systematic Reviews (Jan 2018 to Feb 2019) for systematic reviews of nutritional epidemiology studies. We included a random sample of 150 reviews, on which we collected data.

***Results:*** Most reviews were published by authors from Asia (n=49; 32.7%) or Europe (n=43; 28.9%) and investigated foods or beverages (n=60; 40.0%) and cancer morbidity and mortality (n=54; 36%). Reviews often had important limitations: less than a quarter (n=30; 20.0%) reported preregistration of a protocol and almost one third (n=42; 28.0%) did not report a replicable search strategy. Suboptimal practices and errors in the synthesis of results were common: a quarter of meta-analyses (n=30; 26.1%) selected the meta-analytic model based on statistical indicators of heterogeneity and almost half of meta-analyses (n=50; 43.5%) did not consider dose-response associations even when it was appropriate to do so. Only 16 (10.7%) reviews used an established system to evaluate the certainty of evidence.

***Conclusion:*** Systematic reviews of nutritional epidemiology studies often have serious limitations. Authors can improve future reviews by involving statisticians, methodologists, and researchers with substantive knowledge in the specific area of nutrition being studied and using a rigorous and transparent system to evaluate the certainty of evidence.

**Keywords:** systematic reviews, nutritional epidemiology, risk of bias, quality, credibility

**Background**

Due to the challenges of conducting randomized controlled trials (RCTs) of dietary interventions, most of the evidence in nutrition comes from non-randomized, observational studies of nutritional exposures, hereon referred to simply as nutritional epidemiology studies (1-3). Clinicians, guideline developers, policymakers, and researchers use systematic reviews of these studies to advise patients on optimal dietary habits, formulate recommendations and policies, and plan future research but a review that is of poor methodological quality may be ineffective or even misleading (2, 4, 5). There is empirical evidence that systematic reviews in the biomedical literature often have important limitations (6-8). There are, however, reasons to suspect that reviews of nutritional epidemiology studies may have more serious limitations compared to systematic reviews in other health fields (5). There are unique challenges, for example, to conducting reviews of nutritional exposures, such as the need to summarize dose-response relationships and to consider how the effects of nutritional exposures may differ based on the foods or food compounds that are consumed instead of the exposure of interest (9-13). To our knowledge, there has been no evaluation of the quality of systematic reviews of nutritional epidemiology studies.

The objective of this study was to evaluate the quality of recently published systematic reviews of nutritional epidemiology studies and, based on these findings, to propose guidance addressing major limitations. We define quality as the extent to which a review addresses a sensible research question and uses rigorous methods (including appropriate methodological safeguards against bias) to search the literature, select eligible studies and collect data, appraise the quality of studies, and synthesize and interpret findings (14, 15).

**Methods**

We registered a protocol for this study at the Open Science Framework (https://osf.io/p9vge).

***Search strategy***

A research librarian developed a search strategy to identify systematic reviews of nutritional epidemiology studies (Supplementary Material 1). We searched MEDLINE and EMBASE from January 2018 to August 2019 and the Cochrane Database of Systematic Reviews (CDSR) from January 2018 to February 2019.

***Study selection***

Systematic reviews were eligible for inclusion if they investigated the association between one or more nutritional exposures and health outcomes and reported on one or more epidemiologic studies. We defined systematic reviews as studies that explicitly described a search strategy (including at minimum

databases searched) and eligibility criteria (including at minimum the exposure(s) and health outcome(s) of interest) (16); epidemiologic studies as non-randomized, non-experimental studies (e.g., cohort, case-control, case cohort, nested case-control, cross-sectional, excluding case series) (17); nutritional exposures as macronutrients, micronutrients, bioactive compounds, foods, beverages, dietary patterns/habits, or non-nutritive components of foods (e.g., caffeine); and health outcomes as measures of morbidity, mortality, and quality of life. Reviews using harmonized datasets to conduct analyses on multiple epidemiologic studies were also eligible for inclusion. Reviews that included RCTs were eligible if they included one or more epidemiologic studies. Both English and non-English reviews were eligible for inclusion but we only identified English language reviews. We excluded reviews in which all studies included fewer than 500 participants, since such studies were primarily non-randomized experimental studies instead of observational epidemiologic studies. We excluded other types of reviews (e.g., scoping reviews), reviews that were not systematic in their methods (i.e., narrative reviews that did not describe a search strategy including at minimum the databases searched and eligibility criteria), qualitative syntheses, and reviews of postprandial studies, supplements, and chemicals involuntarily consumed through the diet (e.g., pesticides).

Reviewers (DZ, DM) completed calibration exercises, after which they performed screening independently and in duplicate. Reviewers resolved disagreements by discussion or by third-party adjudication (RJD). We estimated that 150 reviews will allow estimation of the prevalence of even uncommon review characteristics (i.e., prevalence ~5% of studies) with acceptable precision (i.e., ±3.5%) (18). Hence, we selected a random sample of 150 eligible reviews using a computer-generated random number sequence.

***Data collection***

Reviewers (DZ, AB, REM, IC, DOL, AM, ES, KA), following training and calibration exercises to ensure sufficient agreement, extracted the following information from each review, independently and in duplicate: research question; eligibility criteria, search strategy; methods for screening, data extraction, and assessment of risk of bias; analytic methods; results from the primary meta-analysis (if any type of meta-analysis was conducted); characteristics related to the reporting and interpretation of results; and sources of funding and conflicts of interest. Reviewers resolved disagreements by discussion or by third-party adjudication (RJD). Items of the data collection form were drawn from established criteria for assessing the quality of systematic reviews, guidance on optimal practices for conducting systematic reviews, data collection forms of previous studies, and literature on methodological issues relevant to

systematic reviews of non-randomized studies and systematic reviews of nutritional exposures (4, 6-8, 13-15, 17, 19-21).

If a review cited a protocol, reviewers retrieved and reviewed the protocol for additional relevant information. If a review did not explicitly identify a primary meta-analysis, we assumed that the primary meta-analysis was the meta-analysis for which results were first presented in the results section of the manuscript.

***Risk of bias of systematic reviews***

Reviewers (DZ, AB, REM, IC, DOL, AM, ES, KA), working independently and in duplicate, used a modified version of the ROBIS tool to assess the risk of bias of systematic reviews (22). We chose to use the ROBIS tool rather than AMSTAR because the ROBIS tool is more comprehensive in its assessment of risk of bias and because the AMSTAR tool includes several items that address the construct of reporting quality rather than risk of bias (23). We excluded the section on assessing the relevance of the review from the ROBIS tool because we did not apply the results of reviews to address specific questions. We used ROBIS guidance to rate each domain of the tool. For the domain on study eligibility criteria, we rated reviews at 'low concern' if eligibility criteria were pre-specified in a protocol, directly addressed the research question, and were unambiguous. For the domain on the identification and selection of studies, we rated reviews at 'low concern' if the search strategy included at minimum two databases from either MEDLINE or PubMed, EMBASE, and Web of Science (or other databases with similar coverage) and strategies to identify unpublished data, the full search strategy for at least one database was reported and was deemed likely to retrieve as many eligible studies as possible, all search restrictions were appropriate, and the selection of studies was conducted in duplicate. For the domain on data collection and study appraisal, we rated reviews at 'low concern' if data extraction was conducted in duplicate and risk of bias was assessed using an appropriate and comprehensive tool or set of criteria. We considered risk of assessments to be appropriate when they included criteria addressing biases due to confounding, selection of participants, classification of the exposure, departures from the intended exposure, measurement of the outcome, missing data, and selective reporting (24). We deemed risk of bias criteria inappropriate if they failed to address any of the aforementioned criteria or if they included criteria relevant to reporting or generalizability. For the domain on synthesis and findings, we rated reviews at 'low concern' if the synthesis was conducted using appropriate methods (i.e., random-effects dose-response meta-analysis unless compelling reasons for conducting other analyses were presented), included all relevant studies, addressed risk of bias in the synthesis of results (e.g., conducted one or more

subgroup or sensitivity analyses based on risk of bias or presented a narrative discussion of bias), and followed pre-defined analytic methods. We rated reviews at 'low risk of bias' overall if all domains were at 'low concern' or if reviewers acknowledged limitations and described how they may have impacted results in their interpretation of review findings.

***Data synthesis and analysis***

We present frequencies and percentages for dichotomous outcomes and median and interquartile ranges for continuous outcomes.

**Results**

Supplementary Material 2 presents details of the selection of reviews. We retrieved a total of 4,267 unique records and screened a random sample of 2,273 titles and abstracts and 184 full-text articles to identify a sample of 150 eligible reviews.

***General characteristics of systematic reviews***

Table 1 presents general characteristics of reviews and Supplemental Table 3.1 presents additional details and examples. Almost half of the reviews were published in general nutrition journals by authors from Asia or Europe. Only six of the reviews were conducted to inform a particular guideline, policy decision, or to fulfill the needs of a specific evidence user. One third of reviews were funded by either government agencies or institutions (e.g., hospitals, universities) and a very small minority were funded by marketing/advocacy organizations or food companies. Only ten reviews declared any conflicts of interest. Reviews most frequently reported on foods or beverages and cancer morbidity and mortality. Only a minority of reviews studied surrogate outcomes. Reviews included a median of 15 studies and 200,000 participants.

***Methodological characteristics of systematic reviews***

Table 2 presents methodological characteristics of reviews and Supplemental Table 3.2 presents additional details and examples. The majority of reviews did not report preregistration or publication of a protocol. Among those that did, in nearly half, there were unexplained deviations from the protocol. The majority of reviews (138; 92.0%) searched at least two of the following high-yield databases: MEDLINE/PubMed, EMBASE, Scopus, and Web of Science. One third of reviews did not report a replicable search strategy (i.e., the search syntax) for at least one database and only 14 reviews searched for unpublished data (i.e., conference abstracts, dissertations, expert contact, protocol registries). Less than one third of reviews (n=40; 26.7%) conducted screening, data extraction, and assessment of risk of bias in

duplicate. Three quarters of reviews conducted one or more meta-analyses. Among reviews that did not conduct meta-analysis, only a minority presented a tabular or graphical summary of quantitative results of primary studies and less than half explained why meta-analysis was not performed.

***Characteristics of meta-analyses and analytic results***

Table 3 presents characteristics of meta-analyses and their results and Supplemental Table 3.3 presents additional details and examples. All meta-analyses included only aggregate study-level data and none included individual participant data. None of the meta-analyses pooled effect estimates from substitution models (i.e., models that estimate the effect of the substitution of one exposure for another) or joint analyses (i.e., analyses that compare outcomes between participants grouped based on their level of consumption of two or more exposures). Among reviews that conducted more than one type of meta-analysis (e.g., meta-analysis of extreme categories and dose-response meta-analysis) or used more than one meta-analytic model (i.e., fixed-effect and random-effects meta-analysis), only one review explicitly specified the primary meta-analytic method. Among reviews that did not explicitly specify a primary meta-analytic method, we assumed that the method for which results were first presented in the results section was the primary. Based on this assumption, the primary meta-analytic method was most frequently a random-effects meta-analysis comparing extreme categories of exposure. A quarter of reviews selected the meta-analytic model based on a test for statistical heterogeneity or the magnitude of observed heterogeneity. Among reviews for which dose-response meta-analysis would be informative, only half presented dose-response meta-analysis. Two thirds of reviews did not conduct dose-response meta-analysis, among which this decision was only justified, either by the authors or based on the question being investigated, in a quarter. Almost one fifth of reviews included multiple effect estimates from the same study population in meta-analyses (i.e, double-counting studies) and misestimated heterogeneity by pooling stratified data from the same study in the main meta-analysis. More than a quarter of meta-analyses reported very small (relative effect $\leq 1.1$) or small ($1.1 <$ relative effect $\leq 1.5$), but statistically significant, effects (i.e., RR, OR, HR). Heterogeneity was moderate or substantial ($I^2 > 50\%$) in over half of meta-analyses (Median [IQR] $I^2$=60% [31% to 75%]). Nearly all meta-analyses reported at least one subgroup analysis but subgroup analyses were only prespecified for less than one-fifth of reviews. The majority of meta-analyses tested for small study effects, one third of which found evidence of small study effects.

***Reporting and interpretation of findings in systematic reviews***

Table 4 presents characteristics related to the reporting and interpretation of findings of reviews and Supplemental Table 3.4 presents additional details and examples. Only five reviews reported absolute effects. Only one in ten reviews evaluated the certainty of evidence using a formal system. The most commonly used approach was GRADE, followed by NutriGRADE (25, 26). Two reviews made errors in the application or interpretation of GRADE: both reviews failed to initially rate evidence from non-randomized studies at low certainty (27, 28) and one review rated up the certainty of evidence for a large effect despite ORs only ranging between 0.6 to 0.8 (27). In their interpretation of findings, most reviews did not discuss risk of bias (the validity of studies and the risk they may overestimate or underestimate the true effects), consistency (consistency of results across studies), imprecision (random error due to insufficient sample size or number of events), indirectness (differences between the populations, interventions, and outcomes of interest and those investigated in studies) or publication bias (distortion of results caused by the tendency of authors to submit, reviewers to approve, and editors to publish articles containing "positive" findings) (29). More than two thirds of reviews concluded that the certainty of evidence is insufficient to draw meaningful conclusions regarding the effects of the exposure.

***Risk of bias of systematic reviews***

Table 5 presents risk of bias of systematic reviews. All reviews had one or more domains at high concern. More than three quarters of reviews had important limitations related to study eligibility criteria, primarily due to the lack of pre-specification of eligibility criteria. Nearly all reviews had important limitations related to the identification and selection of studies, data collection and study appraisal, and synthesis and findings, primarily due to failure to search for unpublished data, use of inappropriate criteria for assessment of risk of bias, and lack of pre-specified analyses, respectively. All reviews were rated at 'high risk of bias' overall, because of the aforementioned limitations and because these limitations and their impact were not acknowledged in the interpretation of review findings.

***Region of corresponding author***

Supplementary Material 4 presents results stratified by the region of the corresponding author's primary affiliation (i.e., West, including Europe and North America, Asia, and Middle East). We did not observe any appreciable differences in review characteristics or quality between the three regions, though our sample size for each region was small.

## Discussion

### *Main findings*

Our study shows that systematic reviews of nutritional epidemiology studies often have important limitations. More than half of reviews studied the effects of single foods or food compounds without considering dietary patterns (30), substitutions (31, 32), or joint effects (32), which is in contrast to recent efforts to move away from the reductionist approach to nutrition research—an approach that is discouraged because it ignores the potential for the effects of nutritional exposures to differ depending on the foods or food compounds consumed instead of the exposure of interest (13, 31, 33). Fewer than a quarter of reviews reported preregistration or publication of a protocol, a practice that protects against reporting bias and reviewers' methodological decisions being influenced by the observed results (34, 35).

Most reviews had important limitations related to their search strategy, selection of studies, and extraction of data. Nearly a quarter of reviews did not report a replicable search strategy, which precludes evidence users from replicating or updating the review or assessing the comprehensiveness of the search. Only a handful of reviews attempted to search for unpublished data, which risks the perpetuation of reporting bias in the literature—a problem that is likely already highly prevalent in nutritional epidemiology due to the lack of standard registration practices for study protocols and statistical analysis plans (36-39). Fewer than one third of reviews conducted screening, data extraction, and assessment of risk of bias in duplicate, which empirical evidence shows is important for reducing errors (40-42).

Nearly all reviews included one or more suboptimal practices or errors related to the synthesis of results. A quarter of reviews, for example, did not conduct meta-analysis, among which the decision to not conduct meta-analysis was only justified in fewer than half. Review authors may choose to not conduct a meta-analysis if they lack sufficient expertise or resources, though a narrative review for a topic with sufficient evidence for quantitative synthesis is less useful to evidence users (43). Among reviews that investigated questions for which dose-response meta-analysis would be appropriate and informative, only half conducted dose-response meta-analyses. This may be because dose-response meta-analysis, compared to meta-analysis of extreme categories of exposure, requires the collection of additional data (that may not always be reported in primary studies) and greater statistical expertise (9, 10). When dose-response meta-analysis was presented, it was almost always secondary to meta-analysis comparing extreme categories of exposure, which is less useful and may even give misleading results, particularly in situations in which the relationship between the exposure and outcome is non-linear or in cases in which the difference in the magnitude of exposure across extreme categories is unrealistic or unattainable for

patients or the public (e.g., comparing the health effects of <1 serving/day vs. 10 servings/day of fruits and vegetables) (11, 12). Despite prespecification being an important determinant of the validity of subgroup analyses (44, 45), subgroup analyses were seldom prespecified. Other common suboptimal analytic practices included the selection of the meta-analytic model (i.e., random-effects vs. fixed-effect) based on a statistical test of heterogeneity or the observed magnitude of heterogeneity (a practice that is strongly discouraged because of the low reliability of tests and statistics of heterogeneity (46, 47)), the pooling of stratified data in the main meta-analysis (a practice that can lead to the misestimation of heterogeneity (48)), and the double-counting of studies (a practice that produces spurious precision (49)).

Finally, reviews often had significant limitations related to the reporting and interpretation of findings. Reviews, for example, seldom reported absolute effects, despite being essential for informed decision-making (50-52). Only a handful of reviews used a formal system to evaluate the certainty of evidence, possibly as a result of which reviews often neglected to consider important factors in their interpretation of the evidence (53, 54). Those that used a formal system often used systems that lack face validity. For example, NutriGRADE, which was the second most commonly used system, rates the certainty of evidence from rigorously conducted RCTs and cohort studies equally even in the absence of dose-response associations or large effects, which is questionable considering the potential for bias in non-randomized studies due to unknown confounders (26).

Another issue is whether systematic reviews of nutritional epidemiology studies are useful to evidence users. We found that few systematic reviews of nutritional epidemiology provide evidence that can be confidently applied to guide dietary recommendations and policies because of the potential for confounding, biases in the measurement of nutritional exposures, and selective reporting (2, 25, 38, 55-59)—though such reviews may still be important to distinguish between questions for which the evidence is adequate versus inadequate.

***Relation to previous work***

Our findings are consistent with previous studies that have reported on the quality of systematic reviews in the general biomedical literature and in specific health fields (6-8, 60). Page and colleagues, for example, found methodological and reporting limitations to be common in a sample of systematic reviews indexed in MEDLINE (6). Similar to our findings, major issues included failure to prespecify methods in a protocol, report a replicable search strategy, and errors in the application and interpretation of statistical analyses (6-8).

Previous studies have also reported on the scope and quality of systematic reviews in nutrition, though such studies have been primarily comprised of RCTs of nutritional interventions (19, 20). Deficiencies were more common in our sample than in previous studies (e.g., 91% and 100% followed a priori protocols in previous studies vs. 19.3% of reviews in our study) (19, 20)—likely because previous studies have primarily evaluated Cochrane reviews, which must meet established standards prior to publication (15).

***Implications and recommendations***

Given that reviews of nutritional epidemiology studies often have important limitations, evidence users should be cautious when interpreting and applying their results. Based on our findings of the most common deficiencies and errors in reviews of nutritional epidemiology studies and based on prevailing guidance on the conduct of rigorous systematic reviews and meta-analyses (15, 61), we have compiled a list of recommendations for review authors that may improve the quality of future reviews of nutritional epidemiology studies (presented below). We encourage journal editors and peer reviewers to also be mindful of our recommendations because many of the issues we identified can be addressed at the peer review stage (e.g., the double-counting of studies can easily be detected from the list of studies included in meta-analyses or from forest plots).

**Recommendations for authors of systematic reviews of nutritional epidemiology studies**

***Planning a review***

1. Consider whether a systematic review of nutritional epidemiology studies is useful. Few systematic reviews of nutritional epidemiology provide evidence that can be confidently applied to guide dietary recommendations and policies because of the potential for confounding, biases in the measurement of nutritional exposures, and selective reporting (2, 25, 38, 55-59). Due to these concerns, some evidence users may consider prioritizing other types of evidence, such as evidence from RCTs.

2. Choose between conducting a systematic review and meta-analysis of the published literature or a meta-analysis of individual participant data using one or more harmonized datasets (e.g., the Pooling Project)—the latter of which allows standardization of analyses across studies and reduces the effects of publication bias on results but requires accessing primary data that may not always be possible (62, 63).

3. When the exposure of interest is a single food or food compound, to avoid overlooking potentially differential effects of the exposure of interest depending on the foods or food compounds that are consumed instead of the exposure, consider collecting and meta-analyzing effects from substitution or joint models when such models are reported (13, 31). It is important to be mindful, however, of the

potential challenges of this type of analysis. Foods may be grouped together, for example, in ways that are too different to allow meaningful pooling. This issue may be overcome by individual participant data meta-analysis, which allows greater standardization of analyses across studies (63).

4. To avoid unnecessary duplication, search for existing and ongoing systematic reviews using electronic databases and repositories (e.g., PROSPERO, Open Science Framework) that address the question of interest. Avoid undertaking a new review if there are already existing reviews that address the question of interest and that are sufficiently rigorous and up-to-date. If a review is not up-to-date, conducting an update of the review may be more efficient than conducting a review de novo.

5. Register a protocol that includes a detailed account of and justification for all decisions in the review process, including: the review question; study eligibility criteria; the search strategy; methods for data collection and evaluation of risk of bias; methods for the synthesis of results across studies; methods for the assessment of heterogeneity and publication bias; planned subgroup and sensitivity analyses; and criteria for the rating of the certainty of evidence (34, 35).

***Data collection and assessment***

6. Work with a research librarian or information specialist to devise the search strategy. At minimum, search MEDLINE and EMBASE, or databases with similar coverage, such as Scopus (64). Report the full search strategy with sufficient detail to allow replication (65). Search study registries, bibliographies of included studies, abstracts from relevant meetings and conferences, and consider soliciting investigators for unpublished data (66).

7. Screen studies, collect data, and assess risk of bias in duplicate (67-69). Resolve any discrepancies by discussion or by consultation with one third-party.

***Synthesis and evaluation***

8. Conduct a meta-analysis when possible (15). Teams without training in meta-analysis should enlist the help of a statistician (43). Use a random-effects model to meta-analyze results, unless there are too few studies to reliably estimate between-study heterogeneity or if there are compelling reasons to believe that a fixed effect model may be preferable (47). When the question of interest is the relationship between the quantity of intake of a nutritional exposure and health outcomes, conduct a dose-response meta-analysis as the primary meta-analytic method (9, 10, 12). When meta-analysis is not possible or appropriate, present effect estimates and confidence intervals (or some other measure of variability) for all primary studies.

9. Include only one effect estimate from each study in the meta-analysis (49). If a study reports multiple effect estimates at various points of follow-up, in most cases, the effect estimate from the longest point of follow-up is preferred because the longest point of follow-up should include the greatest number of events and hence produce the greatest statistical power. If a study reports separate effect estimates corresponding to subtypes of the exposure of interest (e.g., almonds, walnuts, and pistachios when the exposure of interest is tree nuts) or subtypes of the outcome of interest (e.g., death from myocardial infarction and death from stroke when the outcome of interest is cardiovascular mortality), use a predefined rule to select only one effect estimate for meta-analysis. Alternatively, use more complex meta-analytic methods that can deal with effect estimates that are non-independent. We refer the reader to other sources that describe these methods and how they can be implemented using common statistical software (70, 71). If a study reports results stratified across one or more baseline characteristics (e.g., sex), in order to correctly estimate heterogeneity, first meta-analyze effect estimates across strata using a fixed-effect model and subsequently meta-analyze with other studies.

10. Use a rigorous and transparent system to evaluate the certainty of evidence (25, 72). One such system is the GRADE approach, which is based on comprehensive methodology that has been described in detail in a series of 6 BMJ publications and, thus far, 22 publications in the Journal of Clinical Epidemiology and which has been adopted by over 110 international organizations (25), including the Cochrane Collaboration and the World Health Organization, each of which regularly apply GRADE to nutritional questions.

Recently, the appropriateness of the application of the GRADE approach to nutrition has been questioned and alternative systems for evaluating the certainty of evidence have been proposed (26, 55, 73-75). Criticism of the GRADE approach has largely centered on the challenges of conducting RCTs in nutrition, due to which most of the evidence comes from non-randomized studies that are typically rated at low certainty according to the GRADE approach (74, 75). We do not believe, however, that the challenges of conducting RCTs in nutrition should increase our confidence in findings of non-randomized studies (2, 55). We also believe that there are important merits to maintaining consistent standards for evaluating the certainty of evidence across health fields, such as allowing evidence users to compare the certainty of evidence of different types of interventions for a particular clinical or public health problem (e.g., lifestyle, nutritional, or surgical interventions for obesity) (2, 55). If review authors also prescribe to these beliefs, then we encourage the use of the GRADE approach. We acknowledge, however, that these criteria will not be acceptable to all review authors. If review authors do not prescribe to these beliefs, they may

consider using alternative systems for evaluating the certainty of evidence, such as NutriGRADE or HEALM (26, 73).

***Reporting***

11. Use the PRISMA (16) or MOOSE (76) reporting checklists to ensure that all critical information is reported in the review manuscript. If there were any deviations in the methods described in the original review protocol, describe these deviations and explain why they were necessary.

12. A final issue is the language that authors use to communicate review findings. Journals, noting their limitations in making causal inferences, often recommend for authors to avoid the use of causal language to describe the results of non-randomized studies (77). More often though, the objective of non-randomized studies addressing modifiable risk factors, including nutritional epidemiology studies and reviews of nutritional epidemiology studies, is to infer causal relationships rather than associations (78). It may be that avoiding causal language will obscure this intent.

An alternative approach is for review authors to use causal language to describe their results—language that is consistent with their causal objectives. Authors using causal language for non-randomized studies must, however, point out what will most often be the case: that the certainty of evidence is low or very low. Use of the GRADE system, and its recommended language for communicating low or very low certainty evidence, greatly facilitates this approach (79). For example, when communicating the results of a review of non-randomized studies addressing the relationship between sugar-sweetened beverage consumption and hypertension, the authors may conclude that sugar-sweetened beverages *may increase the risk of* hypertension but that the *certainty of evidence is low* (80).

***Strengths and limitations***

The strengths of our study include the duplicate assessment of review eligibility and collection of data, the evaluation of systematic reviews using widely accepted indicators of methodological quality, and the consideration of issues unique to reviews of nutritional epidemiology studies.

Our study is limited by the subjectivity involved in the assessment of various aspects of review quality. We attempted to reduce subjectivity by providing reviewers with detailed instructions for each of the items in our data collection form and by conducting extensive calibration exercises.

While we identified many deficiencies and errors in the conduct and analyses of reviews, it is unclear the extent to which such issues may have impacted findings. The investigation of this question would require replicating a sample of reviews using optimal methodology, which was considered to be outside the scope

of this study. Empirical evidence, however, suggests that the types of deficiencies and errors we identified in our investigation have the potential to produce misleading results (e.g., (12, 40, 67, 81-83)). Similarly, the extent to which methodological limitations of reviews adversely impact clinical decisions, recommendations, and policy actions is unclear. It is possible that evidence users use the most rigorous systematic reviews to guide decisions, recommendations, and policies, in which case the impact of these issues may be negligible beyond producing research waste.

Our assessment of quality was dependent on the reporting of reviews, which is conceptually distinct from methodological rigor, though complete reporting is necessary to optimally appraise methodology. It is possible that some reviews failed to report important aspects of their methods, such as the registration of a protocol or the prespecification of subgroup analyses. Although reviews may be rigorous despite poor reporting, lack of good reporting leaves readers unable to interpret and confidently apply results.

When a review did not explicitly identify a primary meta-analysis, we assumed that the meta-analysis for which results were first presented in the results section is the primary. Although not random, this is the meta-analysis first encountered by readers and was almost always the meta-analysis that was most discussed in the results and discussion sections of the review.

Finally, our sample of reviews was drawn from only one timepoint (2018-2019) and that the characteristics and quality of reviews published at other timepoints may be different. We expect, for example, older reviews to typically suffer from a greater number of more serious methodological limitations.

**Conclusions**

Systematic reviews of nutritional epidemiology studies often have serious limitations. We encourage evidence users to be mindful of these limitations. Researchers can improve the quality of future reviews by performing comprehensive literature searches, including a search for unpublished data; involving statisticians, methodologists, researchers with substantive knowledge of the nutrition topic area; and using a rigorous and transparent system to evaluate the certainty of evidence and to draw conclusions.

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**Tables**

| **Table 1: General characteristics of systematic reviews** | |
|---|---|
| | **Number of reviews (%) N=150** |
| **Journal** | |
| General nutrition journal (journals with only a nutrition focus) (e.g., *American Journal of Clinical Nutrition*) | 61 (40.7%) |
| Specialized nutrition journal (journals with a focus on nutrition and a specific disease area) (e.g., *Nutrition, Metabolism and Cardiovascular Diseases*) | 7 (4.7%) |
| General medical journal (e.g., *Lancet*) | 28 (18.7%) |
| Specialized medical journal (e.g., *Clinical Breast Cancer)* | 54 (36%) |
| **Country of primary affiliation of corresponding author** | |
| North America | 14 (9.3%) |
| Europe | 43 (28.7%) |
| Oceania | 13 (8.7%) |
| Middle East | 28 (18.7%) |
| Asia | 49 (32.7%) |
| South America | 3 (0.7%) |
| **Was the review conducted to inform a particular guideline or policy decision or to fulfill the needs of a particular evidence user?** | |
| Yes | 6 (4%) |
| No | 144 (96%) |
| **Funding**[1] | |
| Government support | 56 (37.3%) |
| Institutional support | 34 (22.7%) |
| Private not-for-profit foundation | 20 (13.3%) |
| Food marketing/advocacy organizations | 4 (3.3%) |
| Food companies | 2 (1.3%) |
| No funding | 32 (21.3%) |
| Not reported | 34 (22.7%) |
| **Did the authors declare any conflicts of interest?** | |
| Yes | 10 (6.7%) |
| No | 135 (90%) |
| Not reported | 5 (3.3%) |
| **Exposure(s)**[1] | |
| Micronutrient | 27 (18%) |
| Macronutrient | 24 (16%) |
| Bioactive compounds | 15 (10%) |
| Food or beverage | 60 (40%) |
| Food group | 21 (14.0%) |
| Dietary pattern | 49 (32.7%) |

| | |
|---|---|
| Non-nutritive components of foods/beverages | 25 (18.7%) |
| **Outcome(s)[1]** | |
| Cardiometabolic morbidity or mortality | 26 (17.3%) |
| Cancer morbidity or mortality | 54 (36%) |
| Diseases of the digestive system | 10 (6.7%) |
| All-cause mortality | 9 (6%) |
| Anthropometric measures | 8 (5.33%) |
| Surrogate outcomes | 17 (11.3%) |
| Other | 55 (36.7%) |
| **Median number of primary studies [IQR]** | 15 [11 to 23] |
| **Median number of participants [IQR]** | 208,117 [84,951 to 510,954] |
| [1]Each review can be classified in more than one category. | |

| Table 2: Methodological characteristics of systematic reviews | |
|---|---|
| | **Number of reviews (%) N=150** |
| **Did the review cite a reporting guideline?[1]** | |
| PRISMA | 83 (55.3%) |
| MOOSE | 23 (15.3%) |
| None | 45 (30.0%) |
| **Did the review cite a protocol?** | |
| Yes | 30 (20.0%) |
| No | 120 (80.0%) |
| **Among reviews with a protocol (n=30; 20.0%), were there deviations from the methods described in the protocol?** | |
| Yes, and deviations were explained | 2 (6.9%) |
| Yes, but deviations were not explained | 13 (43.3%) |
| The protocol was not publicly accessible | 5 (16.7%) |
| No | 10 (33.33%) |
| **Eligible study designs[1]** | |
| Cohort | 146 (97.3%) |
| Case-control | 97 (64.7%) |
| Cross-sectional | 80 (53.3%) |
| Randomized controlled trials | 74 (49.3%) |
| **Median number of databases searched [IQR]** | 3 [2-3] |
| **Databases searched[1]** | |
| MEDLINE/PubMed | 150 (100%) |
| EMBASE | 98 (65.3%) |
| Web of Science | 63 (42%) |
| Cochrane CENTRAL | 52 (34.7%) |
| Scopus | 45 (30.0%) |
| Google Scholar | 17 (11.3%) |
| CINAHL | 15 (10%) |
| Other | 37 (24.7%) |
| **Did the review report a replicable search strategy?** | |
| Yes, the search strategy is replicable | 108 (72%) |
| No, but key terms are reported | 35 (23.3%) |
| No | 7 (4.7%) |
| **Language restrictions?** | |
| Yes | 75 (50.0%) |
| No | 75 (50.0%) |
| **Did the review search for unpublished data (i.e., conference abstracts, dissertations, unpublished studies, partially published studies, expert solicitation)?** | |
| Yes | 14 (9.3%) |
| No | 136 (90.7%) |
| **Method for screening of studies for eligibility** | |
| Completed in duplicate or more | 106 (70.7%) |
| Completed by one reviewer | 4 (2.7%) |

| | |
|---|---|
| Completed by one reviewer and a subset verified by a second reviewer | 3 (2%) |
| Completed by one reviewer with uncertainties verified by a second reviewer | 1 (0.7%) |
| Not reported | 36 (24%) |
| **Method for data extraction from primary studies** | |
| Completed in duplicate | 88 (58.7%) |
| Completed by one reviewer | 3 (2%) |
| Completed by one reviewer and verified by a second reviewer | 10 (6.7%) |
| Completed by one reviewer with uncertainties verified by a second reviewer | 1 (0.7%) |
| Not reported | 48 (32%) |
| **Method for the assessment of risk of bias among reviews that assessed risk of bias (n=131; 87.3%)** | |
| Completed in duplicate or more | 69 (52.7%) |
| Completed by one reviewer and verified by a second reviewer | 1 (0.7%) |
| Not reported | 61 (46.7) |
| **Method for the synthesis of results** | |
| Meta-analysis | 115 (76.7%) |
| Narrative | 21 (14%) |
| Tabular/graphical summary of quantitative results | 14 (9.3%) |
| **Among reviews without meta-analysis (n=35; 23.33%), was the decision to not perform meta-analysis explained in the review article?** | |
| Yes | 14 (40.0%) |
| No | 21 (60.0%) |

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE: Meta-analyses Of Observational Studies in Epidemiology; CENTRAL: Cochrane Central Register of Controlled Trials; CINAHL: Cumulative Index to Nursing and Allied Health Literature

[1]Each review can be classified in more than one category.

| Table 3: Characteristics of meta-analyses and analytic results | |
|---|---|
| | **Number of meta-analyses (%) N=115** |
| **Among reviews that used more than one method (i.e., model or type) of meta-analysis (n=49; 42.6%), was the primary meta-analytic method explicitly defined?** | |
| Yes | 1 (2.0%) |
| No | 48 (98.0%) |
| **Primary model for meta-analysis** | |
| Random-effects | 84 (73.0%) |
| Fixed-effect | 1 (0.9%) |
| Random-effects with significant or substantial heterogeneity, fixed-effect otherwise | 30 (26.1%) |
| **Primary type of meta-analysis** | |
| Meta-analysis of extreme categories of intake | 87 (75.7%) |
| Dose-response meta-analysis | 8 (7%) |
| Meta-analysis of specific dose categories | 11 (9.6%) |
| Other | 9 (7.8%) |
| **Secondary model for meta-analysis among reviews that used more than one method (i.e., model or type) for meta-analysis (n=49; 42.6%)[1]** | |
| Random-effects | 36 (73.5%) |
| Fixed-effect | 3 (6.1%) |
| Random-effects with significant or substantial heterogeneity, fixed-effect otherwise | 10 (20.4%) |
| **Secondary type for meta-analysis among reviews that used more than one method (i.e., model or type) for meta-analysis (n=49; 42.6%)[1]** | |
| Meta-analysis of extreme categories of intake | 3 (6.1%) |
| Dose-response meta-analysis | 31 (63.3%) |
| Meta-analysis of specific dose categories | 6 (12.2%) |
| Other | 4 (8.2%) |
| **Among reviews that did not conduct dose-response meta-analysis (n=67; 58.3%), was the decision to not conduct dose-response meta-analysis justified, either by the authors in the report or based on the question being investigated?** | |
| Yes | 17 (25.4%) |
| No | 50 (74.6%) |
| **Were any subgroup analyses reported?** | |
| Yes | 103 (89.6%) |
| No | 12 (10.4%) |
| **Median number of subgroup analyses [IQR] among reviews with subgroup analyses (n=103, 89.6%)** | 4 [2-7] |

| | |
|---|---|
| **Among reviews with subgroup analyses (n=103; 89.6%), were subgroup analyses prespecified?** | |
| Yes, all subgroups were prespecified | 6 (5.8%) |
| Yes, some were prespecified and others were post-hoc | 8 (7.8%) |
| No | 4 (3.9%) |
| Not reported | 85 (82.5%) |
| **Study designs pooled in primary meta-analysis** | |
| Cohorts | 32 (27.8%) |
| Case-control | 5 (4.3%) |
| Cross-sectional | 7 (6.1%) |
| RCTs + Cohorts | 1 (0.9%) |
| RCTs + Cohorts + Case-control | 1 (0.9%) |
| Cohorts + Case-control | 30 (26.1%) |
| Cohorts + Cross-sectional | 9 (7.8%) |
| Cohorts + Case-control + Cross-sectional | 13 (11.3%) |
| Case-control + Cross-sectional | 3 (2.6%) |
| Not reported | 14 (12.2%) |
| **Among meta-analyses that included different study designs (n=57; 49.6%), did the review present subgroup analyses by study design?** | |
| Yes | 48 (84.2%) |
| No | 9 (15.8%) |
| **Test for small study effects[1]** | |
| Egger's test | 82 (71.3%) |
| Visual inspection of funnel plot | 72 (62.6%) |
| Begg's test | 35 (30.4%) |
| No test for small study effects | 15 (13%) |
| **Among meta-analyses that tested for small test study effects (n=100;87.0%), was there evidence of small study effects?** | |
| Yes | 38 (38.0%) |
| No | 60 (60.0%) |
| Not reported | 2 (2.0%) |
| **Among meta-analyses with evidence of small study effects (n=38; 33.0%), were results adjusted for small study effects?** | |
| Yes, using trim and fill (1) | 15 (39.5%) |
| Yes, a study was excluded | 2 (5.3 %) |
| No | 21 (55.3%) |
| **Other analytic errors and suboptimal practices[1]** | |
| Misestimation of heterogeneity due to the pooling of stratified data in the main meta-analysis | 21 (18.3%) |
| Double counting of studies in meta-analyses | 20 (17.4%) |
| **Median number of studies included in the primary meta-analysis [IQR]** | 10 [6-14] |
| **Effect size of primary meta-analysis among meta-analyses with dichotomous outcomes (n=110; 95.6%)[2]** | |

| | |
|---|---|
| Very small or no effect (relative effect of **1** to 1.1) | 32 (29.0%) |
| Small (relative effect of 1.1 to 1.5) | 68 (61.8%) |
| Moderate (relative effect of 1.51 to 2) | 8 (7.3%) |
| Large (relative effect greater than 2.01) | 2 (**1**.8%) |
| **Was the primary meta-analysis statistically significant?** | |
| Yes | 79 (68.7%) |
| No | 36 (31.3%) |
| **Magnitude of heterogeneity ($I^2$) in the primary meta-analysis** | |
| < 25% | 23 (20%) |
| 25 to < 50% | 18 (15.7%) |
| 50 to < 75% | 43 (37.4%) |
| 75% to 100% | 28 (24.3%) |
| Not reported | 3 (2.6%) |
| [1]Each review can be classified in more than one category.<br>[2]We converted effect estimates so that increasing levels of exposure were associated with increasing risk for the outcome. | |

| Table 4: Interpretation of results in systematic reviews | |
|---|---|
| | **Number of reviews (%) N=150** |
| **Among reviews with dichotomous outcomes (n=144; 96.0%), were absolute effects reported?** | |
| Yes | 5 (3.5%) |
| No | 139 (96.5%) |
| **Did the review evaluate the certainty of evidence using a formal system?** | |
| Yes, using GRADE (2) | 9 (6%) |
| Yes, using NutriGRADE (3) | 2 (1.3%) |
| Yes, using SIGN (4) | 1 (0.7%) |
| Yes, using the NHMRC FORM methodology (5) | 1 (0.7%) |
| Yes, using a modified version American Diabetes Association system (6) | 1 (0.7%) |
| Yes, using a modified version of the National Osteoporosis Foundation evidence grading system (7) | 1 (0.7%) |
| Yes, using an ad-hoc system | 1 (0.7%) |
| No | 134 (89.3%) |
| **Lowest certainty evidence presented among reviews using GRADE (n=9; 6.0%)** | |
| Very low | 7 (77.8%) |
| Low | 0 (0%) |
| Moderate | 1 (11.1%) |
| High | 0 (0%) |
| Not reported | 1 (11.1%) |
| **Highest certainty evidence presented among reviews among reviews using GRADE (n=9; 6.0%)** | |
| Very low | 2 (22.2%) |
| Low | 1 (11.1%) |
| Moderate | 5 (55.6%) |
| High | 0 (0%) |
| Not reported | 1 (11.1%) |
| **Did the review consider risk of bias of primary studies in the interpretation of results?** | |
| Yes, risk of bias is acknowledged as a limitation | 12 (8.0%) |
| Yes, bias is described as unlikely to have affected findings | 13 (8.7%) |
| No, risk of bias is not discussed | 125 (83.3%) |
| **Did the review consider consistency in the interpretation of results?** | |
| Yes, consistency across primary studies is used to support findings | 13 (8.7%) |
| Yes, inconsistency across primary studies is acknowledged or described as a limitation | 71 (47.3%) |
| No, consistency is not discussed | 66 (44%) |
| **Did the review consider directness in the interpretation of results?** | |

| | |
|---|---|
| Yes, directness across primary studies is used to support findings | 3 (2%) |
| Yes, indirectness across primary studies is acknowledged or described as a limitation | 49 (32.67%) |
| No, indirectness is not discussed | 98 (65.33%) |
| **Did the review consider precision in the interpretation of results?** | |
| Yes, precise results, large sample size, or a large number of events is used to support findings | 24 (16%) |
| Yes, imprecision across primary studies is acknowledged or described as a limitation | 54 (36%) |
| No, indirectness is not discussed | 72 (48%) |
| **Did the review consider the potential for publication bias in the interpretation of results?** | |
| Yes, the potential for publication bias is acknowledged as a limitation | 28 (18.7%) |
| Yes, publication bias is described as unlikely to have affected findings | 20 (13.3%) |
| No, publication bias is not discussed | 102 (68%) |
| **What is the final conclusion of the review?** | |
| The review draws definitive conclusions regarding the effects of the nutritional exposure | 11 (7.3%) |
| The review draws some conclusions regarding the effects of the nutritional exposure on the outcome of interest but suggests that additional evidence is still needed to draw more definitive conclusions | 35 (23.3%) |
| The review suggests that the current evidence is of too low certainty to draw any conclusions on the effects of the nutritional exposure on the outcome of interest | 104 (69.3%) |
| [1]Each review can be classified in more than one category.<br>NHMRC: National Health and Medical Research Council; SIGN: Scottish Intercollegiate Guidelines Network | |

| Table 5: Results from the application of the ROBIS tool to systematic reviews | |
|---|---|
| | **Number of studies (%)** |
| **Concerns related to study eligibility criteria** | |
| High | 122 (81.3%) |
| Low | 28 (18.7%) |
| **Concerns related to identification and selection of studies** | |
| High | 145 (96.7%) |
| Low | 5 (3.3%) |
| **Concerns related to data collection and study appraisal** | |
| High | 150 (100%) |
| Low | 0 (0%) |
| **Concerns related to synthesis and findings** | |
| High | 145 (96.7%) |
| Low | 5 (3.3%) |

Online Supplementary Material

# Systematic reviews and meta-analyses of observational nutritional epidemiology studies often have serious methodological limitations: A cross-sectional study

## Online Supplementary Material

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## Contents

Online Supplementary Material

## Supplementary Material 1: Search strategy

| Supplementary Material Table 1.1: Search strategy for MEDLINE (also adapted for EMBASE) | |
|---|---|
| 1 | (diet* or (food* NOT "Food and Drug Administration") or beverage* or grain* or cereal* or bread* pasta* or rice* or potato* or vegetable* or fruit* or nut* or legume* or bean* or seed* or egg* or dairy or dairies or milk or yogurt or cheese* or fish or seafood or chicken or meat* or processed meat* or sugar-sweetened beverage* or soft drink* or alcohol* or chocolate* or coffee or tea or oil* or vitamin*).tw. |
| 2 | ((carbohydrate* ADJ3 consum*) or (carbohydrate* ADJ3 intake) or (protein ADJ3 consum*) or (protein ADJ3 intake) or (fat ADJ3 consum*) or (fat ADJ3 intake) or (fiber ADJ3 consum*) or (fibre ADJ3 intake)).tw. |
| 3 | (dietary pattern* or eating pattern* or "Mediterranean diet*" or "Western diet*" or "DASH diet*").tw. |
| 4 | (Diet or Beverages or Fermented Foods or Food or Drinking Behavior).sh. |
| 5 | (1 OR 2 OR 3 OR 4) |
| 6 | (MEDLINE OR (systematic AND review)).tw. OR meta analysis.pt |
| 7 | 5 and 6 |
| 8 | (drug* or pharmaceutical* or surgery or surgical or surgeries).tw. |
| 9 | comment.pt. or letter.pt. |
| 10 | 8 and 9 |
| 11 | 7 not 10 |
| 12 | Human filter |
| 13 | 11 and 12 |

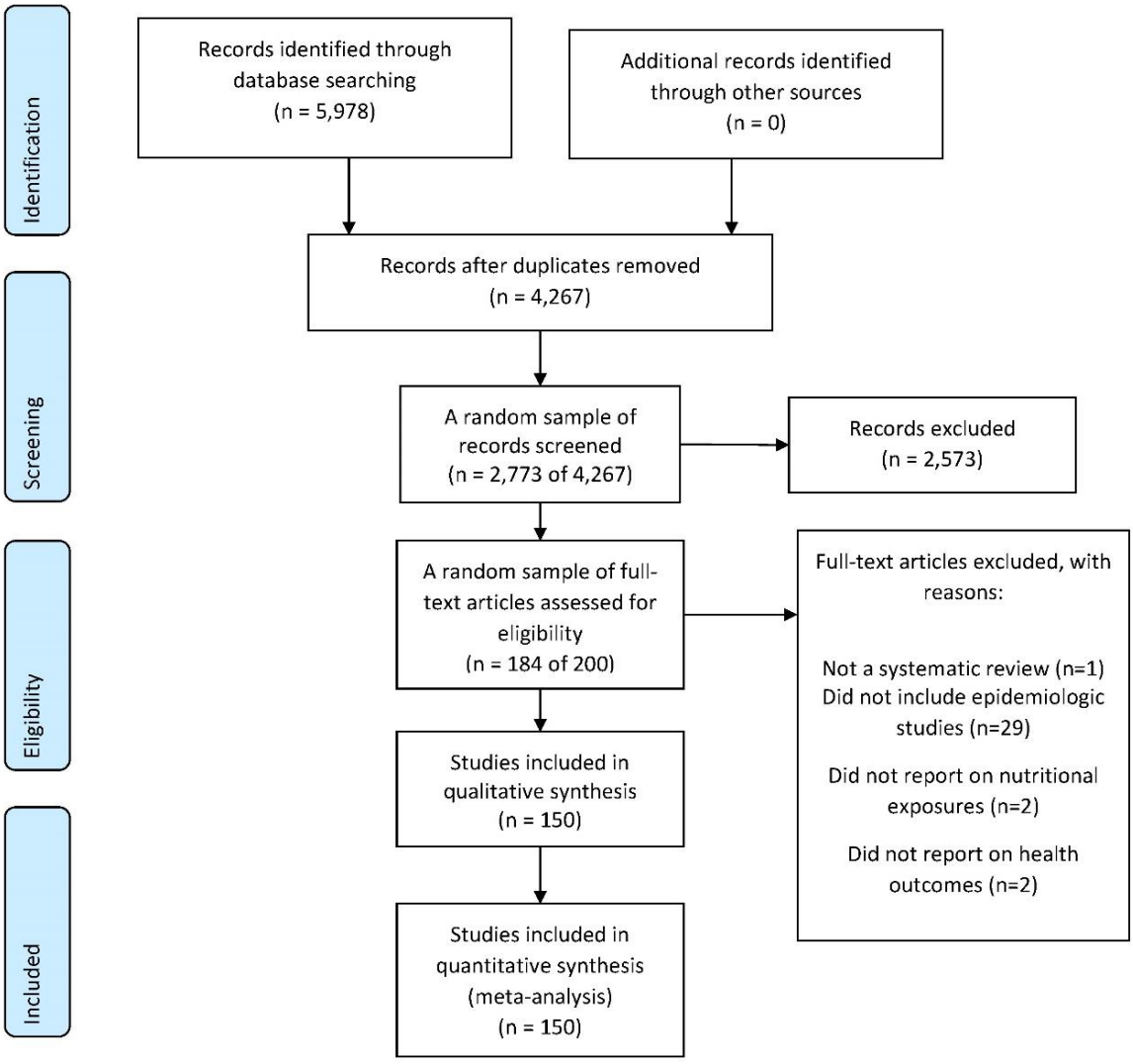
Online Supplementary Material

| Supplementary Material Table 1.1: Search strategy for the Cochrane Database of Systematic Reviews |
|---|
| ((diet* or (food* NOT "Food and Drug Administration") or beverage* or grain* or cereal* or bread* pasta* or rice* or potato* or vegetable* or fruit* or nut* or legume* or bean* or seed* or egg* or dairy or dairies or milk or yogurt or cheese* or fish or seafood or chicken or meat* or processed meat* or sugar-sweetened beverage* or soft drink* or alcohol* or chocolate* or coffee or tea or oil* or vitamin*)):ti,ab,kw OR ((carbohydrate* near/3 consum* or carbohydrate* near/3 intake or protein near/3 consum* or protein near/3 intake or fat near/3 consum* or fat near/3 intake or fiber near/3 consum* or fibre near/3 intake)):ti,ab,kw OR ((dietary pattern* or eating pattern* or "Mediterranean diet*" or "Western diet*" or "DASH diet*")):ti,ab,kw AND ("systematic review"):pt NOT (drug* or pharmaceutical* or surgery or surgical or surgeries):ti,ab,kw |

Limited to publications in 2018/2019.

Online Supplementary Material

**Supplementary Material 2: PRISMA flow diagram**



Online Supplementary Material

## Supplementary Material 3: Examples and descriptions of select categories used to describe systematic reviews

**Supplementary Material Table 3.1: Examples of select categories used to describe the general characteristics of systematic reviews**

| Item | Categories | Examples | Additional details |
|---|---|---|---|
| Journal | General nutrition journal | American Journal of Clinical Nutrition | Specialized nutrition journals were journals with a combined focus of nutrition and a specific disease or biological system. |
| | Specialized nutrition journal | Nutrition and Cancer | |
| | General medical journal | The Lancet | |
| | Specialized medical journal | Heart | |
| Was the review conducted to inform a particular guideline or policy decision or to fulfill the needs of a particular end-user? | Yes | "The research was commissioned by WHO to inform the development of updated recommendations regarding carbohydrate intake." (1) | |
| Funding | Government support | "This study was supported by grants from the National Natural Science Foundation of China (No. 0040205401835)." (2) | Grants awarded to support trainees or the salary of staff or investigators were also considered in the classification of study funding. |
| | Institutional support | "Funding provided by Isfahan University of Medical Sciences, Isfahan, Iran." (3) | |
| | Private not-for-profit foundation | "This research was supported by an American Cancer Society Research Scholar Grant (RSG-12-005-01-CNE) awarded to N.P. The funder did not play any part in the design, execution, or approval of this review." (4) | |
| | Food marketing/advocacy organizations | "Meat & Livestock Australia funded this review but had no input into the review or the manuscript." (5) | |
| | Food companies | "The first author, NMP, is supported by a Training and Research Fellowship awarded by the Nestle Nutrition Institute, Switzerland." (6) | |
| Do the authors declare any conflicts of interest? | Yes | "Dr. Nowson reports grants from Nestle Health Sciences,grants and consultancy fees from Meat and Livestock Australia, and Dairy Health Nutrition Consortium outside the submitted work and she is a member of AWASH and WASH | We recorded all conflicts and did not consider the relevance of the declared conflicts to the topic of the systematic review. |

Online Supplementary Material

| | | | |
|---|---|---|---|
| | | (Australian Division of World Action on Salt and Health) but does not receive any financial support from these organisations." (5) | |
| Exposure(s) | Micronutrient | Calcium, vitamins | |
| | Macronutrient | Glucose, fructose, protein | |
| | Bioactive compounds | Flavonoids | |
| | Food or beverage | Milk, beef | |
| | Food group | Fruits, vegetables, meats | |
| | Dietary pattern | Western dietary pattern, low carbohydrate diet | |
| | Non-nutritive components of foods/beverages | Caffeine | |
| Number of primary studies | | | If the review also included experimental studies or randomized controlled trials, we only counted the number of nutritional epidemiology studies. |
| Number of participants | | | If the review also included experimental studies or randomized controlled trials, we only counted the number of participants included in epidemiologic studies. |

Online Supplementary Material

| **Supplementary Material Table 3.2: Examples of select categories used to describe the methodological characteristics of systematic reviews** | | | |
|---|---|---|---|
| **Item** | **Categories** | **Examples** | **Additional details** |
| Did the review report a replicable search strategy? | Yes, search strategy replicable | "The search terms we used were ("Glycemic Index"[Mesh] OR "Glycemic load"[TIAB] OR "Glycaemic index"[TIAB] OR "Glycaemic load"[TIAB] OR "carbohydrate quality"[TIAB]) AND (Mortality [TW] OR Death [TW] OR fatal [TW] OR Survival [TW]) AND ("observational study"[TIAB] OR "prospective study"[TIAB] OR "longitudinal study"[TIAB] OR "cohort study"[TIAB] OR "incidence study"[TIAB] OR "concurrent study"[TIAB])." (7) | We classified search strategies as replicable when the full Boolean search logic was reported for at least one database. |
| | No, but key terms are reported | "The following search terms were used: "Mediterranean diet" combined with "breast cancer" and "breast carcinoma"." (8) | |
| Language restrictions | Yes | "We excluded studies that were cross-sectional, not published in English, did not have full-text available, or used non-human participants." (9) | When studies did not describe any search filters or eligibility restrictions related to language and when no studies were reported to have been excluded based on language, we assumed that there was no language restriction. |
| Method for the synthesis of results | Narrative | "A narrative review of the included studies was performed as quantitative synthesis could not be performed. For the risk of coronary heart disease outcome, there were 3 studies that met the eligibility criteria. Even though the outcomes measured were all similar (risk of acute-non fatal myocardial infarction), the presentation of palm oil as the exposure was different: daily intake of saturated fatty acids [19], type of vegetable oil used for cooking [20], | We classified reviews as providing a tabular or graphical summary of quantitative results when the review reported the direction, magnitude, and a measure of variation (e.g., standard deviation, standard error, confidence intervals) for all studies either in a |

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| | | and pattern of diet of the studied population [21]. In view of the different forms of exposure of palm oil, the results from all of these studies could not be pooled for an overall effect estimate." (10) | table or in a figure in the main text or in the Supplementary Material. Otherwise, we classified reviews without meta-analyses as narrative. |
| | Tabular/graphical summary of quantitative results | Dandamudi et al. 2018 show measures of association between adherence to dietary patterns and risk of breast cancer in forest plots (11). There is no statistical pooling of study results. | |
| Among reviews without meta-analysis, was the decision to not perform meta-analysis explained in the review article? | Yes | "A narrative review of the included studies was performed as quantitative synthesis could not be performed. For the risk of coronary heart disease outcome, there were 3 studies that met the eligibility criteria. Even though the outcomes measured were all similar (risk of acute-non fatal myocardial infarction), the presentation of palm oil as the exposure was different: daily intake of saturated fatty acids [19], type of vegetable oil used for cooking [20], and pattern of diet of the studied population [21]. In view of the different forms of exposure of palm oil, the results from all of these studies could not be pooled for an overall effect estimate." (10) | |

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**Supplementary Material Table 3.3: Examples of select categories used to describe the meta-analyses and analytic results**

| Item | Categories | Examples | Additional details |
|---|---|---|---|
| Among reviews that used more than one method (i.e., model or type) of meta-analysis, was the primary meta-analytic method explicitly defined? | Yes | "The inverse variance–weighted method was used to combine RRs to produce a pooled RR using random-effects meta-analysis models to allow for between study heterogeneity. In addition, as a sensitivity analysis, we reported the estimates using fixed-effects models as shown in the forest plots."(13) | When reviews used more than one method for meta-analysis but classified all except one as 'sensitivity analyses', we assumed that the primary meta-analytic method was explicitly defined. |
| Type of meta-analysis | Meta-analysis of extreme categories of intake | "Meta-analyses were conducted by comparing cancer risk in the highest reported category of Citrus fruit intake with that in the lowest reported category." (14) | |
| | Dose-response meta-analysis | "We used the method described by Greenland and Longnecker [10] and Orsini et al. [11] to reconstruct study-specific trend from aggregated data, taking into accounts the covariance among the log RR estimates."(15) | |
| | Meta-analysis of specific dose categories | "We created the following categories: light (<1 drink/day), moderate (1–2 drinks/day) and high (>2–4 drinks/day) consumption that were compared with never drinkers. Studies that did not report specific alcohol quantity but characterised the participants as drinkers or non-drinkers were examined separately. We produced pooled effect estimates of the aforementioned categories for the most adjusted models."(16)<br><br>"ORs with the corresponding 95% confidence intervals were chosen as the effective size for all included studies to assess the relationship between alcohol intake (all consumers vs. non- | |

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| | | /occasional consumers, light to moderate vs. non-/ occasional consumers [<21 drinks/week], and high alcohol consumers relative to non-/occasional consumers [>21 drinks/week], respectively) and the incidence of ED."(2) | |
| | Other | "The primary studies reported multiple levels of variables and statistics. For each study, we calculated the correlation coefficient r as an effect size that quantifies the magnitude of the association between family meal frequency and children's nutritional health. We chose r as the effect size because both the frequency of family meals and the frequency of food consumption are naturally continuous. […]We applied random-effects models, because we expected systematic heterogeneity between studies due to differences in study samples, measurements and quality." (17) | |
| Among reviews that did not conduct dose-response meta-analysis, was the decision to not conduct dose-response meta-analysis justified, either by the authors in the report or based on the question being investigated? | Yes | "It was not possible to standardize the appropriate consumption value because green tea consumption was recorded in different units in the original studies. Indeed, tea consumption was reported in grams or cups. Furthermore, when cup unit was used as a reference, the amount of tea per cup differed, ranging from 100 mL to 350 mL. Due to this limitation, it was not possible to perform a dose–response analysis." (18)<br><br>Picasso et al. (2018) on the association between vegetarianism and metabolic syndrome (19). For this question, dose-response meta-analysis is not possible nor is it informative. | For this item, we considered not only whether the authors of the review explicitly justified the decision to not perform dose-response meta-analysis but also whether dose-response meta-analysis would be reasonable and informative give the question being investigated. For reviews for which dose-response meta-analysis was not useful or possible based on the question being investigated, we assumed |

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| | | | that the decision to not conduct dose-response meta-analysis was justified. |
| Median number of subgroup analyses [IQR] among reviews with subgroup analyses | | | We recorded the number of attributes investigated in subgroup analyses for the primary meta-analysis. When reviews presented results from meta-regressions, we recorded the number of attributes investigated in the meta-regressions. For example, if the review investigated effect modification based on sex (female vs. male), location (North America vs. Western Europe vs. Asia), and study design (cohort vs. case-control vs. cross-sectional), we recorded 3 subgroup analyses. |
| Among reviews with subgroup analyses, were subgroup analyses prespecified? | Yes, all subgroups were prespecified | Cirmi et al. (2018) conducted only one subgroup analysis addressing differences in study designs, which was prespecified in their protocol registered on PROSPERO (14).<br><br>Picasso et al. (2019) indicate that subgroup analyses were pre-specified: "Finally, we performed pre-specified subgroup analyses by publication year (before 2001 vs after 2001) and risk of bias (low vs high)." (20) | We classified subgroup analyses as having been prespecified if they were reported to have been prespecified in the review article or were prespecified in a publicly accessible protocol. |

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| | Yes, some were prespecified and others were post-hoc | Simou et al. (2018) conducted subgroup analyses by study design, methodological quality, geographic location, adjustment by confounders, and publication year (21). Of these subgroup analyses, only two (geographical location and adjustment for confounding) were prespecified in the review protocol registered on PROSPERO. | |
| Other analytic errors and suboptimal practices | Misestimation of heterogeneity due to the pooling of stratified data in the main meta-analysis | Psaltopoulou et al. (2018) meta-analyze results from studies that conducted analyses stratified by sex in the main meta-analysis (22). | The pooling of multiple effect estimates coming from the same study in the main meta-analysis can lead to the misestimation of the magnitude of heterogeneity. To correctly account for stratified results without misestimating heterogeneity, a fixed-effect meta-analysis should be used to pool stratified results first and the pooled effect can be subsequently combined with other studies (23). |
| | Double counting of studies in meta-analyses | <u>Double counting of studies by exposure:</u><br>Dai et al. (2018) report on the association between milk and acne (24). One study, Duquia et al., reported on the association between low-fat milk and whole milk and acne. Effect estimates for the association between low-fat and whole milk and acne were treated as separate studies and were both included in the meta-analysis. | |

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| | Double counting of studies by outcome:<br>Moradi et al. (2019) report on the association between food insecurity and weight abnormality (underweight, overweight, obesity, or overweight and obese) (25). When studies reported effect estimates for more than one indicator of weight abnormality (e.g., obesity and overweight/obese), all effect estimates were included in the meta-analysis.<br><br>Double counting by dose categories:<br>Vaseghi et al. (2018) report on the association between coffee consumption and nonmelanoma skin cancer (26). They meta-analyze effect estimates corresponding to different quantities of coffee consumption from the same study together. |

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| **Supplementary Material Table 3.4: Examples of select categories used to describe the interpretation of results in systematic reviews** | | | |
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| **Item** | **Categories** | **Examples** | **Additional details** |
| Among reviews with dichotomous outcomes, were absolute effects reported? | Yes | "We found a 22% decreased risk of all types of pancreatitis and 20% decreased risk of acute pancreatitis among heavy coffee-drinkers versus those who were not heavy coffee-drinkers. Data on the incidence rate of all types of pancreatitis in the reference group were available in one study which was 0.24 cases per 1000 person-years. Therefore, the 22% decreased risk may imply a reduction in five new cases of pancreatitis out of 100,000 heavy coffee-drinkers every year. Taking this information into account, one may say that the magnitude of benefit is rather small as the number needed to treat is approximately 20,000 heavy coffee-drinkers per year." (27) | We defined absolute effects as risk difference, number needed to treat/harm, and population attributable risk (28). |
| Did the review consider risk of bias of primary studies in the interpretation of results? | Yes, risk of bias is acknowledged as a limitation | "However, our meta-analysis is limited because of the concerns of risk-of-bias in the included cohort studies (e.g., potential residual confounding) and imprecise measurements of milk intake due to the limitations of FFQs for assessing dietary exposures in observational studies."(29) | This item refers to the discussion and conclusions sections of the review.<br><br>For this item, we only considered statements related to the overall risk of bias across the body of evidence. |
| | Yes, bias is described as unlikely to have affected findings | "The study has several advantages. […] Second, the studies included in this meta-analysis were with relatively high quality."(30) | |
| Did the review consider consistency in the interpretation of results? | Yes, consistency across primary studies is used to support findings | "Second, there was no between-study heterogeneity in the analysis and no single study affected the overall result, which also implied that the results were robust."(31) | This item refers to the discussion and conclusions sections of the review.<br><br>For this item, we only considered statements related to consistency in |
| | Yes, inconsistency across primary studies is | "Given the inconsistency of results, it appears that there is not good evidence to support the premise that high consumption of dairy | |

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| | acknowledged or described as a limitation | products is associated with the risk of [testicular cancer]."(32) | results of studies and not consistency in study designs or study characteristics. |
| Did the review consider directness in the interpretation of results? | Yes, directness across primary studies is used to support findings | "Secondly, as included studies were conducted on a wide variety of populations (over more than 10 different countries), this increases the generalizability of our results."(33) | This item refers to the discussion and conclusions sections of the review. |
| | Yes, indirectness across primary studies is acknowledged or described as a limitation | "The most included studies were cohort studies from the United States, where the population has specific dietary behaviors different from many other countries." (34) | |
| Did the review consider precision in the interpretation of results? | Yes, precise results, large sample size, or a large number of events is used to support findings | "First, a relatively larger number of participants included, with a reduction in sampling error to a huge extent, enabled a much greater possibility of reaching reasonable conclusions." (35) | This item refers to the discussion and conclusions sections of the review.<br><br>We collected information on comments on the overall precision of the results of reviews and not precision related to subgroup analyses. |
| | Yes, imprecision across primary studies is acknowledged or described as a limitation | "However, given that only one study has focused on the [Mediterranean] dietary pattern and [diabetic retinopathy], with relatively low number of incident DR cases (n = 74), our results should be interpreted with caution." (33) | |
| Did the review consider the potential for publication bias in the interpretation of results? | Yes, the potential for publication bias is acknowledged as a limitation | "Although the included studies were of high quality as reflected by the high Newcastle–Ottawa scores and the meta-analysis has insignificant heterogeneity, we acknowledge that the study has some limitations and the results should be interpreted with caution. First, publication bias in favor of protective studies may have been present in this meta-analysis as suggested by the asymmetry of the funnel plot."(27) | This item refers to the discussion and conclusions sections of the review. |

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| | Yes, publication bias is described as unlikely to have impacted results | "Finally, we detected publication bias in our study; however, the relationships did not change after incorporating theoretical missing studies and thus we consider the data robust." (36) | |
| What is the final conclusion of the review? | The review draws definitive conclusions regarding the effect of the nutritional exposure on the outcome of interest | "Our findings thus provide clear evidence that alcohol increases the risk of pneumonia. Informing people who drink alcohol of this risk, especially those who consume high levels of alcohol, both in clinical contacts and through public health policy, may therefore help to prevent this disease." (37) | This item refers to the discussion and conclusions sections of the review.<br><br>Reviews were classified as having drawn definitive conclusions if they used causal language:<br>"The exposure causes …"<br>"The exposure increases risk of …"<br>"The exposure leads to …"<br>"The exposure prevents…"<br>We did not consider the following to be causal language:<br>"The exposure may cause …"<br>"The exposure could cause…"<br><br>Reviews were classified as having drawn some conclusions if they did not use definitive or causal language but indicated that their findings further clarify the question being investigated or lend support to a certain hypothesis. |
| | The review draws some conclusions regarding the effects of the nutritional exposure on the outcome of interest but suggests that additional evidence is still needed to draw more definitive conclusions | "In conclusion, this meta-analysis indicated that alcohol consumption is related to a significant risk for [gastroesophageal reflux disease (GERD)]. The increase in alcohol intake and drinking frequency showed a stronger correlation with GERD. This finding is important, providing positive implications on GERD prevention. It suggests that drinkers should consider to limit the consumption of alcoholic beverages for preventing the potential injury to esophagus. However, this result should be cautiously interpreted because of high heterogeneity among studies. We hope there will be more well-designed randomized studies to further evaluate the correlation between alcohol consumption and the risk of GERD in the future." (38) | |
| | The review suggests that the current evidence is of too low certainty to draw any conclusions on the effects of the nutritional | "This systematic review revealed that the current evidence (7 cohort studies and 1 RCT) is inadequate to draw a conclusion for the causal relationship between milk or dairy intake and | |

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| | exposure on the outcome of interest | cognitive decline or disorders in older adults." (29) | Reviews were classified as not having drawn any conclusions if they refrained from making any conclusions due to the limitations of the evidence base. |

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## Supplementary Material 4: Results stratified by region of the corresponding author's primary affiliation

*Three studies were published from South America and are not presented in the stratified results.*

| **Supplementary Material Table 4.1: General characteristics of systematic reviews** | | | | |
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| | **All (n=150)** | **North America, Europe, and Oceania (n=70)** | **Asia (n=49)** | **Middle east (n=28)** |
| **Journal** | | | | |
| General nutrition journal | 61 (40.7%) | 24 (34.3%) | 14 (28.6%) | 20 (71.4%) |
| Specialized nutrition journal | 7 (4.7%) | 5 (7.1%) | 1 (2%) | 1 (3.6%) |
| General medical journal | 28 (18.7%) | 10 (14.3%) | 18 (36.7%) | 0 (0%) |
| Specialized medical journal | 54 (36%) | 31 (44.3%) | 16 (32.7%) | 7 (25%) |
| **Was the review conducted to inform a particular guideline or policy decision or to fulfill the needs of a particular evidence user?** | | | | |
| Yes | 6 (4%) | 6 (8.6%) | 0 (0%) | 0 (0%) |
| No | 144 (96%) | 64 (0%) | 0 (0%) | 0 (0%) |
| **Funding**[†] | | | | |
| Government support | 56 (37.3%) | 26 (37.1%) | 25 (51%) | 5 (17.9%) |
| Institutional support | 34 (22.7%) | 8 (11.4%) | 14 (28.6%) | 11 (39.3%) |
| Private not-for-profit foundation | 20 (13.3%) | 19 (27.1%) | 1 (2%) | 0 (0%) |
| Food marketing/advocacy organizations | 4 (3.3%) | 3 (4.3%) | 1 (2%) | 0 (0%) |
| Food companies | 2 (1.3%) | 2 (2.9%) | 0 (0%) | 0 (0%) |
| No funding | 32 (21.3%) | 15 (21.4%) | 6 (12.2%) | 9 (32.1%) |
| Not reported | 34 (22.7%) | 15 (21.4%) | 14 (28.6%) | 5 (17.9%) |
| **Do the authors declare any conflicts of interest?** | | | | |
| Yes | 10 (6.7%) | 10 (14.3%) | 0 (0%) | 0 (0%) |
| No | 135 (90%) | 57 (81.4%) | 47 (95.9%) | 28 (100%) |
| Not reported | 5 (3.3%) | 3 (4.3%) | 2 (4.1%) | 0 (0%) |
| **Exposure(s)**[†] | | | | |
| Micronutrient | 27 (18%) | 15 (21.4%) | 8 (16.3%) | 4 (14.3%) |
| Macronutrient | 24 (16%) | 15 (21.4%) | 8 (16.3%) | 1 (3.6%) |
| Bioactive compounds | 15 (10%) | 12 (17.1%) | 2 (4.1%) | 1 (3.6%) |
| Food or beverage | 60 (40%) | 32 (45.7%) | 20 (40.8%) | 7 (25%) |
| Food group | 21 (14.0%) | 12 (17.1%) | 5 (10.2%) | 4 (14.3%) |
| Dietary pattern | 49 (32.7%) | 26 (37.1%) | 7 (14.3%) | 13 (46.4%) |
| Non-nutritive components of foods/beverages | 25 (18.7%) | 20 (28.6%) | 5 (10.2%) | 0 (0%) |
| **Outcome(s)**[†] | | | | |
| Cardiometabolic morbidity or mortality | 26 (17.3%) | 12 (17.1%) | 8 (16.3%) | 6 (21.4%) |
| Cancer morbidity or mortality | 54 (36%) | 26 (37.1%) | 21 (42.9%) | 7 (25%) |

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| Diseases of the digestive system | 10 (6.7%) | 1 (1.4%) | 6 (12.2%) | 3 (10.7%) |
| All-cause mortality | 9 (6%) | 3 (4.3%) | 0 (0%) | 5 (17.9%) |
| Anthropometric measures | 8 (5.33%) | 5 (7.1%) | 0 (0%) | 1 (3.6%) |
| Surrogate outcomes | 17 (11.3%) | 12 (17.1%) | 2 (4.1%) | 1 (3.6%) |
| Other | 55 (36.7%) | 30 (42.9%) | 12 (24.5%) | 12 (42.9%) |
| **Median number of primary studies [IQR]** | 15 [11 to 23] | 17 [12 to 27] | 14 [10-21] | 15 [7 to 19] |
| **Median number of participants [IQR]** | 208,117 [84,951 to 510,954] | 222,040 [94,135 to 743,099] | 174,826 [67,475 to 472,161] | 256,615 [112,750 to 339,883] |
| [†]Each review can be classified in more than one category. | | | | |

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| **Supplementary Material Table 4.2: Methodological characteristics of systematic reviews** | | | | |
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| | **All (n=150)** | **North America, Europe, and Oceania (n=70)** | **Asia (n=49)** | **Middle east (n=28)** |
| **Did the review cite a reporting guideline?†** | | | | |
| PRISMA | 83 (55.3%) | 43 (61.4%) | 20 (40.8%) | 19 (67.9%) |
| MOOSE | 23 (15.3%) | 12 (17.1%) | 8 (16.3%) | 3 (10.7%) |
| None | 45 (30.0%) | 15 (21.4%) | 22 (44.9%) | 6 (21.4%) |
| **Did the review cite a protocol?** | | | | |
| Yes | 30 (20.0%) | 22 (31.4%) | 2 (4.1%) | 5 (17.9%) |
| No | 120 (80.7%) | 48 (68.6%) | 47 (95.9%) | 23 (82.1%) |
| **Among reviews with a protocol (All: n=30, 20.0%; West: n = 22, 31.4%; Asia: n =2, 4.1%; Middle East: n=5, 17.9%), were there deviations from methods described in the protocol?** | | | | |
| Yes, and deviations were explained | 2 (6.9%) | 2 (9.1%) | 0 (0%) | 0 (0%) |
| Yes, but deviations were not explained | 13 (43.3%) | 9 (40.9%) | 1 (50%) | 3 (60%) |
| The protocol was not publicly accessible | 5 (16.7%) | 4 (18.2%) | 0 (0%) | 1 (20%) |
| No | 10 (33.33%) | 7 (31.8%) | 1 (50%) | 1 (20%) |
| **Eligible study designs†** | | | | |
| Cohort | 146 (97.3%) | 69 (98.6%) | 46 (93.9%) | 28 (100%) |
| Case-control | 97 (64.7%) | 43 (61.4%) | 34 (69.4%) | 17 (60.7%) |
| Cross-sectional | 80 (53.3%) | 39 (55.7%) | 24 (49%) | 14 (50%) |
| Randomized controlled trials | 74 (49.3%) | 45 (64.3%) | 17 (34.7%) | 10 (35.7%) |
| **Median number of databases searched [IQR]** | 3 [2-3] | 3 [2-5] | 3 [3-4] | 4 [3-5] |
| **Databases searched†** | | | | |
| MEDLINE/PubMed | 150 (100%) | 43 (61.4%) | 39 (79.6%) | 14 (50%) |
| EMBASE | 98 (65.3%) | 25 (35.7%) | 22 (44.9%) | 14 (50%) |
| Web of Science | 63 (42%) | 23 (32.9%) | 21 (42.9%) | 7 (25%) |
| Cochrane CENTRAL | 52 (34.7%) | 19 (27.1%) | 3 (6.1%) | 22 (78.6%) |
| Scopus | 45 (30.0%) | 8 (11.4%) | 0 (0%) | 9 (32.1%) |
| Google Scholar | 17 (11.3%) | 14 (20%) | 1 (2%) | 0 (0%) |
| CINAHL | 15 (10%) | 18 (25.7%) | 13 (26.5%) | 5 (17.9%) |
| Other | 37 (24.7%) | 43 (61.4%) | 39 (79.6%) | 14 (50%) |
| **Did the review report a replicable search strategy?** | | | | |
| Yes, search strategy replicable | 108 (72%) | 50 (71.4%) | 32 (65.3%) | 24 (85.7%) |
| No, but key terms are reported | 35 (23.3%) | 15 (21.4%) | 15 (30.6%) | 4 (14.3%) |
| No | 7 (4.7%) | 5 (7.1%) | 2 (4.1%) | 0 (0%) |
| **Language restrictions?** | | | | |
| Yes | 75 (50.0%) | 38 (54.3%) | 21 (42.9%) | 15 (53.6%) |
| No | 75 (50.0%) | 32 (45.7%) | 28 (57.1%) | 13 (46.4%) |

Online Supplementary Material

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|---|---|---|---|---|
| **Did the review search for unpublished data (i.e., conference abstracts, dissertations, unpublished studies, partially published studies, expert solicitation)?** | | | | |
| Yes | 14 (9.3%) | 19 (27.1%) | 1 (2%) | 3 (10.7%) |
| No | 136 (90.7%) | 60 (85.7%) | 48 (98%) | 25 (89.3%) |
| **Method for screening of studies for eligibility** | | | | |
| Completed in duplicate or more | 106 (70.7%) | 48 (68.6%) | 36 (73.5%) | 19 (67.9%) |
| Completed by one reviewer | 4 (2.7%) | 2 (2.9%) | 2 (4.1%) | 0 (0%) |
| Completed by one reviewer and a subset verified by a second reviewer | 3 (2%) | 3 (4.3%) | 0 (0%) | 0 (0%) |
| Completed by one reviewer with uncertainties verified by a second reviewer | 1 (0.7%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| Not reported | 36 (24%) | 16 (22.9%) | 13 (26.5%) | 7 (25%) |
| **Method for data extraction from primary studies** | | | | |
| Completed in duplicate | 88 (58.7%) | 29 (41.4%) | 38 (77.6%) | 19 (67.9%) |
| Completed by one reviewer | 3 (2%) | 2 (2.9%) | 0 (0%) | 1 (3.6%) |
| Completed by one reviewer and verified by a second reviewer | 10 (6.7%) | 8 (11.4%) | 2 (4.1%) | 0 (0%) |
| Completed by one reviewer with uncertainties verified by a second reviewer | 1 (0.7%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| Not reported | 48 (32%) | 30 (42.9%) | 9 (18.4%) | 8 (28.6%) |
| **Method for the assessment of risk of bias among reviews that assessed risk of bias (All: n=134, 89.33%; West: n=65; 92.9%; Asia: n=40, 81.6%, Middle East: n=26 , 92.9%)** | | | | |
| Completed in duplicate or more | 70 (52.2%) | 34 (52.3%) | 21 (52.5%) | 14 (53.8%) |
| Completed by one reviewer and verified by a second reviewer | 1 (0.7%) | 1 (1.5%) | 0 (0%) | 0 (0%) |
| Not reported | 63 (47.0) | 30 (46.2%) | 19 (47.5%) | 12 (46.2%) |
| **Method for the synthesis of results** | | | | |
| Meta-analysis | 115 (76.7%) | 43 (61.4%) | 47 (95.9%) | 24 (85.7%) |
| Narrative | 21 (14%) | 17 (24.3%) | 1 (2%) | 2 (7.1%) |
| Tabular/graphical summary of quantitative results | 14 (9.3%) | 10 (14.3%) | 1 (2%) | 2 (7.1%) |
| **Among reviews without meta-analysis (All: n=35, 23.3%; West: n=27; 38.6%; Asia: n=2; 4.1%; Middle East: n=4; 14.3%), was the decision to not perform meta-analysis explained in the review article?** | | | | |
| Yes | 14 (40.0%) | 10 (37%) | 2 (100%) | 1 (25%) |
| No | 21 (60.0%) | 17 (63%) | 0 (0%) | 3 (75%) |
| PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE: Meta-analyses Of Observational Studies in Epidemiology; CENTRAL: Cochrane Central Register of Controlled Trials ; CINAHL: Cumulative Index to Nursing and Allied Health Literature<br>[†]Each review can be classified in more than one category. | | | | |

Online Supplementary Material

| **Supplementary Material Table 4.3: Characteristics of meta-analyses and analytic results** | | | | |
|---|---|---|---|---|
| | **All (n=115)** | **North America, Europe, and Oceania (n=43)** | **Asia (n=47)** | **Middle east (n=24)** |
| **Among reviews that used more than one method (i.e., model or type) of meta-analysis (All: n=49; 42.6, %; West: n=17; 40.0%; Asia: n=18, 38.3%, Middle East: n=14, 58.3%), was the primary meta-analytic method explicitly defined?** | | | | |
| Yes | 1 (2.0%) | 1 (5.9%) | 0 (0%) | 0 (0%) |
| No | 48 (98.0%) | 16 (94.1%) | 18 (100%) | 14 (100%) |
| **Primary model for meta-analysis** | | | | |
| Random-effects | 84 (73.0%) | 34 (79.2%) | 38 (88.4%) | 28 (59.6%) |
| Fixed-effect | 1 (0.9%) | 0 (0%) | 1 (2.3%) | 0 (0%) |
| Random-effects with significant or substantial heterogeneity, fixed-effect otherwise | 30 (26.1%) | 9 (20.8%) | 5 (11.6%) | 19 (40.4%) |
| **Primary type of meta-analysis** | | | | |
| Meta-analysis of extreme categories of intake | 87 (75.7%) | 29 (67.4%) | 41 (87.2%) | 16 (66.7%) |
| Dose-response meta-analysis | 8 (7%) | 3 (7%) | 1 (2.1%) | 4 (16.7%) |
| Meta-analysis of specific dose categories | 11 (9.6%) | 6 (14%) | 4 (8.5%) | 1 (4.2%) |
| Other | 9 (7.8%) | 5 (11.6%) | 1 (2.1%) | 3 (12.5%) |
| **Secondary model for meta-analysis among reviews that used more than one method (i.e., model or type) for meta-analysis (All: n=49; 42.6, %; West: n=17; 40.0%; Asia: n=18, 38.3%, Middle East: n=14, 58.3%)†** | | | | |
| Random-effects | 36 (73.5%) | 15 (88.2%) | 10 (55.6%) | 11 (78.6%) |
| Fixed-effect | 3 (6.1%) | 1 (5.9%) | 1 (5.6%) | 1 (7.1%) |
| Random-effects with significant or substantial heterogeneity, fixed-effect otherwise | 10 (20.4%) | 1 (5.9%) | 7 (38.9%) | 2 (14.3%) |
| **Secondary type for meta-analysis among reviews that used more than one method (i.e., model or type) for meta-analysis (All: n=49; 42.6, %; West: n=17; 40.0%; Asia: n=18, 38.3%, Middle East: n=14, 58.3%)†** | | | | |
| Meta-analysis of extreme categories of intake | 3 (6.1%) | 0 (0%) | 1 (5.6%) | 2 (14.3%) |
| Dose-response meta-analysis | 40 (81.6%) | 14 (82.4%) | 17 (94.4%) | 9 (64.3%) |
| Meta-analysis of specific dose categories | 6 (12.2%) | 4 (23.5%) | 0 (0%) | 1 (7.1%) |
| Other | 4 (8.2%) | 2 (11.8%) | 0 (0%) | 2 (14.3%) |
| **Among reviews that did not conduct dose-response meta-analysis (All: n=67, 58.3%; West: n=26, 60.5%; Asia: n=29, 61.7%; Middle East: n=11, 45.8%), was the decision to not conduct dose-response meta-analysis justified, either by the authors in the report or based on the question being investigated?** | | | | |
| Yes | 17 (25.4%) | 6 (23.1%) | 8 (27.6%) | 3 (27.3%) |
| No | 50 (74.6%) | 20 (76.9%) | 21 (72.4%) | 8 (72.7%) |

Online Supplementary Material

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|---|---|---|---|---|
| **Were any subgroup analyses reported?** | | | | |
| Yes | 103 (89.6%) | 37 (86.0%) | 43 (91.5%) | 22 (91.7%) |
| No | 12 (10.4%) | 6 (14.0%) | 4 (8.5%) | 2 (8.3%) |
| **Median number of subgroup analyses [IQR] among reviews with subgroup analyses (All: n=103, 89.6%; West: n=37; 86.0%; Asia: n=43, 91.5%; Middle East: n=22, 91.7%)** | 4 [2-7] | 2 [2-2] | 4 [3-7] | 5 [2-7] |
| **Among reviews with subgroup analyses (All: n=103, 89.6%; West: n=37, 86.0%; Asia: n=43, 91.5%; Middle East: n=22, 91.7%), were subgroup analyses prespecified?** | | | | |
| Yes, all subgroups were prespecified | 6 (5.8%) | 4 (10.8%) | 1 (2.3%) | 2 (9.1%) |
| Yes, some were prespecified and others were post-hoc | 8 (7.8%) | 5 (13.5%) | 1 (2.3%) | 2 (9.1%) |
| No | 4 (3.9%) | 3 (8.1%) | 1 (2.3%) | 0 (0%) |
| Not reported | 85 (82.5%) | 25 (67.6%) | 40 (93%) | 18 (81.8%) |
| **Study designs pooled in primary meta-analysis** | | | | |
| Cohorts | 32 (27.8%) | 14 (32.6%) | 11 (23.4%) | 7 (29.2%) |
| Case-control | 5 (4.3%) | 1 (2.3%) | 4 (8.5%) | 0 (0%) |
| Cross-sectional | 7 (6.1%) | 2 (4.7%) | 2 (4.3%) | 2 (8.3%) |
| RCTs + Cohorts | 1 (0.9%) | 0 (0%) | 1 (2.1%) | 0 (0%) |
| RCTs + Cohorts + Case-control | 1 (0.9%) | 0 (0%) | 1 (2.1%) | 0 (0%) |
| Cohorts + Case-control | 30 (26.1%) | 10 (23.3%) | 13 (27.7%) | 7 (29.2%) |
| Cohorts + Cross-sectional | 9 (7.8%) | 4 (9.3%) | 2 (4.3%) | 3 (12.5%) |
| Cohorts + Case-control + Cross-sectional | 13 (11.3%) | 3 (7%) | 8 (17%) | 2 (8.3%) |
| Case-control + Cross-sectional | 3 (2.6%) | 0 (0%) | 3 (6.4%) | 0 (0%) |
| Not reported | 14 (12.2%) | 9 (20.9%) | 2 (4.3%) | 3 (12.5%) |
| **Among meta-analyses that included different study designs (All: n=57, 49.6%; West: n=17, 39.5%; Asia: n=28; 59.6%; Middle East: n=12, 50.0%), did the review present subgroup analyses by study design?** | | | | |
| Yes | 48 (84.2%) | 13 (76.5%) | 26 (92.9%) | 9 (75%) |
| No | 9 (15.8%) | 4 (23.5%) | 2 (7.1%) | 3 (25%) |
| **Test for small study effects**[†] | | | | |
| Egger's test | 82 (71.3%) | 24 (55.8%) | 35 (74.5%) | 23 (95.8%) |
| Visual inspection of funnel plot | 72 (62.6%) | 25 (58.1%) | 30 (63.8%) | 17 (70.8%) |
| Begg's test | 35 (30.4%) | 5 (11.6%) | 20 (42.6%) | 10 (41.7%) |
| No test for small study effects | 15 (13%) | 10 (23.3%) | 4 (8.5%) | 0 (0%) |
| **Among meta-analyses that tested for small test study effects (All: n=100, 87.0%; West: n=33, 76.7%; Asia: n=43; 91.5; Middle East: n=24, 100%), was there evidence of small study effects?** | | | | |
| Yes | 38 (38.0%) | 12 (36.4%) | 17 (39.5%) | 9 (37.5%) |
| No | 60 (60.0%) | 20 (60.6%) | 26 (60.5%) | 14 (58.3%) |
| Not reported | 2 (2.0%) | 1 (3%) | 0 (0%) | 1 (4.2%) |
| **Among meta-analyses with evidence of small study effects (All: n=38, 33.0%; West: n=12, 17.1%; Asia: n=17, 36.2%; Middle East: n=9; 32.1%), were results adjusted for small study effects?** | | | | |
| Yes, using trim and fill (25) | 15 (39.5%) | 4 (33.3%) | 7 (41.2%) | 4 (44.4%) |

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|---|---|---|---|---|
| Yes, a study was excluded | 2 (5.3 %) | 0 (0%) | 2 (11.8%) | 0 (0%) |
| No | 21 (55.3%) | 8 (66.7%) | 8 (47.1%) | 6 (66.7%) |
| **Other analytic errors and suboptimal practices[†]** | | | | |
| Misestimation of heterogeneity due to the pooling of stratified data in the main meta-analysis | 21 (18.3%) | 11 (25.6%) | 5 (10.6%) | 5 (20.8%) |
| Double counting of studies in meta-analyses | 20 (17.4%) | 4 (9.3%) | 11 (23.4%) | 5 (20.8%) |
| **Median number of studies included in the primary meta-analysis [IQR]** | 10 [6-14] | 10 [5-14] | 11 [6-14] | 9 [6-14] |
| **Effect size of primary meta-analysis among meta-analyses with dichotomous outcomes (All: n=110, 95.6%; West: n=41, 95.3%; Asia: n=46, 97.9%; Middle East: n=23, 95.9%)** | | | | |
| Very small or no effect (relative effect of 1 to 1.1) | 32 (29.0%) | 16 (39%) | 9 (19.6%) | 7 (30.4%) |
| Small (relative effect of 1.11 to 1.5) | 68 (61.8%) | 20 (48.8%) | 33 (71.7%) | 15 (65.2%) |
| Moderate (relative effect of 1.51 to 2) | 8 (7.3%) | 5 (12.2%) | 3 (6.5%) | 0 (0%) |
| Large (relative effect greater than 2.01) | 2 (1.8%) | 0 (0%) | 1 (2.2%) | 1 (4.3%) |
| **Was the primary meta-analysis statistically significant?** | | | | |
| Yes | 79 (68.7%) | 26 (60.5%) | 32 (68.1%) | 20 (83.3%) |
| No | 36 (31.3%) | 17 (39.5%) | 15 (31.9%) | 4 (16.7%) |
| **Magnitude of heterogeneity ($I^2$) in the primary meta-analysis** | | | | |
| < 25% | 23 (20%) | 11 (25.6%) | 11 (23.4%) | 1 (4.2%) |
| 25 to < 50% | 18 (15.7%) | 5 (11.6%) | 10 (21.3%) | 3 (12.5%) |
| 50 to < 75% | 43 (37.4%) | 16 (37.2%) | 16 (34%) | 10 (41.7%) |
| 75% to 100% | 28 (24.3%) | 10 (23.3%) | 10 (21.3%) | 8 (33.3%) |
| Not reported | 3 (2.6%) | 1 (2.3%) | 0 (0%) | 2 (8.3%) |
| [†]Each review can be classified in more than one category. | | | | |

Online Supplementary Material

| **Supplementary Material Table 4.4: Interpretation of results in systematic reviews** | | | | |
|---|---|---|---|---|
| | **Number of reviews (%)** | | | |
| | **All (n=150)** | **North America, Europe, and Oceania (n=70)** | **Asia (n=49)** | **Middle east (n=28)** |
| **Among reviews with dichotomous outcomes (All: n=144, 96.0%; West: n=67, 44.7%; Asia: n=48, 98.0; Middle East: n=27, 96.4%), were absolute effects reported?** | | | | |
| Yes | 5 (3.5%) | 3 (4.5%) | 2 (4.2%) | 0 (0%) |
| No | 139 (96.5%) | 64 (95.5%) | 46 (95.8%) | 27 (100%) |
| **Did the review evaluate the certainty of evidence using a formal system?** | | | | |
| Yes, using GRADE | 9 (6%) | 5 (7.1%) | 3 (6.1%) | 1 (3.6%) |
| Yes, using NutriGRADE | 2 (1.3%) | 1 (1.4%) | 0 (0%) | 1 (3.6%) |
| Yes, using SIGN | 1 (0.7%) | 1 (1.4%) | (0%) | (0%) |
| Yes, using the NHMRC FORM methodology | 1 (0.7%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| Yes, using a modified version American Diabetes Association system | 1 (0.7%) | 0 (0%) | 1 (2%) | 0 (0%) |
| Yes, using a modified version of the National Osteoporosis Foundation evidence grading system | 1 (0.7%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| Yes, using an ad-hoc system | 1 (0.7%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| No | 134 (89.3%) | 60 (85.7%) | 45 (91.8%) | 26 (92.9%) |
| **Lowest certainty evidence presented among reviews using GRADE (n=9; 6.0%)** | | | | |
| Very low | 7 (77.8%) | 3 (4.3%) | 3 (6.1%) | 1 (3.6%) |
| Low | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Moderate | 1 (11.1%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| High | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Not reported | 1 (11.1%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| **Highest certainty evidence presented among reviews among reviews using GRADE (n=9; 6.0%)** | | | | |
| Very low | 2 (22.2%) | 1 (1.4%) | 1 (2%) | 0 (0%) |
| Low | 1 (11.1%) | 0 (0%) | 1 (2%) | 0 (0%) |
| Moderate | 5 (55.6%) | 3 (4.3%) | 1 (2%) | 1 (3.6%) |
| High | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Not reported | 1 (11.1%) | 1 (1.4%) | 0 (0%) | 0 (0%) |
| **Did the review consider risk of bias of primary studies in the interpretation of results?** | | | | |
| Yes, risk of bias is acknowledged as a limitation | 12 (8.0%) | 7 (10%) | 3 (6.1%) | 2 (7.1%) |
| Yes, bias is described as unlikely to have affected findings | 13 (8.7%) | 6 (8.6%) | 5 (10.2%) | 2 (7.1%) |
| No, risk of bias is not discussed | 125 (83.3%) | 57 (81.4%) | 41 (83.7%) | 24 (85.7%) |
| **Did the review consider consistency in the interpretation of results?** | | | | |

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|---|---|---|---|---|
| Yes, consistency across primary studies is used to support findings | 13 (8.7%) | 4 (5.7%) | 7 (14.3%) | 2 (7.1%) |
| Yes, inconsistency across primary studies is acknowledged or described as a limitation | 71 (47.3%) | 30 (42.9%) | 23 (46.9%) | 16 (57.1%) |
| No, consistency is not discussed | 66 (44%) | 36 (51.4%) | 19 (38.8%) | 10 (35.7%) |
| **Did the review consider directness in the interpretation of results?** | | | | |
| Yes, directness across primary studies is used to support findings | 3 (2%) | 1 (1.43%) | 2 (4.08%) | 0 (0%) |
| Yes, indirectness across primary studies is acknowledged or described as a limitation | 49 (32.67%) | 19 (27.14%) | 17 (34.69%) | 13 (46.43%) |
| No, indirectness is not discussed | 98 (65.33%) | 50 (71.43%) | 30 (61.22%) | 15 (53.57%) |
| **Did the review consider precision in the interpretation of results?** | | | | |
| Yes, precise results, large sample size, or a large number of events is used to support findings | 24 (16%) | 4 (5.71%) | 14 (28.57%) | 6 (21.43%) |
| Yes, imprecision across primary studies is acknowledged or described as a limitation | 54 (36%) | 28 (40%) | 13 (26.53%) | 11 (39.29%) |
| No, indirectness is not discussed | 72 (48%) | 38 (54.29%) | 22 (44.9%) | 11 (39.29%) |
| **Did the review consider the potential for publication bias in the interpretation of results?** | | | | |
| Yes, potential for publication bias is acknowledged as a limitation | 28 (18.7%) | 10 (14.3%) | 11 (22.4%) | 6 (21.4%) |
| Yes, publication bias is described as unlikely to have affected findings | 20 (13.3%) | 5 (7.1%) | 13 (26.5%) | 2 (7.1%) |
| No, publication bias is not discussed | 102 (68%) | 55 (78.6%) | 25 (51%) | 20 (71.4%) |
| **What is the final conclusion of the review?** | | | | |
| The review draws definitive conclusions regarding the effects of the nutritional exposure | 11 (7.3%) | 6 (8.6%) | 3 (6.1%) | 2 (7.1%) |
| The review draws some conclusions regarding the effects of the nutritional exposure on the outcome of interest but suggests that additional evidence is still | 35 (23.3%) | 12 (17.1%) | 13 (26.5%) | 9 (32.1%) |

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| needed to draw more definitive conclusions | | | | |
| The review suggests that the current evidence is of too low certainty to draw any conclusions on the effects of the nutritional exposure on the outcome of interest | 104 (69.3%) | 52 (74.3%) | 33 (67.3%) | 17 (60.7%) |
| †Each review can be classified in more than one category.<br>NHMRC: National Health and Medical Research Council; SIGN: Scottish Intercollegiate Guidelines Network | | | | |

Online Supplementary Material

| **Supplementary Material Table 4.5: Risk of bias of reviews** | | | | |
|---|---|---|---|---|
| | **All (n=150)** | **North America, Europe, and Oceania (n=70)** | **Asia (n=49)** | **Middle east (n=28)** |
| **Concerns related to study eligibility criteria** | | | | |
| High | 122 (81.3%) | 50 (71.4%) | 47 (95.9%) | 23 (82.1%) |
| Low | 28 (18.7%) | 20 (28.6%) | 2 (4.1%) | 5 (17.9%) |
| **Concerns related to identification and selection of studies** | | | | |
| High | 145 (96.7%) | 68 (97.1%) | 48 (98%) | 26 (92.9%) |
| Low | 5 (3.3%) | 2 (2.9%) | 1 (2%) | 2 (7.1%) |
| **Concerns related to data collection and study appraisal** | | | | |
| High | 150 (100%) | 70 (100%) | 49 (100%) | 28 (100%) |
| Low | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **Concerns related to synthesis and findings** | | | | |
| High | 145 (96.7%) | 66 (94.3%) | 48 (98%) | 28 (100%) |
| Low | 5 (3.3%) | 4 (5.7%) | 1 (2%) | 0 (0%) |

# CHAPTER 4: RED AND PROCESSED MEAT CONSUMPTION AND RISK FOR ALL-CAUSE MORTALITY AND CARDIOMETABOLIC OUTCOMES—A SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT STUDIES

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.

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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 . . . . . 711, 721, 732, 742, 756
Editorial comment . . . . . 767

*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 sub-

groups 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 esti-

mates 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.

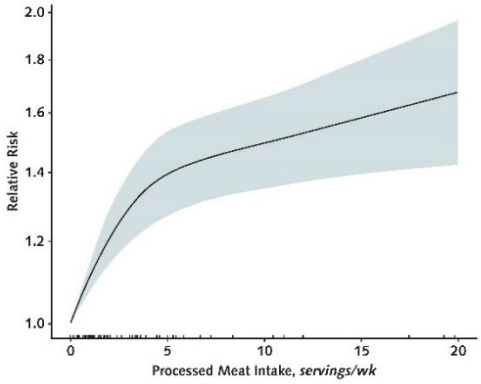
The certainty of evidence was downgraded to very low for cardiovascular mortality, fatal stroke, and fatal and nonfatal MI because of a lack of periodic repeated

***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 robust-

ness 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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**Reproducible Research Statement:** *Study protocol:* Registered with PROSPERO (CRD42017074074). *Statistical code and data set:* Available from Ms. Zeraatkar (e-mail, dena.zera@gmail.com). For sample code, see **Supplement 2** (available at Annals.org).

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# Supplementary Material*

Zeraatkar D, Han MA, Guyatt GH, et al. Red and Processed Meat Consumption and Risk for All-Cause Mortality and Cardiometabolic Outcomes. A Systematic Review and Meta-analysis of Cohort Studies. Ann Intern Med. 1 October 2019 [Epub ahead of print]. doi:10.7326/M19-0655

*Supplement 1.* **Search Strategy and Supplement Tables and Figures**



* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

**Appendix 1 – Search strategy**

**Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

| # | Searches |
|---|---|
| 1 | meat/ or meat products/ or red meat/ |
| 2 | ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)).tw,kf. |
| 3 | 1 or 2 |
| 4 | limit 3 to "all adult (19 plus years)" |
| 5 | middle aged.sh. or "of age".tw,kf. |
| 6 | (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers).tw,kf. |
| 7 | 5 or 6 |
| 8 | 3 and 7 |
| 9 | 4 or 8 |
| 10 | 9 not (cattle or cow or cows or herd or herds or heifer or heifers or steers or bulls or bovines or calves or broiler or broilers or chickens or chicks or drakes or ducks or pigs or piglet or piglets or sow or sows or boars or porcine or swine or ewe or ewes or sheep or rabbit or rabbits or mouse or mice or canine or canines or cats).tw,kf. |
| 11 | randomized controlled trial.pt. |
| 12 | controlled clinical trial.pt. |
| 13 | randomized.ab. |
| 14 | placebo.ab. |
| 15 | clinical trials as topic.sh. |
| 16 | randomly.ab. |
| 17 | trial.ti. |
| 18 | Epidemiologic studies/ |
| 19 | exp case control studies/ |
| 20 | case control.tw,kf. |
| 21 | exp cohort studies/ |
| 22 | (cohort adj (study or studies)).tw,kf. |
| 23 | cohort analy*.tw,kf. |
| 24 | (follow up adj (study or studies)).tw,kf. |
| 25 | observational study/ |
| 26 | (observational adj (study or studies)).tw,kf. |
| 27 | longitudinal.tw,kf. |
| 28 | retrospective.tw,kf. |
| 29 | Cross-sectional studies/ |
| 30 | cross sectional.tw,kf. |

| | |
|---|---|
| 31 | or/11-30 |
| 32 | 10 and 31 |
| 33 | remove duplicates from 32 |

**Embase Classic+Embase** 1947 to 2017 Week 19
Search Strategy:

| # | Searches |
|---|---|
| 1 | red meat/ or meat/ or beef/ or lamb meat/ or mutton/ or pork/ or rabbit meat/ or veal/ or venison/ |
| 2 | ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)).tw,kw. |
| 3 | 1 or 2 |
| 4 | limit 3 to (adult <18 to 64 years> or aged <65+ years>) |
| 5 | middle aged.sh. or "of age".tw,kw. |
| 6 | (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers).tw,kw. |
| 7 | 5 or 6 |
| 8 | 3 and 7 |
| 9 | 4 or 8 |
| 10 | 9 not (cattle or cow or cows or herd or herds or heifer or heifers or steers or bulls or bovines or calves or broiler or broilers or chickens or chicks or drakes or ducks or pigs or piglet or piglets or sow or sows or boars or porcine or swine or ewe or ewes or sheep or rabbit or rabbits or mouse or mice or canine or canines or cats).tw,kw. |
| 11 | random*.tw. or placebo*.mp. or double-blind*.tw. |
| 12 | clinical study/ |
| 13 | case control study/ |
| 14 | family study/ |
| 15 | longitudinal study/ |
| 16 | retrospective study/ |
| 17 | prospective study/ |
| 18 | randomized controlled trials/ |
| 19 | 17 not 18 |
| 20 | cohort analysis/ |
| 21 | (cohort adj (study or studies)).mp. |
| 22 | (case control adj (study or studies)).tw. |
| 23 | (follow up adj (study or studies)).tw. |
| 24 | (observational adj (study or studies)).tw. |
| 25 | (epidemiologic* adj (study or studies)).tw. |
| 26 | (cross sectional adj (study or studies)).tw. |
| 27 | or/11-16,19-26 |

| | |
|---|---|
| 28 | 10 and 27 |

**Cochrane Central Register of Controlled Trials** March 2017

Search Strategy:

| # | Searches |
|---|---|
| 1 | meat/ or meat products/ or red meat/ |
| 2 | ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)).tw,kw. |
| 3 | 1 or 2 |
| 4 | middle aged.sh. or "of age".tw,kw. |
| 5 | (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers).mp. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | remove duplicates from 7 |

[Web of Science]

**Science Citation Index Expanded (SCI-EXPANDED) --1900-present**

**Social Sciences Citation Index (SSCI) --1956-present**

**Conference Proceedings Citation Index- Science (CPCI-S) --1990-present**

**Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present**

| # | Searches |
|---|---|
| 20 | #19 AND #5<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 19 | #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 18 | TS=("case control" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 17 | TS=("cross sectional" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 16 | TS=("follow up" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 15 | TS=(comparative NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 14 | TS=(cohort NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 13 | TS=(correlation* NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 12 | TS=(epidemiologic* NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 11 | TS=(evaluation NEAR (study or studies)) |

| | |
|---|---|
| | Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 10 | TS=("follow up" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 9 | TS=(longitudinal NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 8 | TS=(observational NEAR(study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 7 | TS=(prospective NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 6 | TS=(random* or placebo* or "double-blind" or "single blind*" or "treble blind" or "triple blind" or "cross over*" or crossover* or "clinical trial*" or "controlled trial*")<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 5 | #3 NOT #4<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 4 | TS=(cattle or cow or cows or herd or herds or heifer or heifers or steers or bulls or bovines or calves or broiler or broilers or chickens or chicks or drakes or ducks or pigs or piglet or piglets or sow or sows or boars or porcine or swine or ewe or ewes or sheep or rabbit or rabbits or mouse or mice or canine or canines or cats)<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 3 | #2 AND #1<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 2 | TS=(human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers)<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 1 | TS=(meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and TS=(consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |

**CINAHL**

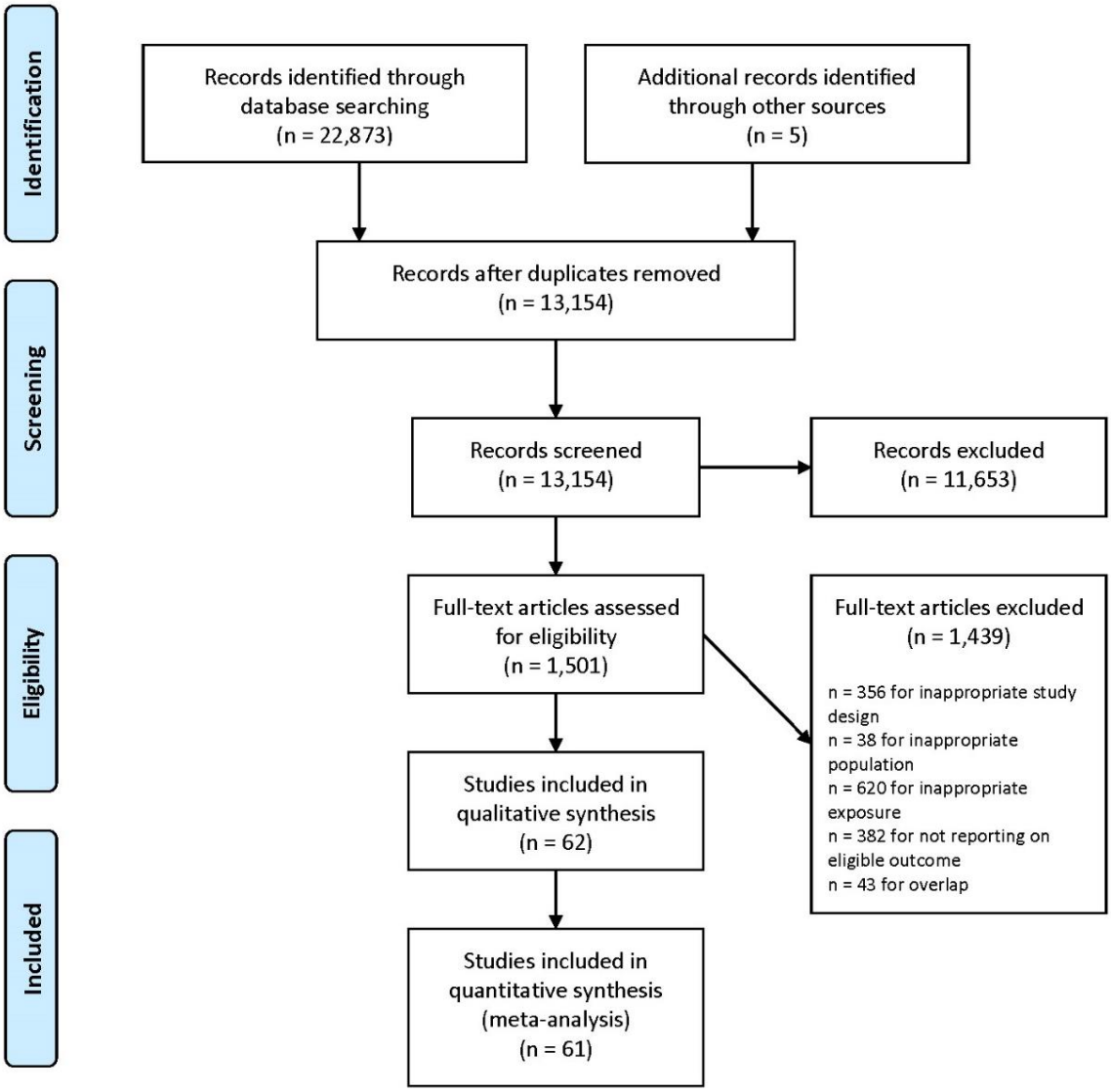
| # | Searches |
|---|---|
| S25 | S8 AND S24 |
| S24 | S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 |
| S23 | TI (observational N1 (study or studies)) OR AB (observational N1 (study or studies)) |
| S22 | TI (cohort N1 (study or studies)) OR AB (cohort N1 (study or studies)) |
| S21 | (MH "Correlational Studies") OR (MH "Case Control Studies+") OR (MH "Cross Sectional Studies") OR (MH "Prospective Studies") OR (MH "Nonconcurrent Prospective Studies") |
| S20 | TI allocat* random* OR AB allocat* random* |

| | |
|---|---|
| S19 | (MH "Quantitative Studies") |
| S18 | (MH "Placebos") |
| S17 | TI placebo* OR AB placebo* |
| S16 | TI random* allocat* OR AB random* allocat* |
| S15 | (MH "Random Assignment") |
| S14 | TI (randomi* control* trial*) OR AB (randomi* control* trial*) |
| S13 | AB ( (singl* N1 blind*) or (singl* N1 mask*) ) or AB ( (doubl* N1 blind*) or (doubl* N1 mask*) ) or AB ( (tripl* N1 blind*) or (tripl* N1 mask*) ) or AB ( (trebl* N1 blind*) or (trebl* N1 mask*) ) |
| S12 | TI ( (singl* N1 blind*) or (singl* N1 mask*) ) or TI ( (doubl* N1 blind*) or (doubl* N1 mask*) ) or TI ( (tripl* N1 blind*) or (tripl* N1 mask*) ) or TI ( (trebl* N1 blind*) or (trebl* N1 mask*) ) |
| S11 | TI (clinic* N1 trial*) OR TX clinic* N1 trial*) |
| S10 | PT Clinical trial |
| S9 | (MH "Clinical Trials+") |
| S8 | S4 AND S7 |
| S7 | S5 OR S6 |
| S6 | TI (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers) OR AB (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers) |
| S5 | (MH "Adult") OR (MH "Aged+") OR (MH "Middle Age") OR (MH "Young Adult") |
| S4 | S1 OR S2 OR S3 |
| S3 | AB ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)) |
| S2 | TI ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)) |
| S1 | (MH "Meat") |

**ProQuest Dissertations & Theses Global**

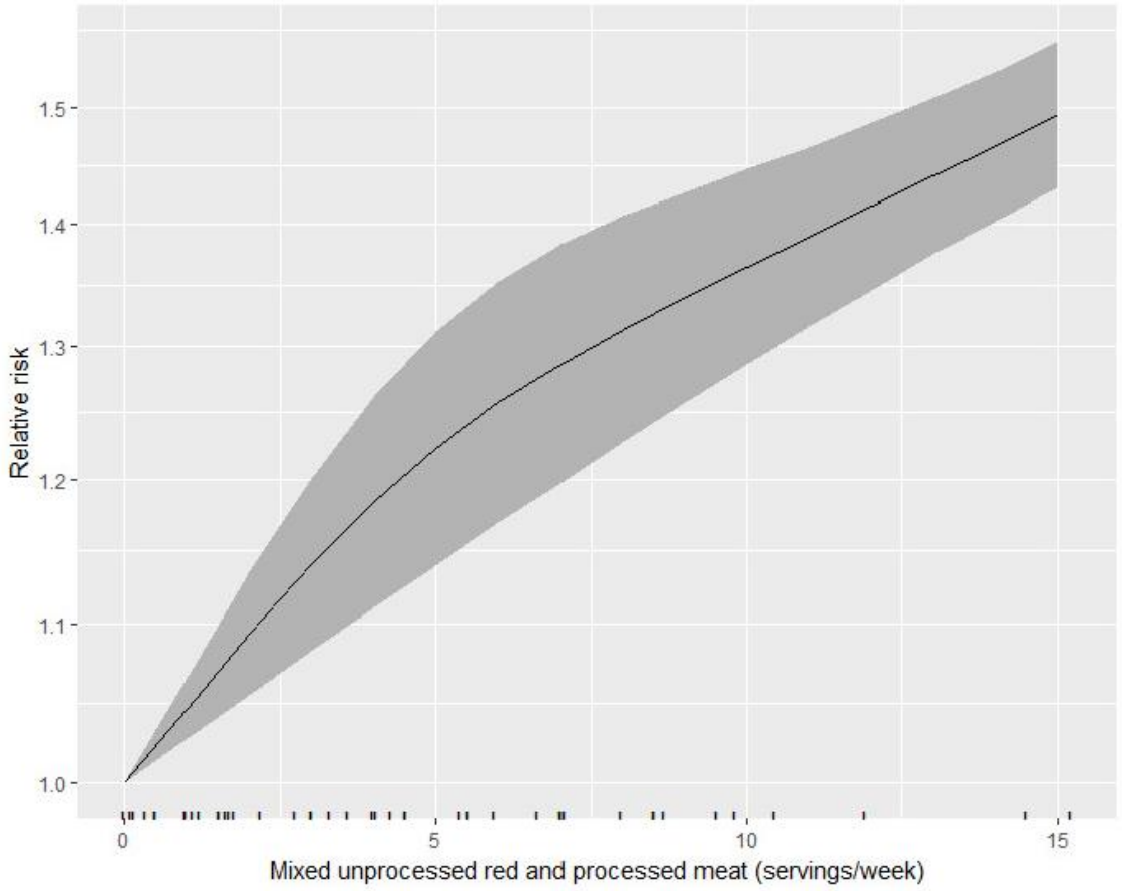
| # | Search |
|---|---|
| S1 | ((((TI(meat OR meats OR beef OR lamb OR mutton OR pork OR sausage OR sausages OR bacon) AND TI(consum* OR consumption OR cooked OR diet OR diets OR dietary OR eat OR eaters OR eating OR intake OR intakes)) OR (AB(meat OR meats OR beef OR lamb OR mutton OR pork OR sausage OR sausages OR bacon) AND AB(consum* OR consumption OR cooked OR diet OR diets OR dietary OR eat OR eaters OR eating OR intake OR intakes))) AND (TI(human OR humans OR adult OR adults OR man OR men OR woman OR women OR patient OR patients OR person OR persons OR individuals OR people OR controls OR participant OR participants OR subject OR subjects OR volunteer OR volunteers) OR AB(human OR humans OR adult OR adults OR man OR men OR woman OR women OR patient OR patients OR person OR persons OR individuals OR people OR controls OR participant OR participants OR subject OR subjects OR volunteer OR volunteers))) AND (TI(("case control" OR "cross sectional" OR "follow up" OR comparative OR cohort OR correlational OR epidemiologic* OR evaluation OR "follow up" OR longitudinal OR observational OR prospective) NEAR/5 (study OR studies)) OR AB(("case control" OR "cross sectional" OR "follow up" OR comparative OR cohort OR correlational OR epidemiologic* OR evaluation OR "follow up" OR longitudinal OR observational OR prospective) NEAR/5 (study OR studies)) OR TI(random* OR placebo* OR "double-blind" OR "single blind*" OR "treble blind" OR "triple blind" OR "cross over*" OR crossover* OR "clinical trial*" OR "controlled trial*") OR AB(random* OR placebo* OR "double-blind" OR "single blind*" OR "treble blind" OR "triple blind" OR "cross over*" OR crossover* OR "clinical trial*" OR "controlled trial*"))) NOT (TI(cattle OR cow OR cows OR herd OR herds OR heifer OR heifers OR steers OR bulks OR bovines OR calves OR broiler OR broilers OR chickens OR chicks OR drakes OR ducks OR pigs OR piglet OR piglets OR sow OR sows OR boars OR porcine OR swine OR ewe OR ewes OR sheep OR rabbit OR rabbits OR mouse OR mice OR canine OR canines OR cats) OR AB(cattle OR cow OR cows OR herd OR herds OR heifer OR heifers OR steers OR bulks OR bovines OR calves OR broiler OR broilers OR chickens OR chicks OR drakes OR ducks OR pigs OR piglet OR piglets OR sow OR sows OR boars OR porcine OR swine OR ewe OR ewes OR sheep OR rabbit OR rabbits OR mouse OR mice OR canine OR canines OR cats)) |

**Appendix Figure 1: Search and selection of studies**




*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

**For more information, visit www.prisma-statement.org.**




**Appendix Figure 2: Non-linear association between mixed unprocessed red and processed meat and all-cause mortality. The solid black line represents the point estimate, the shaded region represents the 95% confidence intervals, and tick marks represent the positions of the study-specific estimates.**

<table>
<tr><th colspan="3">Appendix Table 1: Detailed guidance for assessment of risk of bias</th></tr>
<tr><td>1. Was selection of exposed and non-exposed cohorts drawn from the same population?</td><td colspan="2">This field queries whether participants consuming different amounts of red meat and/or processed meat were drawn from the same population.</td></tr>
<tr><td></td><td>Definitely yes</td><td>Studies in which selection for participation is not dependent on exposure level. For example, the New York University Women's Health Study recruited women 34 to 65 years old from the Guttman Breast Diagnostic Institute in New York City or the Strax Breast Cancer Institute. Enrolment in the study was independent of dietary characteristics.</td></tr>
<tr><td></td><td>Probably yes</td><td>Studies in which methods for recruitment of the cohort is not adequately described to be able to determine whether recruitment into the study was dependent on intake of red meat and/or processed meat.</td></tr>
<tr><td></td><td>Probably no</td><td></td></tr>
<tr><td></td><td>Definitely no</td><td>Studies that compare vegetarian and non-vegetarian populations but draw vegetarians from a different cohort. For example, a study may report on the EPIC-Oxford cohort but also include a subsample of participants from the Oxford Vegetarian Study. The study may then compare omnivores from the EPIC-Oxford cohort with vegetarians from Oxford Vegetarian study.</td></tr>
<tr><td>2. Can we be confident in the assessment of exposure?</td><td colspan="2">This field queries how confident we are about the quantification of intake of red meat and/or processed meat.</td></tr>
<tr><td></td><td>Definitely yes</td><td>Participants complete a dietary measure at least once every five years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has undergone validation against a weighted food record specifically for red meat and/or processed meat. A weighted food record is a record of food consumption over one or more days where an individual or investigator weighs each item of food before consumption. Some studies may provide a citation to the study validating the dietary measure and other studies may simply say that the measure has been validated against a weighted food record for red meat and/or processed meat. The correlation coefficient between the dietary measure and the weighted food record should be greater than 0.4 for red meat and/or processed meat.</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Probably yes</td><td>Participants complete a dietary measure at least once every six to eight years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has undergone validation against a dietary measure other than a weighted food record (e.g., 24 h food record, biomarker). Some studies may provide a citation to the study validating the dietary measure and other studies may simply say that the measure has been validated against another dietary measure for red meat and/or processed meat and/or meat (white and red). The correlation coefficient for red meat and/or processed meat and/or meat is not reported.</td></tr>
<tr><td>Probably no</td><td>Participants complete a dietary measure at least once every nine to 10 years. The authors of the study do not report on the validity of the dietary measure for red meat/processed meat.<br><br>The correlation coefficient of the dietary measure against another measure for validation is less than 0.40 for red meat/processed meat.<br><br>The dietary measure has not been validated for red meat and/or processed meat and/or meat or validation for red meat and/or processed meat and/or meat is not reported.</td></tr>
<tr><td>Definitely no</td><td>Participants complete a dietary measure only at baseline or the dietary measure is repeated less frequently than once every 10 years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has not undergone any validation.<br><br>Some studies may report that diet was assessed at multiple timepoints throughout the trial but only baseline dietary data is used for analysis.</td></tr>
</table>
<br>Please note that if a study provides a citation to another paper that reports on the validation of the dietary measure, you <u>MUST</u> retrieve and read the paper to complete this field.
</td></tr>
<tr><td>3. Can we be confident that the outcome of interest was not present at start of study?</td><td>
<table>
<tr><td>Definitely yes</td><td>The outcome of interest is fatal. In that case, we can be certain that participants did not have the outcome at baseline.</td></tr>
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<table>
<tr><td></td><td><table>
<tr><td></td><td>Continuous outcomes (i.e., hemoglobin, quality of life, and satisfaction with diet) should be specified as 'definitely yes'.<br><br>For dichotomous outcomes, authors have made an effort to exclude participants with the outcome of interest at baseline. The outcome may be self-reported with some external validation (e.g., validation against medical records).</td></tr>
<tr><td>Probably yes</td><td>The authors have made an effort to exclude participants with the outcome of interest at baseline. The outcome is self-reported and there is no external validation.<br><br>The authors have made an effort to exclude participants with the outcome of interest at baseline. The authors do not report how the outcome at baseline was ascertained.</td></tr>
<tr><td>Probably no</td><td></td></tr>
<tr><td>Definitely no</td><td>The authors have made no effort to exclude participants with the outcome of interest at baseline.</td></tr>
</table></td></tr>
<tr><td>4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?</td><td>This field queries how confident we are that the reported association or lack thereof is not due to confounding.<br><br><table>
<tr><td>Definitely yes</td><td>The study adjusts at a minimum for age, sex, smoking, at least one measure of socioeconomic status such as level of income or education or occupation, family history (of cancer for cancer outcomes, cardiovascular disease for cardiovascular outcomes, and diabetes for the outcome of diabetes), aspirin use (necessary only for colon cancer), diabetes (necessary only for cardiovascular outcomes, excluding diabetes), alcohol consumption (only for cancers of the mouth, pharynx, larynx, esophagus, colorectum, and breast), weight or BMI (only for cancers of the esophagus, pancreas, liver, breast, endometrium) and physical activity (only for cardiovascular outcomes) in the analysis.</td></tr>
<tr><td>Probably yes</td><td>Adjusts at a minimum for age, sex, smoking, family history (of cancer for cancer outcomes, coronary heart disease for cardiovascular outcomes, and diabetes for the outcome of diabetes), and diabetes (only for cardiovascular outcomes, excluding diabetes).</td></tr>
<tr><td>Probably no</td><td>Adjusts at a minimum for age, sex, and smoking.</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Definitely no</td><td>The study does not adjust for any prognostic variables relevant to the outcome or does not adjust for age, sex, or smoking.</td></tr>
</table>
<br>Note that if a study excludes a group of participants (e.g., women), then adjusting for that variable (e.g., sex) is not necessary.<br><br>If age is used as the time scale of a survival model (e.g., Cox proportional hazards model), additional adjustment for age is not necessary since analyses will be age-adjusted.
</td></tr>
<tr><td>5. Can we be confident in the assessment of the presence or absence of prognostic factors?</td><td>This field queries whether we are confident in the measurement or ascertainment of prognostic factors that were used either for matching or were adjusted for in the model.<br><br>
<table>
<tr><td>Definitely yes</td><td>Typically, prognostic factors are self-reported by participants. This is considered acceptable.</td></tr>
<tr><td>Probably yes</td><td>Some studies may not report how prognostic variables were measured. Most of the time we can assume they were self-reported. These studies should be classified as ‘probably yes’.</td></tr>
<tr><td>Probably no</td><td>Some studies may make assumptions regarding various prognostic factors. For example, a study may assume that all participants who did not answer the question on diabetes disease at baseline did not have diabetes.</td></tr>
<tr><td>Definitely no</td><td></td></tr>
</table>
<br>Note that for this item, we are only concerned with the measurement of the prognostic factors listed in question four of the risk of bias assessment tool. We are not concerned with the measurement of any additional prognostic factors the authors choose to consider.<br><br>If there is a significant proportion of the study population (>10%) that is missing data on an important prognostic factors or if missing prognostic factors are inappropriately handled in data analysis, we would consider rating the study at higher risk of bias only if the prognostic factor is essential to the rating in question 4.</td></tr>
<tr><td>6. Can we be confident in the assessment of outcome?</td><td>This field queries our confidence in the accuracy of the measurement of the outcome.<br><br>
<table>
<tr><td>Definitely yes</td><td>All-cause mortality based on a government registry (e.g., National Death Index) with or without review by study physician or study staff<br><br>National or local registries (e.g., National Program of Cancer Registries (NPCR)) with review by a study physician or study staff</td></tr>
</table>
</td></tr>
</table>

| | | |
|---|---|---|
| | | Medical records reviewed by a study physician or study staff<br><br>Measurement of hemoglobin by trained medical professionals or by a qualified medical facility (e.g., medical lab)<br><br>Measurement of a lab value indicative of the outcome by trained medical professionals or by a qualified medical facility<br><br>Measurement of quality of life and satisfaction with diet with previously validated instruments |
| | Probably yes | Self-report with external validation by medical records. For example, a study may ask participants whether they have been diagnosed with breast cancer every two years. Medical records may be retrieved for participants who indicate a diagnosis of breast cancer. The authors may report that medical records confirmed self-report breast cancer for over 98% of cases. A minimum of 80% agreement must be reached.<br><br>External validation may only be done for a subsample of participants. This is acceptable as long as the rate of concordance between self-report and medical records is high (>95%).<br><br>Active follow-up with no external validation for all-cause mortality.<br><br>Active follow-up with external validation for cause-specific mortality (a minimum of 80% of events must be correctly classified in validation) |
| | Probably no | Medical records without review by study physician or study staff.<br><br>The authors do not specify how outcomes were measured.<br><br>Active follow-up without external validation for cause-specific mortality.<br><br>Self-report with external validation by medical records where the rate of agreement between self-report and medical records is low (<80%). |

<table>
<tr><td></td><td><table>
<tr><td>Definitely no</td><td>Self-report with no external validation.</td></tr>
</table></td></tr>
<tr><td>7. Was the follow-up of cohorts adequate?</td><td>This field queries the risk of bias associated with loss to follow-up and missing outcome data.<br><br><table>
<tr><td>Definitely yes</td><td>At least 90% retention for the duration of the study.</td></tr>
<tr><td>Probably yes</td><td>80 to 89% retention for the duration of the study with loss to follow-up unlikely to be related to outcomes.<br><br>If rate of follow-up is not reported but the study is likely to have low rates of loss to follow-up through government or local databases and registries.</td></tr>
<tr><td>Probably no</td><td>80 to 89% retention for the duration of the study with loss to follow-up likely to be related to outcomes. For example, if the study requires participants to make special clinic visits for ascertainment of outcomes, participants who are more ill with more comorbidities may be less likely to be able to attend these clinics.<br><br>Loss to follow-up is not reported or cannot be estimated from information provided in the paper.</td></tr>
<tr><td>Definitely no</td><td>Less than 80% follow-up.</td></tr>
</table></td></tr>
</table>

**Appendix Table 2: Study characteristics**

| Author | Year | Cohort(s) | Country | Participants (n) | Age at baseline | % Female | Duration of follow-up (years) | Outcomes | Exposures | Dose-response? |
|---|---|---|---|---|---|---|---|---|---|---|
| G. E. Fraser | 1999 | Adventist Health Study | United States | 34,198 | Mean: 54.23 | 59.48 | Up to: 6 | all-cause mortality, cardiovascular disease | M | |
| T. J. Key | 1999 | Adventist Health Study | United States | 28,952 | Median: 52 (non-vegetarian men); 51 (vegetarian men); 52 (non-vegetarian women); 54 (vegetarian women) | 57.81 | Mean: 11.1 | all-cause mortality, cardiovascular mortality, fatal stroke | M | |
| S. Tonstad | 2013 | Adventist Health Study 2 (AHS-2) | United States, Canada | 41,387 | Mean: 57.9 | 63.3 | Up to: 2 | diabetes | M | |
| S. M. Alshahrani | 2019 | Adventist Health Study 2 (AHS-2) | United States | 72149 | Mean: 56.39 | 65.68 | Mean: 11.8 | all-cause mortality, cardiovascular mortality | UPR, P, M | ✓ |
| T. J. Key | 1999 | Adventist Mortality Study | United States | 24,538 | Median: 49 (non-vegetarian men); 51 (vegetarian men); 50 (nonvegetarian women); 54 (vegetarian women) | 63.35 | Mean: 5.6 | all-cause mortality, cardiovascular mortality, fatal stroke | M | |
| A. Vang | 2008 | Adventist Mortality Study, Adventist Health Study | United States | 8,401 | Mean: 64.58 | 38.41 | Up to: 17 | diabetes | M | |
| S. Mannisto | 2010 | Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) | Finland | 25,943 | Range: 50 to 69 | 0 | Up to: 12 | diabetes | UPR, P | ✓ |
| B. Haring | 2015 | Atherosclerosis Risk in Communities Study (ARIC) | United States | 11,601 | Mean: 53.76 | 55.9 | Median: 22.7 | fatal and non-fatal stroke | UPR, P, M | ✓ |
| B. Haring | 2014 | Atherosclerosis Risk in Communities Study (ARIC) | United States | 12,066 | Mean: 53.8 | 55.8 | Median: 22 | cardiovascular disease | UPR, P | |
| D. A. Boggs | 2015 | Black Women's Health Study (BWHS) | United States | 37,001 | Mean: 41.89 | 100 | Up to: 16 | all-cause mortality | M | ✓ |
| L. Jung Eun | 2013 | Cadiovascular Diseases Risk Factor Two-Township Study (CVDFACTS) | Taiwan | 3,472 | Range: 18 to 92 | 56.45 | Mean: 14.9 (men), 15.6 (women) | all-cause mortality, cardiovascular mortality | M | |
| J. Lv | 2017 | China Kadoorie Biobank (CKB) | China | 461,211 | Mean: 50.71 | 58.99 | Median: 7.2 | diabetes | M | |
| S. C. Larsson | 2011 | Cohort of Swedish Men (COSM) | Sweden | 40,291 | Mean: 59.95 | 0 | Mean: 10.1 | fatal and non-fatal stroke | UPR, P, M | ✓ |
| J. Kaluza | 2014 | Cohort of Swedish Men (COSM) | Sweden | 36,882 | Range: 45 to 79 | 0 | Mean: 11.7 | cardiovascular mortality | UPR, P | |
| A. Bellavia | 2016 | Cohort of Swedish Men (COSM), Swedish Mammography Cohort (SMC) | Sweden | 74,645 | Mean: 60.28 | 46.29 | Up to: 16 | all-cause mortality, cardiovascular mortality | UPR, P, M | ✓ |
| A. M. Wurtz | 2016 | Diet, Cancer and Health | Denmark | 55,171 | Median: 55 (men); 56 (women) | 52.82 | Median: 13.6 | fatal and non-fatal myocardial infarction | UPR, P, M | ✓ |

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|---|---|---|---|---|---|---|---|---|---|---|
| **M. Lajous** | 2012 | Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (E3N) | France | 66,118 | NR | 100 | Median: 13.8 | diabetes | UPR, P | ✓ |
| **F. L. Crowe** | 2013 | European Prospective Investigate into Cancer and Nutrition - Oxford (EPIC-Oxford) | United Kingdom | 44,561 | Mean: 44.4 | 76.21 | Mean: 11.6 | cardiovascular disease | M | |
| **J. Praagman** | 2015 | European Prospective Investigation into Cancer and Nutrition - Netherlands (EPIC-NL) | The Netherlands | 34,409 | Mean: 48.93 | 74.13 | Mean: 15 | all-cause mortality, cardiovascular mortality, fatal stroke | P | ✓ |
| **M. B. Schulze** | 2007 | European Prospective Investigation into Cancer and Nutrition - Potsdam (EPIC-Potsdam) | Germany | 25,167 | Range: 35 to 65 | 61.34 | Mean: 7 | diabetes | M | ✓ |
| **A. von Ruesten** | 2013 | European Prospective Investigation into Cancer and Nutrition - Potsdam (EPIC-Potsdam) | Germany | 23,531 | Range: 35 to 65 | 61.34 | Mean: 8 | cardiovascular disease, diabetes | UPR, P | ✓ |
| **P. Amiano** | 2016 | European Prospective Investigation into Cancer and Nutrition - Spain (EPIC-Spain) | Spain | 41,020 | Mean: 49.37 | 62.24 | Mean: 13.8 | fatal and non-fatal stroke | UPR, P | ✓ |
| **S. Rohrmann** | 2013 | European Prospective Investigation into Cancer and Nutrition (EPIC) | France, Italy, Spain, The Netherlands, United Kingdom, Greece, Germany, Sweden, Norway, Denmark | 448,568 | Median: 52.3 (men); 50.9 (women) | 71.62 | Median: 12.7 | all-cause mortality, cardiovascular mortality | P, M | ✓ |
| **J. Montonen** | 2005 | Finnish Mobile Clinic Health Examination Survey | Finland | 4,304 | Mean: 51.88 | 46.9 | Up to: 23 | diabetes | P, M | |
| **T. J. Key** | 1999 | German Vegetarian Study | Germany | 1,757 | Median: 45 (non-vegetarian men); 43 (vegetarian men); 49 (non-vegetarian women); 53 (vegetarian women) | 55.38 | Mean: 9.9 | all-cause mortality, cardiovascular mortality, fatal stroke | M | |
| **J. Chang-Claude** | 2005 | German Vegetarian Study | Germany | 1,904 | NR | 54.94 | Up to: 21 | all-cause mortality, cardiovascular mortality, fatal stroke | M | |
| **M. S. Farvid** | 2017 | Golestan Cohort Study | Iran | 42,466 | Mean: 51.62 | 56.93 | Median: 8.1 | all-cause mortality, cardiovascular mortality, fatal stroke | M | ✓ |
| **L. Jung Eun** | 2013 | Health Effects of Arsenic Longitudinal Study (HEALS) | Bangladesh | 11,396 | Range: 17 to 75 | 57.14 | Mean: 6.6 | all-cause mortality, cardiovascular mortality | M | |
| **T. J. Key** | 1999 | Health Food Shoppers Study | United Kingdom | 9,878 | Median: 46 (non-vegetarian men); 41 (vegetarian men); 45 (non-vegetarian women); 47 (vegetarian women) | 59.7 | Mean: 18.4 | all-cause mortality, cardiovascular mortality, fatal stroke | M | |

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|---|---|---|---|---|---|---|---|---|---|---|
| **A. Pan** | 2011 | Health Professionals Follow-up Study (HPFS) | United States | 37,083 | Mean: 52.63 | 0 | Up to: 20 | diabetes | UPR, P, M | ✓ |
| **A. Pan** | 2012 | Health Professionals Follow-up Study (HPFS) | United States | 37,698 | Mean: 52.72 | 0 | Up to: 22 | all-cause mortality, cardiovascular mortality | UPR, P, M | ✓ |
| **A. M. Bernstein** | 2012 | Health Professionals Follow-up Study (HPFS) | United States | 43,150 | Mean: 61.67 | 0 | Up to: 22 | fatal and non-fatal stroke | UPR, P, M | ✓ |
| **D. H. Lee** | 2004 | Iowa Women's Health Study (IWHS) | United States | 35,698 | Mean: 61.6 | 100 | Up to: 11 | diabetes | M | |
| **L. E. Kelemen** | 2005 | Iowa Women's Health Study (IWHS) | United States | 29,017 | Median: 76.2 (Q1); 76.0 (Q2); 75.9 (Q3); 75.7 (Q4); 75.4 (Q5) | 100 | Up to: 15 | all-cause mortality, cardiovascular mortality | M | |
| **M. Nagao** | 2012 | Japan Collaborative Cohort Study (JACC) | Japan | 51,683 | Mean: 55.91 | 60.4 | Median: 18.4 | cardiovascular mortality | P, M | ✓ |
| **L. Jung Eun** | 2013 | Japan Public Health Center-based Prospective study cohort I (JPHC I) | Japan | 43,038 | Range: 40 to 59 | 52.15 | Up to: 14.2 (men), 14.7 (women) | all-cause mortality, cardiovascular mortality | M | |
| **K. Kurotani** | 2013 | Japan Public Health Center-based Prospective study cohort I (JPHC I), Japan Public Health Center-based Prospective study cohort II (JPHC II) | Japan | 63,849 | Mean: 51.36 | 57.04 | Up to: 5 | diabetes | UPR, P, M | ✓ |
| **L. Jung Eun** | 2013 | Japan Public Health Center-based Prospective study cohort II (JPHC II) | Japan | 56,411 | Range: 40 to 69 | 52.63 | Up to: 11.2 (men), 11.7 (women) | all-cause mortality, cardiovascular mortality | M | |
| **K. Park** | 2017 | Korean Genome and Epidemiology Study (KoGES) | South Korea | 9,370 | Mean: 52.08 | 52.09 | Median: 7.8 | cardiovascular disease | UPR | ✓ |
| **J. Son** | 2018 | Korean Genome Epidemiology Study (KoGES) | South Korea | 8618 | Mean: 51.73 | 52.43 | Up to: 10 | cardiovascular disease, diabetes | P | ✓ |
| **H. E. K. Virtanen** | 2017 | Kuopio Ischaemic Heart Disease (KIHD) Risk Factor Study | Finland | 2,332 | Mean: 52.97 | 0 | Mean: 19.3 | diabetes | UPR, P, M | ✓ |
| **C. Sauvaget** | 2003 | Life Span Study (LSS) | Japan | 37,130 | Mean: 56 | 61.73 | Up to: 16.33 | fatal stroke | M | ✓ |
| **U. Ericson** | 2013 | Malmo Diet and Cancer Cohort (MDC) study | Sweden | 27,140 | Mean: 58.7 | 61.13 | Mean: 12 | diabetes | UPR, P | ✓ |
| **L. Jung Eun** | 2013 | Miyagi Cohort Study (Miyagi) | Japan | 44,966 | Range: 40 to 64 | 52.11 | Mean: 12.6 (men), 12.9 (women) | all-cause mortality, cardiovascular mortality | M | |
| **A. Steinbrecher** | 2011 | Multiethnic Cohort (MEC) - Hawaiian component | United States | 75,512 | Range: 45 to 75 | 51.99 | Median: 13.5 | diabetes | P, M | ✓ |
| **M. C. de Oliveira Otto** | 2012 | Multi-Ethnic Study of Atherosclerosis (MESA) | United States | 5,285 | Mean: 61.8 | 52.7 | Mean: 6.2 | cardiovascular disease | M | |
| **A. G. Mainous** | 2004 | National Health and Nutrition Examination Survey II (NHANES II) | United States | 9,229 | Range: 30 to 75 | 52.49 | Up to: 12.8 | all-cause mortality | M | |
| **R. Kappeler** | 2013 | National Health and Nutrition Examination Survey III (NHANES III) | United States | 17,611 | Mean: 41.42 | 53.22 | Up to: 22 | all-cause mortality, cardiovascular mortality | P, M | |
| **A. Etemadi** | 2017 | National Institute of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study | United States | 536,969 | Mean: 62.16 | 41.06 | Median: 15.6 | all-cause mortality, cardiovascular mortality, fatal stroke | UPR, P, M | ✓ |
| **L. Qi** | 2007 | Nurses' Health Study (NHS) | United States | 6,161 | Mean: 48.67 | 100 | Up to: 21 | cardiovascular mortality, cardiovascular | M | ✓ |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | disease, non-fatal myocardial infarction | | |
| **A. M. Bernstein** | 2010 | Nurses' Health Study (NHS) | United States | 84,136 | Range: 30 to 55 | 100 | Up to: 26 | cardiovascular disease | UPR, P, M | ✓ |
| **A. Pan** | 2011 | Nurses' Health Study (NHS) | United States | 79,570 | Mean: 46.23 | 100 | Up to: 28 | diabetes | UPR, P, M | ✓ |
| **A. Pan** | 2012 | Nurses' Health Study (NHS) | United States | 83,644 | Mean: 46.08 | 100 | Up to: 28 | all-cause mortality, cardiovascular mortality | UPR, P, M | ✓ |
| **A. M. Bernstein** | 2012 | Nurses' Health Study (NHS) | United States | 84,010 | Mean: 57.44 | 100 | Up to: 26 | fatal and non-fatal stroke | UPR, P, M | ✓ |
| **A. Pan** | 2011 | Nurses' Health Study-2 (NHS-2) | United States | 87,504 | Mean: 36.03 | 100 | Up to: 16 | diabetes | UPR, P, M | ✓ |
| **L. Jung Eun** | 2013 | Ohsaki National Health Insurance Cohort Study (Ohsaki) | Japan | 48,905 | Range: 40 to 80 | 52.03 | Mean: 9.8 (men), 10 (women) | all-cause mortality, cardiovascular mortality | M | |
| **D. Whiteman** | 1999 | OXCHECK Study | United Kingdom | 10,522 | Range: 35 to 64 | 53.16 | Up to: 9 | all-cause mortality, cardiovascular mortality | UPR, P | ✓ |
| **T. J. Key** | 1999 | Oxford Vegetarian Study | United Kingdom | 11,047 | Median: 34 (non-vegetarian men); 33 (vegetarian men); 34 (non-vegetarian women); 32 (vegetarian women) | 62.21 | Mean: 13.7 | all-cause mortality, cardiovascular mortality, fatal stroke | M | |
| **P. N. Appleby** | 2016 | Oxford Vegetarian Study, European Prospective Investigate into Cancer and Nutrition-Oxford (EPIC-Oxford) | United Kingdom | 60,310 | Mean: 43.45 | 75.27 | Up to: 34.3 | all-cause mortality, cardiovascular mortality, fatal stroke | M | |
| **M. Guasch-Ferre** | 2017 | PREDIMED | Spain | 3,443 | Mean: 67 | 62.17 | Median: 4.3 | diabetes | P, M | ✓ |
| **G. J. van Woudenbergh** | 2012 | Rotterdam study | The Netherlands | 4,366 | Mean: 67.3 | 63 | Median: 12.4 | diabetes | P, M | ✓ |
| **L. J. Dominguez** | 2018 | Seguimiento Universidad de Navarra (SUN) | Spain | 18,540 | NR | NR | Mean: 9.5 | all-cause mortality | UPR, P, M | ✓ |
| **A. Mari-Sanchis** | 2016 | Seguimiento Universidad de Navarra (SUN) | Spain | 20,375 | Mean: 38.13 | 61.06 | Mean: 8.84 | diabetes | P, M | ✓ |
| **L. Jung Eun** | 2013 | Seoul Male Cohort Study (Seoul) | South Korea | 13,600 | Range: 25 to 82 | 0 | Mean: 14.7 | all-cause mortality, cardiovascular mortality | M | |
| **Y. Takata** | 2013 | Shanghai Men's Health Study (SMHS) | China | 61,142 | Mean: 55.45 | 0 | Median: 5.5 | all-cause mortality, cardiovascular mortality, fatal ischemic stroke | UPR | ✓ |
| **R. Villegas** | 2006 | Shanghai Women's Health Study (SWHS) | China | 70,609 | Mean: 51.7 | 100 | Mean: 4.6 | diabetes | UPR, P | ✓ |
| **L. Jung Eun** | 2013 | Shanghai Women's Health Study (SWHS) | China | 74,933 | Range: 40 to 71 | 100 | Mean: 8.6 | all-cause mortality, cardiovascular mortality | M | |
| **Y. Takata** | 2013 | Shanghai Women's Health Study (SWHS) | China | 73,167 | Mean: 52.85 | 100 | Median: 11.2 | all-cause mortality, cardiovascular mortality | UPR | ✓ |

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|---|---|---|---|---|---|---|---|---|---|---|
| **M. Talaei** | 2017 | Singapore Chinese Health Study | Singapore | 45,411 | Mean: 55 | 57.3 | Mean: 10.9 | diabetes | UPR, P, M | ✓ |
| **A. M. Fretts** | 2012 | Strong Heart Family Study (SHFS) | United States | 2,279 | Mean: 35.03 | 61.05 | Up to: 8 | diabetes | UPR, P | |
| **S. C. Larsson** | 2011 | Swedish Mammography Cohort (SMC) | Sweden | 34,670 | Mean: 61.34 | 100 | Mean: 10.4 | fatal and non-fatal stroke | UPR, P, M | ✓ |
| **T. H. T. Chiu** | 2018 | Tzu Chi Health Study (TCHS) | Taiwan | 2,918 | Mean: 53.22 | 75.36 | Median: 5.2 | diabetes | M | |
| **L. M. Nilsson** | 2012 | Västerbotten Intervention Program (VIP) Cohort | Sweden | 77,319 | Median: 49 | 51.32 | Median: 10 | all-cause mortality | M | |
| **C. A. Thomson** | 2011 | Women's Health Initiative Observational Study (WHI-OS) | United States | 56,384 | Mean: 63.2 | 100 | Up to: 3 | anemia | M | ✓ |
| **S. Yaemsiri** | 2012 | Women's Health Initiative Observational Study (WHI-OS) | United States | 87,025 | Mean: 63.5 | 100 | Mean: 7.6 | ischemic stroke | M | ✓ |
| **M. Isanejad** | 2017 | Women's Health Initiative Observational Study (WHI-OS) and Women's Health Initiative Clinical Trial (WHI-CT) | United States | 94,265 | Mean: 63.89 | 100 | Up to: 15 | diabetes | P, M | ✓ |
| **Y. Song** | 2004 | Women's Health Study (WHS) | United States | 37,309 | Mean: 53.98 | 100 | Mean: 8.8 | diabetes | P, M | ✓ |

UPR=unprocessed red meat; P=processed meat; M=mixed unprocessed red and processed meat

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**Appendix Table 3: Risk of bias assessments for studies reporting on all-cause mortality**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| T. J. Key | 1999 | Adventist Health Study | DY | DN | DY | PY | PY | DY | PY | Low |
| S. M. Alshahrani | 2019 | Adventist Health Study 2 (AHS-2) | DY | DN | DY | DY | DY | DY | PY | Low |
| T. J. Key | 1999 | Adventist Mortality Study | DY | PN | DY | PY | PY | DY | PY | Low |
| D. A. Boggs | 2015 | Black Women's Health Study (BWHS) | DY | PN | DY | DY | DY | DY | DY | Low |
| L. Jung Eun | 2013 | Cadiovascular Diseases Risk Factor Two-Township Study (CVDFACTS) | PY | DN | DY | DY | DY | PY | PN | High |
| A. Bellavia | 2016 | Cohort of Swedish Men (COSM), Swedish Mammography Cohort (SMC) | DY | DN | DY | DY | DY | DY | DY | Low |
| J. Praagman | 2015 | European Prospective Investigation into Cancer and Nutrition - Netherlands (EPIC-Netherlands) | DY | DN | DY | DY | DY | DY | DY | Low |
| S. Rohrmann | 2013 | European Prospective Investigation into Cancer and Nutrition (EPIC) | DN | DN | DY | DY | DY | DY | DY | High |
| J. Chang-Claude | 2005 | German Vegetarian Study | DN | DN | DY | DY | DY | DY | DY | High |
| T. J. Key | 1999 | German Vegetarian Study | DY | PN | DY | PY | PY | PY | PN | High |
| M. S. Farvid | 2017 | Golestan Cohort Study | DY | PN | DY | DY | DY | DY | DY | Low |
| L. Jung Eun | 2013 | Health Effects of Arsenic Longitudinal Study (HEALS) | PY | PY | DY | DY | DY | PY | PN | Low |
| T. J. Key | 1999 | Health Food Shoppers Study | PY | DN | DY | PY | PY | DY | PY | Low |

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|---|---|---|---|---|---|---|---|---|---|---|
| A. Pan | 2012 | Health Professionals Follow-up Study (HPFS) | DY | DY | DY | PY | DY | DY | DY | Low |
| L. E. Kelemen | 2005 | Iowa Women's Health Study (IWHS) | DY | DN | DY | DY | DY | DY | PY | Low |
| L. Jung Eun | 2013 | Japan Public Health Center-based Prospective study cohort I (JPHC I) | PY | DN | DY | DY | DY | PY | PN | High |
| L. Jung Eun | 2013 | Japan Public Health Center-based Prospective study cohort II (JPHC II) | PY | DN | DY | DY | DY | PY | PN | High |
| L. Jung Eun | 2013 | Miyagi Cohort Study (Miyagi) | PY | DN | DY | DY | DY | PY | PN | High |
| A. G. Mainous | 2004 | National Health and Nutrition Examination Survey II (NHANES II) | DY | DN | DY | DY | DY | DY | DY | Low |
| R. Kappeler | 2013 | National Health and Nutrition Examination Survey III (NHANES III) | DY | DN | DY | DY | DY | DY | PY | Low |
| A. Etemadi | 2017 | National Institute of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study | DY | DN | DY | DY | DY | DY | PY | Low |
| A. Pan | 2012 | Nurses' Health Study (NHS) | DY | DY | DY | DY | DY | DY | DY | Low |
| L. Jung Eun | 2013 | Ohsaki National Health Insurance Cohort Study (Ohsaki) | PY | DN | DY | DY | DY | PY | PN | High |
| D. Whiteman | 1999 | OXCHECK Study | DY | PN | DY | PY | DY | DY | DY | Low |
| T. J. Key | 1999 | Oxford Vegetarian Study | DN | DN | DY | PY | PY | DY | PY | High |
| L. J. Dominguez | 2018 | Seguimiento Universidad de Navarra (SUN) | DY | PN | DY | DY | DY | DY | DY | Low |
| L. Jung Eun | 2013 | Seoul Male Cohort Study (Seoul) | PY | DN | DY | DY | DY | PY | PN | High |
| Y. Takata | 2013 | Shanghai Men's Health Study (SMHS) | PY | PY | DY | DY | PY | DY | DY | Low |
| L. Jung Eun | 2013 | Shanghai Women's Health Study (SWHS) | DY | PN | DY | DY | DY | DY | DY | Low |
| Y. Takata | 2013 | Shanghai Women's Health Study (SWHS) | DY | DN | DY | DY | PY | DY | DY | Low |
| L. M. Nilsson | 2012 | Västerbotten Intervention Program (VIP) Cohort | DY | PN | DY | DY | PY | DY | PY | Low |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 4: Risk of bias assessments for studies reporting on cardiovascular mortality**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| T. J. Key | 1999 | Adventist Health Study | DY | DN | DY | PN | PY | DY | PY | High |
| S. M. Alshahrani | 2019 | Adventist Health Study 2 (AHS-2) | DY | DN | DY | PN | DY | DY | PY | High |
| T. J. Key | 1999 | Adventist Mortality Study | DY | PN | DY | PN | PY | DY | PY | High |
| J. Kaluza | 2014 | Cohort of Swedish Men (COSM) | DY | DN | DY | DY | DY | DY | DY | Low |
| A. Bellavia | 2016 | Cohort of Swedish Men (COSM), Swedish Mammography Cohort (SMC) | DY | DN | DY | PN | DY | DY | DY | High |
| J. Praagman | 2015 | European Prospective Investigation into Cancer and Nutrition - Netherlands (EPIC-Netherlands) | DY | DN | DY | PN | DY | DY | DY | High |
| S. Rohrmann | 2013 | European Prospective Investigation into Cancer and Nutrition (EPIC) | DN | DN | DY | PN | DY | PY | PN | High |
| J. Chang-Claude | 2005 | German Vegetarian Study | DN | DN | DY | PN | DY | DY | DY | High |
| T. J. Key | 1999 | German Vegetarian Study | DY | PN | DY | PN | PY | PN | PN | High |
| M. S. Farvid | 2017 | Golestan Cohort Study | DY | PN | DY | PN | DY | PY | DY | High |
| T. J. Key | 1999 | Health Food Shoppers Study | PY | DN | DY | PN | PY | DY | PY | High |
| A. Pan | 2012 | Health Professionals Follow-up Study (HPFS) | DY | DY | DY | PY | DY | DY | DY | Low |
| L. E. Kelemen | 2005 | Iowa Women's Health Study (IWHS) | DY | DN | DY | PN | DY | DY | PY | High |
| M. Nagao | 2012 | Japan Collaborative Cohort Study (JACC) | DY | DN | DY | PN | DY | DY | PY | High |
| L. Jung Eun | 2013 | Japan Public Health Center-based Prospective | PY | DN | DY | PN | DY | PN | PN | High |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | study cohort I (JPHC I), Japan Public Health Center-based Prospective study cohort II (JPHC II), Miyagi Cohort Study (Miyagi), Ohsaki National Health Insurance Cohort Study (Ohsaki), Health Effects of Arsenic Longitudinal Study (HEALS), Seoul Male Cohort Study (Seoul), Shanghai Women's Health Study (SWHS), Cadiovascular Diseases Risk Factor Two-Township Study (CVDFACTS) | | | | | | | | | |
| R. Kappeler | 2013 | National Health and Nutrition Examination Survey III (NHANES III) | DY | DN | DY | DY | DY | DY | PY | Low |
| A. Etemadi | 2017 | National Institute of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study | DY | DN | DY | PN | DY | DY | PY | High |
| A. Pan | 2012 | Nurses' Health Study (NHS) | DY | DY | DY | DY | DY | DY | DY | Low |
| D. Whiteman | 1999 | OXCHECK Study | DY | PN | DY | PN | DY | DY | DY | High |
| T. J. Key | 1999 | Oxford Vegetarian Study | DN | DN | DY | PN | PY | DY | PY | High |
| Y. Takata | 2013 | Shanghai Men's Health Study (SMHS) | PY | PY | DY | PN | PY | DY | DY | Low |
| Y. Takata | 2013 | Shanghai Women's Health Study (SWHS) | DY | DN | DY | PN | PY | DY | DY | High |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 5: Risk of bias assessments for studies reporting on cardiovascular disease**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| G. E. Fraser | 1999 | Adventist Health Study | DY | PY | PN | DN | PY | DY | DY | Low |
| B. Haring | 2014 | Atherosclerosis Risk in Communities Study (ARIC) | DY | DN | PY | PN | DY | DY | PN | Low |
| F. L. Crowe | 2013 | European Prospective Investigate into Cancer and Nutrition - Oxford (EPIC-Oxford) | DN | DN | PY | PN | DY | DY | PY | Low |
| A. von Ruesten | 2013 | European Prospective Investigation into Cancer and Nutrition - Potsdam (EPIC-Potsdam) | DY | PY | PY | PN | DY | PY | DY | High |
| K. Park | 2017 | Korean Genome and Epidemiology Study (KoGES) | DY | PY | PY | PN | DY | DN | PN | High |
| K. Park | 2017 | Korean Genome and Epidemiology Study (KoGES) | DY | PY | PY | PN | DY | DN | PN | High |
| M. C. de Oliveira Otto | 2012 | Multi-Ethnic Study of Atherosclerosis (MESA) | DY | PN | PY | PN | DY | DY | PN | Low |
| A. M. Bernstein | 2010 | Nurses' Health Study (NHS) | DY | DY | PY | DY | DY | PY | DY | High |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 6: Risk of bias assessments for studies reporting on fatal and non-fatal stroke**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| B. Haring | 2015 | Atherosclerosis Risk in Communities (ARIC) Study | DY | DN | PY | PN | DY | DY | PY | High |
| S. C. Larsson | 2011 | Cohort of Swedish Men (COSM) | DY | DN | PY | DY | DY | DY | PY | Low |
| P. Amiano | 2016 | European Prospective Investigation into Cancer and Nutrition - Spain (EPIC-Spain) | PY | DN | PY | PN | DY | DY | PY | High |
| A. M. Bernstein | 2012 | Health Professionals Follow-up Study (HPFS) | DY | DY | PY | PY | DY | DN | DY | Low |
| A. M. Bernstein | 2012 | Nurses' Health Study (NHS) | DY | DY | PY | DY | DY | DN | DY | Low |
| S. C. Larsson | 2011 | Swedish Mammography Cohort (SMC) | DY | DN | DY | DY | DY | DY | PY | Low |
| S. Yaemsiri | 2012 | Women's Health Initiative Observational Study (WHI-OS) | DY | PN | PY | PN | DY | PY | DY | High |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 7: Risk of bias assessments for studies reporting on fatal stroke**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| T. J. Key | 1999 | Adventist Health Study | DY | DN | DY | PN | PY | DY | PY | Low |
| T. J. Key | 1999 | Adventist Mortality Study | DY | PN | DY | PN | PY | DY | PY | High |
| J. Praagman | 2015 | European Prospective Investigation into Cancer and Nutrition - Netherlands (EPIC-Netherlands) | DY | DN | DY | PN | DY | DY | DY | High |
| J. Chang-Claude | 2005 | German Vegetarian Study | DN | DN | DY | DN | DY | DY | DY | High |
| M. S. Farvid | 2017 | Golestan Cohort Study | DY | PN | DY | PN | DY | PY | DY | High |
| T. J. Key | 1999 | Health Food Shoppers Study | PY | DN | DY | PN | PY | DY | PY | High |
| T. J. Key | 1999 | Heidelberg Study | DY | PN | DY | PN | PY | PN | PN | High |
| C. Sauvaget | 2003 | Life Span Study (LSS) | DY | DN | DY | PN | DY | DY | PY | High |
| A. Etemadi | 2017 | National Institute of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study | DY | DN | DY | PN | DY | DY | PY | High |
| T. J. Key | 1999 | Oxford Vegetarian Study | DN | DN | DY | PN | PY | DY | PY | High |
| P. N. Appleby | 2016 | Oxford Vegetarian Study, European Prospective Investigate into Cancer and Nutrition-Oxford (EPIC-Oxford) | DN | DN | DY | PN | DY | DY | PY | High |
| Y. Takata | 2013 | Shanghai Men's Health Study (SMHS) | PY | PY | DY | PN | PY | DY | DY | Low |
| Y. Takata | 2013 | Shanghai Women's Health Study (SWHS) | DY | DN | DY | PN | PY | DY | DY | High |
| T. J. Key | 1999 | Adventist Health Study | DY | DN | DY | PN | PY | DY | PY | Low |
| T. J. Key | 1999 | Adventist Mortality Study | DY | PN | DY | PN | PY | DY | PY | High |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| J. Praagman | 2015 | European Prospective Investigation into Cancer and Nutrition - Netherlands (EPIC-Netherlands) | DY | DN | DY | PN | DY | DY | DY | High |
| J. Chang-Claude | 2005 | German Vegetarian Study | DN | DN | DY | DN | DY | DY | DY | High |
| M. S. Farvid | 2017 | Golestan Cohort Study | DY | PN | DY | PN | DY | PY | DY | High |
| T. J. Key | 1999 | Health Food Shoppers Study | PY | DN | DY | PN | PY | DY | PY | High |
| T. J. Key | 1999 | Heidelberg Study | DY | PN | DY | PN | PY | PN | PN | High |
| C. Sauvaget | 2003 | Life Span Study (LSS) | DY | DN | DY | PN | DY | DY | PY | High |
| A. Etemadi | 2017 | National Institute of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study | DY | DN | DY | PN | DY | DY | PY | High |
| T. J. Key | 1999 | Oxford Vegetarian Study | DN | DN | DY | PN | PY | DY | PY | High |
| P. N. Appleby | 2016 | Oxford Vegetarian Study, European Prospective Investigate into Cancer and Nutrition-Oxford (EPIC-Oxford) | DN | DN | DY | PN | DY | DY | PY | High |
| Y. Takata | 2013 | Shanghai Men's Health Study (SMHS) | PY | PY | DY | PN | PY | DY | DY | Low |
| Y. Takata | 2013 | Shanghai Women's Health Study (SWHS) | DY | DN | DY | PN | PY | DY | DY | High |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 8: Risk of bias assessments for studies reporting on fatal and non-fatal myocardial infarction**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| A. M. Wurtz | 2016 | Diet, Cancer and Health | DY | DN | PY | PN | DY | DY | PY | High |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 9: Risk of bias assessments for studies reporting on non-fatal myocardial infarction**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| L. Qi | 2007 | Nurses' Health Study (NHS) | DY | DY | PY | DY | DY | PY | PN | Low |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 10: Risk of bias assessments for studies reporting on type 2 diabetes**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| S. Tonstad | 2013 | Adventist Health Study 2 (AHS-2) | DY | PN | PY | PN | DY | DN | PN | High |
| A. Vang | 2008 | Adventist Mortality Study, Adventist Health Study | DY | DN | PY | PN | DY | DN | PN | High |
| S. Mannisto | 2010 | Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) | PY | DN | DY | PN | DY | DY | PY | High |
| J. Lv | 2017 | China Kadoorie Biobank (CKB) | DY | PN | DY | DY | DY | DY | DY | Low |
| M. Lajous | 2012 | Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (E3N) | DY | DN | PY | DY | DY | DN | PY | High |
| M. B. Schulze | 2007 | European Prospective Investigation into Cancer and Nutrition - Potsdam (EPIC-Potsdam) | DY | PY | PY | DN | DY | PY | DY | Low |
| A. von Ruesten | 2013 | European Prospective Investigation into Cancer and Nutrition - Potsdam (EPIC-Potsdam) | DY | PY | PY | PN | DY | PY | DY | Low |
| J. Montonen | 2005 | Finnish Mobile Clinic Health Examination Survey | DY | DN | PY | PY | DY | DY | PY | Low |
| A. Pan | 2011 | Health Professionals Follow-up Study (HPFS) | DY | DY | PY | PY | DY | PY | DY | Low |
| A. Pan | 2011 | Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS), Nurses' Health Study-2 (NHS-2) | DY | DY | PY | PY | DY | PY | DY | Low |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| D. H. Lee | 2004 | Iowa Women's Health Study (IWHS) | DY | DN | PY | PN | DY | DN | DN | High |
| K. Kurotani | 2013 | Japan Public Health Center-based Prospective study cohort I (JPHC I), Japan Public Health Center-based Prospective study cohort II (JPHC II) | DY | DY | PY | PY | PY | PY | DN | Low |
| H. E. K. Virtanen | 2017 | Kuopio Ischaemic Heart Disease Risk Factor Study | DY | DN | PY | DY | DY | DY | DY | Low |
| J. Son | 2018 | Korean Genome Epidemiology Study (KoGES) | DY | PY | PY | PN | DY | DN | PY | High |
| U. Ericson | 2013 | Malmo Diet and Cancer Cohort (MDC) study | DY | DN | PY | PN | DY | DY | PY | High |
| A. Steinbrecher | 2011 | Multiethnic Cohort (MEC) - Hawaiian component | DY | DN | PY | DN | DY | PY | PY | High |
| A. Pan | 2011 | Nurses' Health Study (NHS) | DY | DY | PY | DY | DY | PY | DY | Low |
| A. Pan | 2011 | Nurses' Health Study-2 (NHS-2) | DY | DY | PY | DY | DY | PY | DY | Low |
| M. Guasch-Ferre | 2017 | PREDIMED | DY | PY | PY | PN | DY | DY | PY | Low |
| G. J. van Woudenbergh | 2012 | Rotterdam study | DY | DN | DY | PY | DY | DY | PN | High |
| A. Mari-Sanchis | 2016 | Seguimiento Universidad de Navarra (SUN) project | DY | PN | PY | PY | DY | PY | DY | Low |
| R. Villegas | 2006 | Shanghai Women's Health Study (SWHS) | DY | PY | PY | PN | DY | DN | DY | High |
| M. Talaei | 2017 | Singapore Chinese Health Study | DY | DN | PY | PN | DY | PY | PN | High |
| A. M. Fretts | 2012 | Strong Heart Family Study (SHFS) | PY | PN | PY | DY | DY | DN | PY | High |
| T. H. T. Chiu | 2018 | Tzu Chi Health Study (TCHS) | DY | PN | PY | DY | DY | DN | DY | High |
| M. Isanejad | 2017 | Women's Health Initiative Observational Study (WHI-OS) and Women's Health Initiative Clinical Trial (WHI-CT) | DY | DN | PY | DY | DY | PN | PN | High |
| Y. Song | 2004 | Women's Health Study (WHS) | DY | PN | DY | PY | PY | PY | PN | High |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 11: Risk of bias assessments for studies reporting on anemia**

| Author | Year | Cohort | Was selection of exposed and non-exposed cohorts drawn from the same population? | Can we be confident in the assessment of exposure? | Can we be confident that the outcome of interest was not present at start of study? | Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | Can we be confident in the assessment of the presence or absence of prognostic factors? | Can we be confident in the assessment of outcome? | Was the follow-up of cohorts adequate? | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| C. A. Thomson | 2011 | Women's Health Initiative Observational Study (WHI-OS) | DY | PN | DY | DY | PY | DY | PY | Low |

DY=definitely yes; PY=probably yes; PN= probably no; DN=definitely no; N=no; Y=yes

**Appendix Table 12: Results from linear dose-response meta-analyses for a reduction of 3 servings/week of unprocessed red meat**

| Outcome/Subgroup | Cohorts (Number of participants) | Random-effects RR (95% CIs) | $I^2$ (%) | Q-test (p-value) | Egger's test (p-value) [a] | Interaction p-value | Non-linearity (p-value) [b] |
|---|---|---|---|---|---|---|---|
| All-cause mortality | 8 (893,436) | 0.93 (0.87 to 1.00) | 96.0 | <0.001 | NA | NA | 0.54 |
| Low risk | 8 (893,436) | 0.93 (0.87 to 1.00) | 96.0 | <0.001 | NA | NA | 0.54 |
| High risk | 0 (0) | NA | NA | NA | NA | | NA |
| Cardiovascular mortality | 7 (874,896) | 0.90 (0.88 to 0.91) | 0.0 | 0.024 | NA | NA | 0.16 |
| Low risk | 3 (182,470) | 0.89 (0.86 to 0.92) | 0.0 | 0.74 | NA | 0.34 | NA |
| High risk | 4 (692,426) | 0.98 (0.8 to 1.19) | 86.9 | 0.004 | NA | | 0.48 |
| Cardiovascular disease | 3 (191,803) | 0.95 (0.85 to 1.06) | 37.2 | 0.161 | NA | NA | NA |
| Low risk | 2 (107,667) | 0.92 (0.88 to 0.97) | 0.0 | 0.43 | NA | 0.084 | NA |
| High risk | 1 (84,136) | 1.13 (0.91 to 1.42) | NA | NA | NA | | NA |
| Fatal and non-fatal stroke | 6 (254,742) | 0.94 (0.90 to 0.98) | 0.0 | 0.50 | NA | NA | NA |
| Low risk | 4 (202,121) | 0.95 (0.90 to 1.00) | 0.0 | 0.57 | NA | 0.42 | NA |
| High risk | 2 (52,621) | 0.91 (0.79 to 1.05) | 40.1 | 0.20 | NA | | NA |
| Fatal stroke | 3 (671,259) | 0.94 (0.89 to 0.99) | 0.0 | 0.54 | NA | NA | NA |
| Low risk | 1 (61,128) | 0.92 (0.69 to 1.23) | NA | NA | NA | 0.83 | NA |
| High risk | 2 (610,131) | 0.95 (0.87 to 1.05) | 17.5 | 0.27 | NA | | NA |
| Fatal and non-fatal MI | 1 (55,171) | 0.93 (0.87 to 0.99) | NA | NA | NA | NA | NA |
| Low risk | 0 (0) | NA | NA | NA | NA | NA | NA |
| High risk | 1 (55,171) | 0.91 (0.8 to 1.03) | NA | NA | NA | | NA |
| Type 2 diabetes | 11 (531,843) | 0.94 (0.89 to 0.98) | 64.9 | 0.006 | 0.81 | NA | 0.28 |
| Low risk | 6 (293,869) | 0.90 (0.88 to 0.92) | 0.1 | 0.27 | NA | <0.001 | 0.59 |
| High risk | 5 (237,974) | 1 (0.94 to 1.06) | 18.6 | 0.22 | NA | | 0.46 |

[a] Only tested if there were ≥10 studies

[b] Only tested if there were ≥5 studies presenting results for ordered categories of exposure

CI=confidence intervals; MI = myocardial infarction; RR = relative risk

**Appendix Table 13: Results from linear dose-response meta-analyses for a reduction of 3 servings/week of processed meat**

| Outcome/Subgroup | Cohorts (Number of participants) | Random-effects RR (95% CIs) | $I^2$ (%) | Q-test (p-value) | Egger's test (p-value) [a] | Interaction p-value | Non-linearity (p-value) [b] |
|---|---|---|---|---|---|---|---|
| All-cause mortality | 8 (1,241,900) | 0.92 (0.87 to 0.96) | 87.4 | <0.001 | NA | NA | 0.44 |
| Low risk | 7 (793,332) | 0.91 (0.86 to 0.96) | 86.0 | <0.001 | NA | 0.70 | 0.44 |
| High risk | 1 (448,568) | 0.93 (0.91 to 0.96) | NA | NA | NA | | NA |
| Cardiovascular mortality | 7 (1,240,634) | 0.90 (0.84 to 0.97) | 84.9 | <0.001 | NA | NA | 0.48 |
| Low risk | 3 (121,342) | 0.85 (0.79 to 0.92) | 61.1 | 0.109 | NA | 0.120 | NA |
| High risk | 4 (1,119,292) | 0.97 (0.75 to 1.26) | 98.2 | <0.001 | NA | | NA |
| Cardiovascular disease | 3 (200,421) | 0.97 (0.87 to 1.09) | 59.6 | 0.098 | NA | NA | NA |
| Low risk | 2 (191,803) | 0.98 (0.87 to 1.09) | 75.1 | 0.045 | NA | 0.41 | NA |
| High risk | 1 (8,618) | 0.59 (0.18 to 1.95) | NA | NA | NA | | NA |
| Fatal and non-fatal stroke | 6 (254,742) | 0.94 (0.9 to 0.98) | 40.2 | 0.11 | NA | NA | NA |
| Low risk | 4 (202,121) | 0.92 (0.890 to 0.96) | 0.0 | 0.24 | NA | 0.15 | NA |
| High risk | 2 (52,621) | 0.98 (0.90 to 1.08) | 50.5 | 0.16 | NA | | NA |
| Fatal stroke | 2 (571,378) | 0.95 (0.92 to 0.98) | 0.0 | 0.93 | NA | NA | NA |
| Low risk | 0 (0) | NA | NA | NA | NA | NA | NA |
| High risk | 2 (571,378) | 0.95 (0.92 to 0.98) | 0.0 | 0.93 | NA | | NA |
| Fatal and non-fatal MI | 1 (55,171) | 0.94 (0.91 to 0.98) | NA | NA | NA | NA | NA |
| Low risk | 0 (0) | NA | NA | NA | NA | NA | NA |
| High risk | 1 (55,171) | 0.94 (0.91 to 0.98) | NA | NA | NA | | NA |
| Type 2 diabetes | 17 (758,540) | 0.85 (0.79 to 0.92) | 92.0 | <0.001 | 0.3708 | NA | <0.001 |
| Low risk | 8 (317,593) | 0.89 (0.82 to 0.96) | 83.4 | <0.001 | NA | 0.27 | <0.001 |
| High risk | 9 (440,947) | 0.81 (0.72 to 0.92) | 93.8 | <0.001 | NA | | <0.001 |

[a] Only tested if there were ≥10 studies

[b] Only tested if there were ≥5 studies presenting results for ordered categories of exposure

CI=confidence intervals; MI = myocardial infarction; RR = relative risk

**Appendix Table 14: Summary of finding for mixed unprocessed red and processed meat intake (reduction of 3 serving/week) and risk of cardiometabolic outcomes**

| Outcome | No of studies (follow-up period) (no of participants) | Relative risk (95% CI) | Population risk over 10.8 years [a] | Risk difference | Certainty of the evidence (GRADE) | Plain language summary |
|---|---|---|---|---|---|---|
| All-cause mortality [b] | 8 (Up to: 11 to 28 years follow-up) (903,049 participants) | 0.88 (0.84 to 0.93) [c] | 113/1000 | 14 fewer per 1,000 (from 8 fewer to 18 fewer) | LOW due to observational design | Reduction of mixed unprocessed red and processed meat may result in a small decrease in all-cause mortality. |
| Cardiovascular mortality | 7 (Up to: 11 to 28 years follow-up) (899,461 participants) | 0.92 (0.90 to 0.93) | 41/1000 | 3 fewer per 1,000 (from 3 fewer to 4 fewer) | VERY LOW due to observational design, risk of bias [d] | We are uncertain of the effects of mixed unprocessed red and processed meat on cardiovascular mortality. |
| Cardiovascular disease | 1 (Up to: 26 years follow-up) (84,136 participants) | 0.94 (0.92 to 0.96) | 76/1000 | 5 fewer per 1,000 (from 3 fewer to 6 fewer) | LOW due to observational design | Reduction of mixed unprocessed red and processed meat may result in a very small decrease in cardiovascular disease. |
| Stroke (fatal and non-fatal) | 6 (Up to: 11 to 26 years follow-up) (300,747 participants) | 0.95 (0.92 to 0.97) | 19/1000 | 1 fewer per 1,000 (from 1 fewer to 2 fewer) | LOW due to observational design | Reduction of mixed unprocessed red and processed meat may result in a very small decrease in stroke. |
| Fatal stroke | 3 (Up to: 11 to 16.3 years follow-up) (613,825 participants) | 0.93 (0.90 to 0.96) | 1/1000 | 0 fewer per 1,000 (from 0 fewer to 0 fewer) | VERY LOW due to observational design, risk of bias [e] | We are uncertain of the effects of mixed unprocessed red and processed meat on fatal stroke. |
| Myocardial infarction (fatal and non-fatal) | 1 (Median follow-up: 13.6 years) (55,171 participants) | 0.93 (0.89 to 0.97) | 36/1000 | 3 fewer per 1,000 (from 1 fewer to 4 fewer) | VERY LOW due to observational design risk of bias [f] | We are uncertain of the effects of mixed unprocessed red and processed meat on myocardial infarction. |
| Non-fatal myocardial infarction | 1 (Up to: 21 years follow-up) (3,697 participants) | 1.02 (0.91 to 1.14) | 24/1000 | 0 fewer per 1,000 (from 2 fewer to 3 more) | LOW due to observational design | Reduction of mixed unprocessed red and processed meat may have little or no effect on non-fatal myocardial infarction. |
| Type 2 diabetes [b] | 7 (Up to: 5 to 28 years follow-up) (298,854 participants) | 0.92 (0.91 to 0.93) | 56/1000 | 4 fewer per 1,000 (from 4 fewer to 5 fewer) | LOW due to observational design | Reduction of mixed unprocessed red and processed meat may result in a very small decrease in type 2 diabetes. |

CI=Confidence interval; GRADE=Grading of Recommendations, Assessment, Development and Evaluation

a. Emerging Risk Factors Collaboration. The Emerging Risk Factors Collaboration is comprised of 102 cohorts, including 698,782 participants, with median follow-up 10.8 years ($5^{th}$/$95^{th}$ percentile: 2.8 to 25.6). The numbers of events accrued are 78853, 28964, 52765, 13113, 768, 24848, 16737, 38851 for all-cause mortality, cardiovascular mortality, cardiovascular disease, fatal and non-fatal stroke, fatal stroke, and fatal and non-fatal myocardial infarction, non-fatal myocardial infarction, and type 2 diabetes, respectively.

b. We found a statistically significant difference between studies at high and low risk. Here, we report results from studies at low risk of bias.

c. Non-linear relationship. Effect estimate presented represents reduction of intake from 3 servings/week to 0 servings.

d. 5/7 studies at high risk of bias, primarily due to lack of periodic repeated measurement of diet and inadequate adjustment for confounders.
e. Studies at high risk of bias due to lack of periodic repeated measurement of diet and inadequate adjustment for confounders.
f. Study at high risk of bias due to assessment of diet only at baseline for 13.6 years of follow-up and lack of adjustment for family history of cardiovascular disease.

**Appendix Table 15: Results from linear dose-response meta-analyses for a reduction of 3 servings/week of mixed unprocessed red and processed meat**

| Outcome/Subgroup | Cohorts (Number of participants) | Random-effects RR (95% CIs) | $I^2$ (%) | Q-test (p-value) | Egger's test (p-value) [a] | Interaction p-value | Non-linearity (p-value) [b] |
|---|---|---|---|---|---|---|---|
| All-cause mortality | 9 (1,351,617) | 0.93 (0.91 to 0.96) | 93.1 | <0.0001 | NA | NA | 0.037 |
| Low risk | 8 (903,049) | 0.92 (0.91 to 0.94) | 77.8 | <0.0001 | NA | 0.002 | 0.037 |
| High risk | 1 (448,568) | 0.99 (0.98 to 1.01) | NA | NA | NA | | NA |
| Cardiovascular mortality | 7 (899,461) | 0.92 (0.90 to 0.93) | 16.1 | 0.158 | NA | NA | 0.20 |
| Low risk | 2 (121,342) | 0.92 (0.90 to 0.95) | 50.2 | 0.157 | NA | 0.29 | NA |
| High risk | 5 (777,849) | 0.91 (0.90 to 0.92) | 0.0 | 0.22 | NA | | 0.041 |
| Cardiovascular disease | 1 (84136) | 0.94 (0.92 to 0.96) | NA | NA | NA | NA | NA |
| Low risk | 1 (84136) | 0.94 (0.92 to 0.96) | NA | NA | NA | NA | NA |
| High risk | 0 (0) | NA | NA | NA | NA | | NA |
| Fatal and non-fatal stroke | 6 (300,747) | 0.95 (0.92 to 0.97) | 0.0 | 0.98 | NA | NA | 0.37 |
| Low risk | 4 (202,121) | 0.95 (0.92 to 0.98) | 0.0 | 0.87 | NA | 0.99 | NA |
| High risk | 2 (98,626) | 0.95 (0.90 to 1.00) | 0.0 | 0.89 | NA | | NA |
| Fatal stroke | 3 (613,825) | 0.93 (0.90 to 0.96) | 0.0 | 0.74 | NA | NA | NA |
| Low risk | 0 (0) | NA | NA | NA | NA | NA | NA |
| High risk | 3 (613,825) | 0.93 (0.9 to 0.96) | 0.0 | 0.74 | NA | | NA |
| Fatal and non-fatal MI | 1 (55,171) | 0.93 (0.89 to 0.97) | NA | NA | NA | NA | NA |
| Low risk | 0 (0) | NA | NA | NA | NA | NA | NA |
| High risk | 1 (55,171) | 0.93 (0.89 to 0.97) | NA | NA | NA | | NA |
| Non-fatal MI | 1 (3,697) | 1.02 (0.91 to 1.14) | NA | NA | NA | NA | NA |
| Low risk | 1 (3.697) | 1.02 (0.91 to 1.14) | NA | NA | NA | NA | NA |
| High risk | 0 (0) | NA | NA | NA | NA | | NA |
| Type 2 diabetes | 12 (555,717) | 0.89 (0.86 to 0.92) | 77.4 | <0.001 | 0.77 | NA | 0.014 |
| Low risk | 7 (298,854) | 0.92 (0.91 to 0.93) | 0.10 | 0.35 | NA | 0.027 | 0.12 |

**Appendix Table 16: Results for meta-analyses comparing the lowest category of consumption of unprocessed red meat with the highest category of exposure**

| Outcome/Subgroup | Cohorts (Number of participants) | HKSJ RR (95% CI | Random-effects RR (95% CIs) | $I^2$ (%) | Q-test (p-value) | Interaction p-value |
|---|---|---|---|---|---|---|
| All-cause mortality | 9 (413,760) | 0.90 (0.77 to 1.04) | 0.90 (0.80 to 1.01) | 94.6 | <0.001 | NA |
| Low risk of bias | 9 (413,760) | 0.90 (0.77 to 1.04) | 0.90 (0.80 to 1.01) | 94.6 | <0.001 | NA |
| High risk of bias | 0 (0) | NA | NA | NA | NA | |
| Cardiovascular mortality | 8 (389,528) | 0.88 (0.73 to 1.06) | 0.88 (0.77 to 1.01) | 83.4 | 0.001 | NA |
| Low risk of bias | 4 (87,741) | 0.79 (0.63 to 1.00) | 0.79 (0.70 to 0.9) | 54.4 | 0.099 | 0.33 |
| High risk of bias | 4 (301,788) | 0.99 (0.61 to 1.61) | 0.99 (0.77 to 1.03) | 86.4 | 0.002 | |
| Cardiovascular disease | 4 (65,736) | 0.92 (0.69 to 1.22) | 0.92 (0.8 to 1.06) | 22.7 | 0.16 | NA |
| Low risk of bias | 2 (57,185) | 0.87 (0.39 to 1.96) | 0.87 (0.76 to 0.99) | 0.0 | 0.34 | 0.42 |
| High risk of bias | 2 (8,550) | 1.04 (0.11 to 10) | 1.04 (0.73 to 1.47) | 65.7 | 0.088 | |
| Fatal and non-fatal stroke | 6 (102,024) | 0.90 (0.82 to 0.99) | 0.90 (0.83 to 0.97) | 0.1 | 0.42 | NA |
| Low risk of bias | 4 (80,848) | 0.90 (0.83 to 0.98) | 0.90 (0.83 to 0.98) | 0.0 | 0.75 | 0.69 |
| High risk of bias | 2 (21,176) | 0.88 (0.43 to 1.82) | 0.88 (0.64 to 1.22) | 56.6 | 0.10 | |
| Fatal stroke | 3 (268,504) | 0.89 (0.64 to 1.25) | 0.89 (0.76 to 1.05) | 15.1 | 0.34 | NA |
| Low risk of bias | 1 (24,451) | NA | 0.82 (0.47 to 1.45) | NA | NA | 0.76 |
| High risk of bias | 2 (244,053) | 0.94 (0.15 to 6.25) | 0.94 (0.71 to 1.27) | 53.0 | 0.14 | |
| Fatal and non-fatal MI | 1 (55,171) | NA | 0.85 (0.73 to 0.98) | NA | NA | NA |
| Low risk of bias | 0 (0) | NA | NA | NA | NA | NA |
| High risk of bias | 1 (55,171) | NA | 0.79 (0.59 to 1.08) | NA | NA | |
| Type 2 diabetes | 12 (>211,467)* | 0.91 (0.84 to 0.99) | 0.91 (0.84 to 0.98) | 61.8 | 0.001 | NA |
| Low risk of bias | 6 (138,284) | 0.85 (0.74 to 0.98) | 0.85 (0.76 to 0.94) | 64.8 | 0.016 | 0.062 |
| High risk of bias | 6 (>73,183)* | 0.97 (0.88 to 1.06) | 0.97 (0.9 to 1.05) | 23.7 | 0.32 | |

CI=confidence intervals; MI = myocardial infarction; RR = relative risk

*Lajous et al., 2013 do not report number of participants in extreme categories

**Appendix Table 17: Results for meta-analyses comparing the lowest category of consumption of processed meat with the highest category of exposure**

| Outcome/Subgroup | Cohorts (Number of participants) | HKSJ RR (95% CI | Random-effects RR (95% CIs) | $I^2$ (%) | Q-test (p-value) | Interaction p-value |
|---|---|---|---|---|---|---|
| All-cause mortality | 10 (>696,822)* | 0.88 (0.85 to 0.91) | 0.88 (0.85 to 0.90) | 17.3 | 0.150 | NA |
| Low risk of bias | 9 (>584,457)* | 0.88 (0.87 to 0.90) | 0.88 (0.87 to 0.90) | 0.0 | 0.85 | 0.003 |
| High risk of bias | 1 (112,366) | NA | 0.70 (0.61 to 0.82) | NA | NA | |
| Cardiovascular mortality | 9 (>472,128)* | 0.88 (0.74 to 1.04) | 0.88 (0.77 to 1) | 79.1 | 0.001 | NA |
| Low risk of bias | 4 (>63,290)* | 0.81 (0.69 to 0.93) | 0.81 (0.75 to 0.87) | 0.0 | 0.24 | 0.72 |
| High risk of bias | 5 (408,839) | 0.93 (0.64 to 1.33) | 0.93 (0.7 to 1.22) | 84.5 | 0.007 | |
| Cardiovascular disease | 4 (69,186) | 0.97 (0.88 to 1.05) | 0.97 (0.88 to 1.05) | 0.0 | 0.63 | NA |
| Low risk of bias | 2 (57,185) | 0.99 (0.44 to 2.22) | 0.99 (0.88 to 1.12) | 20.1 | 0.26 | 0.63 |
| High risk of bias | 2 (12,000) | 0.93 (0.54 to 1.61) | 0.93 (0.79 to 1.11) | 0.0 | 0.62 | |
| Fatal and non-fatal stroke | 6 (101,861) | 0.85 (0.78 to 0.94) | 0.85 (0.8 to 0.93) | 0.0 | 0.40 | NA |
| Low risk of bias | 4 (80,848) | 0.84 (0.76 to 0.93) | 0.84 (0.78 to 0.91) | 0.0 | 0.63 | 0.30 |
| High risk of bias | 2 (21,013) | 0.98 (0.78 to 1.69) | 0.98 (0.76 to 1.28) | 38.7 | 0.21 | |
| Fatal stroke | 2 (231,992) | 0.92 (0.88 to 0.96) | 0.92 (0.84 to 1) | 0.0 | 0.94 | NA |
| Low risk of bias | 0 (0) | NA | NA | NA | NA | NA |
| High risk of bias | 2 (231,992) | 0.92 (0.88 to 0.96) | 0.92 (0.84 to 1) | 0.0 | 0.94 | |
| Fatal and non-fatal MI | 1 (55,171) | NA | 0.87 (0.79 to 0.95) | NA | NA | NA |
| Low risk of bias | 0 (0) | NA | NA | NA | NA | NA |
| High risk of bias | 1 (55,171) | NA | 0.87 (0.79 to 0.95) | NA | NA | |
| Type 2 diabetes | 19 (>25,032)* | 0.83 (0.79 to 0.88) | 0.83 (0.79 to 0.88) | 56.9 | 0.002 | NA |
| Low risk of bias | 10 (>143,785)† | 0.83 (0.75 to 0.92) | 0.83 (0.75 to 0.92) | 64.4 | 0.004 | 0.65 |
| High risk of bias | 9 (>106,536) ‡ | 0.86 (0.8 to 0.92) | 0.86 (0.81 to 0.91) | 29.1 | 0.161 | |

CI=confidence intervals; MI = myocardial infarction; RR = relative risk

* Villegas et al., 2016, Lajous et al., 2013, and Mari-Sanchis et al., 2016 do not report number of participants in extreme categories

† Mari-Sanchis et al., 2017 do not report number of participants in extreme categories

**Appendix Table 18: Results for meta-analyses comparing the lowest category of consumption of mixed unprocessed red and processed meat with the highest category of exposure**

| Outcome/Subgroup | Cohorts (Number of participants) | HKSJ RR (95% CI | Random-effects RR (95% CIs) | $I^2$ (%) | Q-test (p-value) | Interaction p-value |
|---|---|---|---|---|---|---|
| All-cause mortality | 27 (1,037,469) | 0.93 (0.88 to 1.00) | 0.93 (0.88 to 0.99) | 88.6 | <0.001 | NA |
| Low risk of bias | 21 (868,286) | 0.88 (0.82 to 0.94) | 0.88 (0.83 to 0.93) | 86.6 | <0.001 | <0.001 |
| High risk of bias | 6 (169,183) | 1.08 (0.99 to 1.16) | 1.08 (0.99 to 1.15) | 63.2 | 0.003 | |
| Cardiovascular mortality | 17 (763,532) | 0.83 (0.76 to 0.92) | 0.83 (0.77 to 0.91) | 80.5 | <0.001 | NA |
| Low risk of bias | 3 (52,801) | 0.71 (0.63 to 0.81) | 0.71 (0.65 to 0.77) | 0.0 | 0.62 | 0.096 |
| High risk of bias | 14 (710,731) | 0.86 (0.78 to 0.95) | 0.86 (0.79 to 0.94) | 79.5 | <0.001 | |
| Cardiovascular disease | 5 (119,320) | 0.75 (0.67 to 0.85) | 0.75 (0.68 to 0.83) | 0.0 | 0.56 | NA |
| Low risk of bias | 1 (33,654) | NA | 0.78 (0.67 to 0.89) | NA | NA | 0.63 |
| High risk of bias | 4 (85,665) | 0.74 (0.61 to 0.90) | 0.74 (0.65 to 0.84) | 0.0 | 0.44 | |
| Fatal and non-fatal stroke | 6 (172,581) | 0.85 (0.8 to 0.91) | 0.85 (0.79 to 0.92) | 0.0 | 0.83 | NA |
| Low risk of bias | 4 (80,848) | 0.85 (0.79 to 0.93) | 0.85 (0.62 to 0.98) | 0.0 | 0.81 | 0.88 |
| High risk of bias | 2 (91,733) | 0.84 (0.28 to 2.56) | 0.84 (0.71 to 1.00) | 12.5 | 0.29 | |
| Fatal stroke | 8 (340,172) | 0.93 (0.81 to 1.06) | 0.93 (0.83 to 1.04) | 40.7 | 0.12 | NA |
| Low risk of bias | 0 (0) | NA | NA | NA | NA | NA |
| High risk of bias | 8 (340,172) | 0.95 (0.8 to 1.14) | 0.95 (0.83 to 1.1) | 38.7 | 0.15 | |
| Fatal and non-fatal MI | 1 (55,171) | NA | 0.85 (0.77 to 0.93) | NA | NA | NA |
| Low risk of bias | 0 (0) | NA | NA | NA | NA | NA |
| High risk of bias | 1 (55,171) | NA | 0.85 (0.77 to 0.93) | NA | NA | |
| Non-fatal MI | 1 (2,464) | NA | 1.10 (0.68 to 1.79) | NA | NA | NA |
| Low risk of bias | 1 (2,464) | NA | 1.10 (0.68 to 1.79) | NA | NA | NA |
| High risk of bias | 0 (0) | NA | NA | NA | NA | |
| Type 2 diabetes | 19 (>760,824)* | 0.78 (0.71 to 0.85) | 0.78 (0.72 to 0.83) | 71.0 | <0.001 | NA |
| Low risk of bias | 10 (618,983) | 0.80 (0.72 to 0.88) | 0.80 (0.73 to 0.87) | 64.3 | <0.001 | 0.50 |

**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 three cohort studies reporting on the association between unprocessed red meat and fatal stroke. The first two studies presented results across categories of exposure. The third study reported presented results from a regression in which unprocessed red meat intake was treated as a continuous variable. The relative effect below from the third study corresponds to an increase in intake of 120 g/day.

Data are presented below along with definitions of variables.

| Ref | Cohort | RType | Quantity | N | PY | Events | Adj_point | CI_lower | CI_upper |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Shanghai Men's Health Study (SMHS) | ir | 20 | 12226 | 66856.2 | 66 | 1 | | |
| 1 | Shanghai Men's Health Study (SMHS) | ir | 37.7 | 12225.67 | 66856.2 | 47 | 1.02 | 0.70 | 1.50 |
| 1 | Shanghai Men's Health Study (SMHS) | ir | 53.9 | 12225.67 | 66856.2 | 27 | 0.82 | 0.52 | 1.31 |
| 1 | Shanghai Men's Health Study (SMHS) | ir | 74.6 | 12225.67 | 66856.2 | 23 | 0.91 | 0.55 | 1.51 |
| 1 | Shanghai Men's Health Study (SMHS) | ir | 114.9 | 12225 | 66856.2 | 21 | 1.22 | 0.69 | 2.15 |
| 2 | Shanghai Women's Health Study (SWHS) | ir | 15 | 14633 | 160653 | 124 | 1 | | |
| 2 | Shanghai Women's Health Study (SWHS) | ir | 29.9 | 14632.33 | 160653 | 68 | 0.79 | 0.58 | 1.07 |
| 2 | Shanghai Women's Health Study (SWHS) | ir | 43.4 | 14632.33 | 160653 | 44 | 0.64 | 0.44 | 0.91 |
| 2 | Shanghai Women's Health Study (SWHS) | ir | 60.1 | 14632.33 | 160653 | 45 | 0.81 | 0.56 | 1.18 |
| 2 | Shanghai Women's Health Study (SWHS) | ir | 94.8 | 14632 | 160653 | 39 | 0.84 | 0.55 | 1.28 |

| Ref | Cohort | Quantity | Adj_point | CI_lower | CI_upper |
|---|---|---|---|---|---|
| 3 | National Institute of Heatlh-American Association of Retired Persons (NIH-AARP) Diet and Health Study | 120 | 1.17 | 1.03 | 1.33 |

*RType: type of study (ir=incidence rate; cc=case-control; ci=cumulative incidence)*

*Quantity: g/day of unprocessed red meat intake*

*N: number of participants (if total number of participants in a study were reported and results were presented across quantiles of intake, the number of participants in each quantile was approximated by dividing the total number of participants in the study by the number of quantiles)*

*PY: number of person-years (if total number of person-years in a study were reported and results were presented across quantiles of intake, the number of person-years for each quantile was approximated by dividing the total number of person-years in the study by the number of quantiles)*

*Events: number of events*

*Adj_point: Adjusted point estimate in relative risk, odds ratio, or hazard ratio*

*CI_lower: Lower bounds of confidence interval for the adjusted point estimate*

*CI_upper: Upper bounds of confidence interval for the adjusted point estimate*

The following code loads 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 standard errors. The natural logarithm of effect estimates and standard errors 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 two studies using the method by Greenland & Longnecker (1992) 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 (i.e., the regression coefficient) for the first two studies can be extracted from the above dose-response meta-analysis. Note that regression coefficients extracted from the dose-response meta-analysis correspond to one unit of intake (in this case, 1 g/day), but can be converted to correspond with any quantity of intake and can subsequently be meta-analyzed with the third study that that treats the exposure as a continuous variable.

Here, we calculate effects for one serving/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 two studies that were derived based on the method by Greenland & Longnecker (1992).

```
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 one serving/day to a reduction of three servings/day by calculating the inverse of the effect, dividing by seven, multiplying by three, and then subsequently exponentiating. This process can also be replicated for the upper and lower bounds of the confidence intervals. This yields relative effect estimates corresponding to a reduction of three servings/week.

```
exp(-meta$beta/7*3)

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

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

The following code tests for non-linearity 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)
```

**References**


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# CHAPTER 5: PATTERNS OF RED AND PROCESSED MEAT CONSUMPTION AND RISK FOR CARDIOMETABOLIC AND CANCER OUTCOMES—A SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT STUDIES

REVIEW

Annals of Internal Medicine

# Patterns of Red and Processed Meat Consumption and Risk for Cardiometabolic and Cancer Outcomes

## A Systematic Review and Meta-analysis of Cohort Studies

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**Background:** Studying dietary patterns may provide insights into the potential effects of red and processed meat on health outcomes.

**Purpose:** To evaluate the effect of dietary patterns, including different amounts of red or processed meat, on all-cause mortality, cardiometabolic outcomes, and cancer incidence and mortality.

**Data Sources:** Systematic search of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, and ProQuest Dissertations & Theses Global from inception to April 2019 with no restrictions on year or language.

**Study Selection:** Teams of 2 reviewers independently screened search results and included prospective cohort studies with 1000 or more participants that reported on the association between dietary patterns and health outcomes.

**Data Extraction:** Two reviewers independently extracted data, assessed risk of bias, and evaluated the certainty of evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria.

**Data Synthesis:** Eligible studies that followed patients for 2 to 34 years revealed low- to very-low-certainty evidence that dietary patterns lower in red and processed meat intake result in very small or possibly small decreases in all-cause mortality, cancer mortality and incidence, cardiovascular mortality, nonfatal coronary heart disease, fatal and nonfatal myocardial infarction, and type 2 diabetes. For all-cause, cancer, and cardiovascular mortality and incidence of some types of cancer, the total sample included more than 400 000 patients; for other outcomes, total samples included 4000 to more than 300 000 patients.

**Limitation:** Observational studies are prone to residual confounding, and these studies provide low- or very-low-certainty evidence according to the GRADE criteria.

**Conclusion:** Low- or very-low-certainty evidence suggests that dietary patterns with less red and processed meat intake may result in very small reductions in adverse cardiometabolic and cancer outcomes.

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Observational studies have reported higher incidence of all-cause mortality, cardiometabolic diseases, and cancer outcomes in people who consume greater quantities of red meat (1–6). Consequently, most guidelines from national and international agencies recommend limiting intake of red and processed meat (7–9). However, additional scrutiny of the evidence to determine the extent to which current recommendations are justified is warranted, particularly given the possible methodological limitations of systematic reviews to date (for example, the lack of consideration of the overall certainty of evidence) and other confounding factors (10, 11).

Foods and nutrients are not consumed in isolation, and their effects may differ depending on the totality of one's diet and how dietary habits change over time. Moreover, interventions focusing on modification of intake of particular foods or nutrients require compensatory changes in other dietary components. Nevertheless, most nutritional epidemiologic research since the 1970s has focused on the effects of individual foods or nutrients (12). Given the potential for interaction, an increasingly common alternative to focusing on individual foods or nutrients is to examine the effects of dietary patterns on health outcomes (13). Two approaches are commonly used to define dietary patterns: data-driven methods, including factor analysis or principal-components analysis, or a priori approaches that use diet indices or scores based on dietary recommendations or characteristics.

This review was done to inform recommendations on red and processed meat intake from the NutriRECS (Nutritional Recommendations) consortium (14). We conducted 4 additional systematic reviews addressing evidence from randomized trials on the effect of red meat consumption on health outcomes (15), observational evidence on the association between red and processed meat consumption and cardiometabolic outcomes (16), observational evidence on the associa-

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tion between red and processed meat consumption and cancer outcomes (17), and qualitative and quantitative evidence on public values and preferences regarding meat consumption (18). We used the results of these to develop guideline recommendations on red and processed meat consumption (19). In this article, we report the results of a systematic review addressing the association between dietary patterns that are lower versus higher in red and processed meat intake and the risk for cardiometabolic and cancer outcomes.

## METHODS

This article complies with the recommendations of PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (20). We registered the protocol in PROSPERO (CRD42017074074) on 10 August 2017.

### Data Sources and Searches

With assistance from an experienced librarian, we developed a comprehensive search strategy for 5 databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Web of Science, and CINAHL. We searched each database without restrictions on year or language of publication from inception to 8 July 2018, with an updated search of MEDLINE through to April 2019 (**Supplement Table 1**, available at Annals.org). In addition, we searched the following gray literature sources: ProQuest Dissertations & Theses Global (1989 to 2018), trial registries (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform Search Portal), bibliographies of included articles, and relevant literature reviews. This search strategy informed all supporting NutriRECS reviews on red and processed meat (15–17) except the one addressing public values and preferences (18).

### Study Selection

We included cohort studies with 1000 or more participants that reported an association between dietary patterns and 1 or more of our outcomes of interest in adults with or without cardiometabolic conditions but without cancer or any infectious or chronic noncardiometabolic conditions. We excluded studies that did not report the quantity of consumption of red and processed meat across categories of dietary habits. Red meat was defined as mammalian meat, and processed meat was defined as white or red meat preserved by smoking, curing, salting, or adding preservatives (21). We assumed serving sizes of 120 g for unprocessed red meat, 50 g for processed meat, and 100 g for mixed unprocessed red and processed meat. These were selected to be comparable to serving sizes used in other systematic reviews and to reflect those used by the U.S. Department of Agriculture and the U.K. Food Standards Agency (4–7). We also included studies comparing vegetarians with nonvegetarians. When more than 1 eligible article reported on the same exposure and cohort and addressed the same outcome, we included only results from the article with the longest follow-up. If the duration of follow-up was the same across articles, we included the article with the largest number of participants, resulting in each unique cohort study as the unit of analysis.

The panel for the NutriRECS guideline on red and processed meat, which comprised members of the public and clinicians, including dietitians, epidemiologists, and methodologists, selected the outcomes of interest for this systematic review (14, 22). These included major cardiometabolic morbidity and mortality; incidence of or mortality associated with gastrointestinal, breast, gynecologic, and prostate cancer; quality of life; and satisfaction with diet.

Reviewers conducted pilot screening exercises and received detailed instructions for each item before screening. Pairs of reviewers independently screened titles and abstracts in duplicate and reviewed the full-text articles of those found to be potentially eligible. Reviewers resolved disagreements by discussion or, if necessary, by third-party adjudication.

### Data Extraction and Risk-of-Bias Assessment

Reviewers conducted calibration exercises and worked in duplicate to independently extract data. We used a standardized, piloted data abstraction form. The reviewers resolved disagreements by discussion or, if necessary, by third-party adjudication involving a senior investigator. We extracted the following information from each study: setting, number of participants at baseline and follow-up, age, sex, method of diet assessment, dietary pattern data (intake of red and processed meat), type of cancer or cardiometabolic disease, years of follow-up, and effect estimates and corresponding 95% CIs.

Reviewers, independently and in duplicate, assessed risk of bias of each eligible study by using a modified version of the CLARITY (Clinical Advances Through Research and Information Translation) instrument (23, 24), with omission of 1 item related to cointerventions that was not relevant to our review (**Supplement Table 3**, available at Annals.org). We rated each item as having definitely low, probably low, probably high, or definitely high risk of bias. We adapted item 2 (assessment of exposure) to address the validity of dietary measures. For example, if a study measured diet at least once every 5 years using a food-frequency questionnaire validated against a weighted food record for red and processed meat, it was deemed to have definitely low risk of bias for this item. We also adapted item 4 (adjustment for prognostic factors) on the basis of established prognostic factors for each outcome of interest. Consultation with research methodologists and nutrition researchers confirmed the appropriateness of the instrument and informed criteria to evaluate each item. We considered each item to be equally important. Risk of bias was evaluated at the outcome level and not the study level. We considered studies that were rated to have high risk of bias on 2 or more of the 7 domains to have high overall risk of bias. Although this threshold is arbitrary, it represents a compromise between excessive stringency and leniency and facilitates subgroup analysis by providing an ap-

proximately even division between studies at higher versus lower risk of bias.

### Data Synthesis and Analysis

The lowest category (for example, tertiles or quartiles) of adherence to dietary patterns high in red and processed meat was compared with the highest category as a proxy to determine the dietary patterns lower versus higher in red and processed meat consumption. When a single study investigated multiple dietary patterns, our analysis focused on the one with the greatest difference in red or processed meat intake between the lowest and highest categories. In studies that investigated multiple dietary patterns, we used factor analysis or principal-component analysis to analyze the patterns with the highest factor loadings for red meat, processed meat, or both. Using the Hartung-Knapp-Sidik-Jonkman model (25, 26) and a DerSimonian–Laird random-effects model as a sensitivity analysis (27), we conducted meta-analyses comparing the lowest and highest categories of intake. For studies in which the outcomes of interest were reported stratified by participant characteristics (for example, sex) with no overlap in participants or events across strata, we meta-analyzed across subgroups. We calculated the risk difference by multiplying the pooled effect estimate from our meta-analyses by the baseline risk for cancer incidence or mortality, which was based on GLOBOCAN cumulative lifetime risks (28, 29). For cardiometabolic disease, data from the Emerging Risk Factors Collaboration (30) provided the baseline risk to calculate risk differences over 10.8 years.

We conducted subgroup analyses for each outcome based on our assessment of overall risk of bias for each study. When we found a statistically significant subgroup effect based on risk of bias, we present results for studies with low risk of bias. We also conducted a subgroup analysis based on the methods for defining dietary patterns.

### Certainty of Evidence

One investigator assessed the certainty of evidence as high, moderate, low, or very low for each outcome using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria (31), with all assessments confirmed by senior investigators. According to the GRADE approach, observational studies may provide moderate- or high-certainty evidence if they show a large magnitude of effect or a dose-response gradient and when suspected biases work against the observed direction of effect. Observational studies without these characteristics provide low-certainty evidence, and those that are also limited by risk of bias, inconsistency, indirectness, imprecision, or publication bias provide very-low-certainty evidence (32–37).

### Role of the Funding Source

This study received no funding.

## RESULTS

Of the 13 154 unique citations initially identified by our search, 11 653 were deemed ineligible after title and abstract screening (**Figure**). Among the 1501 full-text articles evaluated, 105 were potentially eligible, yielding 70 unique cohorts with 6 035 051 participants. Most of the cohorts (83%) were also included in the accompanying systematic reviews (16, 17) to support the guideline recommendation.

The articles were published between 1994 and 2018 and included 1804 to 492 382 participants followed for 2.0 to 34.3 years. The mean age of participants at enrollment ranged from 33 to 71 years, with most studies including a majority of participants aged 50 to 60 years, and the proportion of women ranged from 0% to 100%, with most studies including a similar number of men and women. Six studies recruited participants with preexisting cardiometabolic conditions, the most common being hypertension. **Supplement Table 2** (available at Annals.org) shows additional study characteristics.

Investigators used a wide variety of methods to define dietary patterns (**Supplement Table 2**). In 63 cohort studies (60%), a posteriori dietary patterns derived from factor analyses, principal-component analyses, cluster analyses, or reduced-rank regressions were used. Among studies using factor analysis or principal-component analysis, dietary patterns were derived by the covariance matrix of individual foods to reduce the dimensionality from a high number of foods to a few patterns of food consumption that explained the maximum variation in dietary habits (13). The resultant patterns were aggregates of foods that were highly correlated with one another. Patterns derived by principal-component analysis were linear combinations of the observed variables, whereas factors derived by factor analysis were latent constructs. The emerging patterns were often adjusted using an "orthogonal rotation" so that the final patterns were uncorrelated. For each pattern, summary factor scores were obtained that defined each participant's degree of adherence. Among studies in which reduced-rank regression was used, linear combinations of foods that maximally explained a set of intermediate or surrogate measures of the outcome of interest (such as biomarker levels) were derived and pattern scores were obtained that, similar to factor scores, represented each participant's degree of adherence to the pattern (38). In studies that used cluster analysis, the *k*-means method was used to identify aggregates of participants with similar dietary habits (13).

In 15 studies, dietary patterns were defined a priori using indices or scoring systems. Of the eligible studies, 19 investigated vegetarian versus nonvegetarian participants for at least 1 of our outcomes of interest. Our subgroup analyses found no differences among the various methods used to determine dietary patterns for any outcome (**Supplement Table 4**, available at Annals.org).

Red and processed meat intake varied widely across categories. Thirty studies recorded a quantitative estimate of red or processed meat consumption (for example, grams per day or servings per week), and others solely reported the factor loadings or compared vegetarians versus nonvegetarians without information on meat consumption. Among the 27 studies report-

ing on red meat intake (unprocessed, unspecified, or mixed), the difference between extreme adherence categories was less than 2 servings per week in 6 studies, 2 to 5 servings per week in 17 studies, and more than 5 servings per week in 4 studies. In the 19 studies reporting on intake of processed meat, the difference between extreme adherence categories was less than 2 servings per week in 4 studies, 2 to 5 servings per week in 13 studies, and more than 5 servings per week in 2 studies.

### Risk-of-Bias Assessment

Supplement Table 3 presents risk of bias for each study and outcome. The percentage of studies with high overall risk of bias varied across outcomes (10 of 24 [42%] for all-cause mortality, 13 of 25 [52%] for cardiovascular mortality, 3 of 5 [60%] for fatal and nonfatal stroke, 0 of 2 [0%] for myocardial infarction, 7 of 12 [58%] for cardiovascular disease, 2 of 3 [67%] for overall cancer incidence, 8 of 18 [44%] for overall cancer mortality, and 9 of 14 [64%] for type 2 diabetes). The most common methodological limitations were lack of repeated measurement of intake in the dietary patterns, use of a measure that was not validated for red and/or processed meat, and inadequate adjustment for potential confounders. We did not find significant differences in any outcome for the studies judged to have high versus low risk of bias (Supplement Table 5, available at Annals.org).

### All-Cause Mortality

We found a small decrease in risk for all-cause mortality associated with dietary patterns lower in red or processed meat intake. Evidence was rated to have very low certainty due to inconsistency (Table 1).

### Cardiovascular Outcomes

Dietary patterns lower in red and processed meat intake were associated with decreased risk for cardiovascular mortality, based on very-low-certainty evidence due to inconsistency (Table 1). Low-certainty evidence showed a small reduction in risk for nonfatal stroke for dietary patterns low in red and processed meat intake but no statistically significant associations for risk for overall stroke and fatal stroke.

We did not observe a statistically significant association between dietary patterns and risk for fatal and nonfatal myocardial infarction, fatal and nonfatal cardiovascular disease, and nonfatal cardiovascular disease (Table 1).

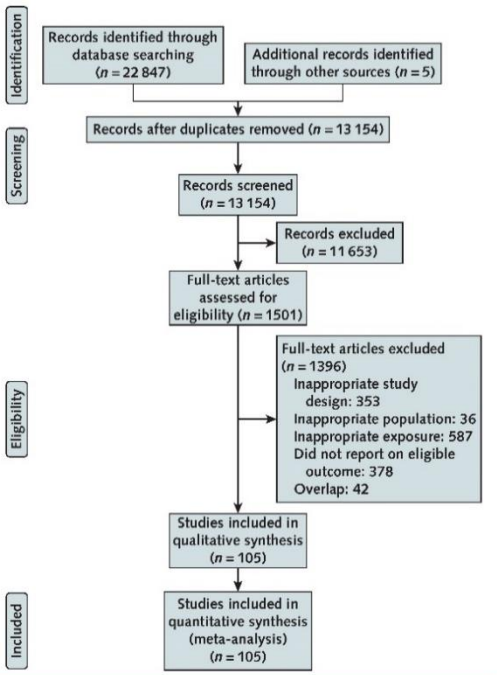
### Type 2 Diabetes

We found a very small reduction in risk for type 2 diabetes associated with dietary patterns lower in red or processed meat consumption (Table 1). The overall certainty of this evidence was very low due to inconsistency.

### Cancer Outcomes

Dietary patterns lower in red and processed meat intake were associated with a small to very small reduction in risk for overall cancer incidence and mortality (Table 2). However, this evidence was considered to have very low certainty for overall cancer incidence

*Figure.* Evidence search and selection.




(due to imprecision) and overall cancer mortality (due to inconsistency). No statistically significant risk was found for dietary patterns lower in red and processed meat intake for incidence of breast, colorectal, endometrial, liver, ovarian, pancreatic, prostate, stomach, and uterine cancer. Similarly, we found no differences among dietary patterns in risk estimates for mortality associated with breast, colorectal, esophageal, liver, ovarian, prostate, and stomach cancer.

We found low-certainty evidence that dietary patterns lower in red or processed meat consumption were associated with a very small reduction in risk for incidence of extrahepatic and gallbladder cancer. Low-certainty evidence also suggested that risk for death due to pancreatic cancer was lower for the dietary patterns with low intake of red or processed meat.

## DISCUSSION

In this systematic review and meta-analysis of 70 unique cohorts with 6 035 051 participants, we found low- to very-low-certainty evidence that dietary patterns lower in red or processed meat intake result in a small to very small reduction in risk for all-cause mortality, cardiovascular mortality, fatal coronary heart disease, fatal myocardial infarction, overall cancer mortality,

*Table 1.* Summary of Findings for Lower Adherence to Dietary Patterns High in Red and Processed Meat Intake and Risk for Cardiometabolic Outcomes

| Outcome | Studies (Participants), *n* | Follow-up, *y* | Relative Risk (95% CI) | Population Risk per 1000 Persons Older Than 10.8 Years* | Risk Difference per 1000 Persons (95% CI) | GRADE Certainty of Evidence | Plain-Language Summary |
|---|---|---|---|---|---|---|---|
| All-cause mortality | 24 (545 071) | 4 to 26 | 0.87 (0.82 to 0.92) | 113 | −15 (−20 to −9) | Very low† | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on all-cause mortality. |
| Cardiovascular mortality | 25 (858 554) | 4 to 26 | 0.86 (0.79 to 0.94) | 41 | −6 (−9 to −2) | Very low‡ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on cardiovascular mortality. |
| Stroke (fatal and nonfatal) | 6 (132 950) | 4 to 29 | 0.75 (0.53 to 1.05) | 19 | −5 (−9 to 1) | Very low§ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on stroke. |
| Fatal stroke | 9 (550 278) | 6 to 34 | 1.00 (0.88 to 1.14) | 1 | 0 | Very low‖ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on fatal stroke. |
| Nonfatal stroke | 2 (38 937) | 6 to 12 | 0.86 (0.81 to 0.92) | 18 | −3 (−3 to −1) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have a very small effect on nonfatal stroke. |
| Myocardial infarction (fatal and nonfatal) | 2 (4974) | 4 to 6 | 1.04 (0.78 to 1.39) | 36 | 1 (−8 to 14) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on myocardial infarction. |
| Cardiovascular disease (fatal and nonfatal) | 12 (113 737) | 4 to 17 | 0.87 (0.75 to 1.01) | 76 | −10 (−19 to 1) | Very low¶ | – |
| Nonfatal cardiovascular disease | 2 (47 043) | 6 to 24 | 0.85 (0.17 to 4.27) | 24 | −4 (−20 to 78) | Very low‖¶ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on nonfatal coronary heart disease. |
| Type 2 diabetes | 14 (378 788) | 2 to 34 | 0.76 (0.68 to 0.86) | 56 | −13 (−18 to −8) | Very low** | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on type 2 diabetes. |

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* Baseline risk comes from the Emerging Risk Factors Collaboration, with a median of 10.8 y of follow-up for a total of 102 international cohorts.
† Downgraded due to inconsistency ($I^2$ = 81.2%).
‡ Downgraded due to inconsistency ($I^2$ = 68.5%).
§ Downgraded due to inconsistency ($I^2$ = 74.5%).
‖ Downgraded due to inconsistency ($I^2$ = 51.0%).
¶ Downgraded due to imprecision (CI around absolute effect includes both appreciable benefit and no appreciable benefit or harm).
** Downgraded due to inconsistency ($I^2$ = 80.4%).

overall cancer incidence, and type 2 diabetes (Tables 1 and 2).

Strengths of our review include a priori–defined methods (22); a comprehensive search of 6 primary databases using a strategy developed by an expert librarian; duplicate screening of studies for eligibility, data extraction, and assessment of risk of bias; and inclusion of a large number of studies and participants. Further,

*Table 2.* Summary of Findings for Lower Adherence to Dietary Patterns High in Red and Processed Meat Intake and Risk for Cancer Incidence and Mortality

| Outcome | Studies (Participants), *n* | Follow-up, *y* | Relative Risk (95% CI) | Lifetime Population Risk per 1000 Persons* | Risk Difference per 1000 Persons (95% CI) | GRADE Certainty of Evidence | Plain-Language Summary |
|---|---|---|---|---|---|---|---|
| Breast cancer incidence | 18 (425 662) | 4 to 23 | 0.95 (0.88 to 1.02) | 46 | −2 (−6 to 1) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on breast cancer incidence. |
| Breast cancer mortality | 6 (141 480) | 6 to 34 | 1.04 (0.63 to 1.73) | 14 | 1 (−5 to 10) | Very low† | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on breast cancer mortality. |
| Colorectal cancer incidence | 16 (840 980) | 5 to 26 | 0.94 (0.85 to 1.05) | 20 | −1 (−3 to 1) | Very low‡ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on colorectal cancer incidence. |
| Colorectal cancer mortality | 7 (152 527) | 6 to 34 | 0.96 (0.76 to 1.21) | 9 | 0 (−2 to 2) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on colorectal cancer mortality. |
| Endometrial cancer incidence | 1 (53 035) | 15 | 0.99 (0.68 to 1.45) | 10 | 0 (−3 to 5) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on endometrial cancer incidence. |
| Esophageal cancer mortality | 1 (13 281) | 19 | 0.87 (0.49 to 1.54) | 6 | −1 (−3 to 3) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on esophageal cancer mortality. |
| Extrahepatic cancer incidence | 1 (50 012) | 13 | 0.41 (0.26 to 0.64) | 11 | −6 (−8 to −4) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have a very small effect on extrahepatic cancer incidence. |
| Gallbladder cancer incidence | 1 (50 012) | 13 | 0.36 (0.20 to 0.64) | 2 | −1 (−2 to −1) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have a very small effect on gallbladder cancer incidence. |
| Liver cancer incidence | 2 (not reported) | 11 | 0.79 (0.32 to 1.94) | 11 | −2 (−7 to 10) | Very low§ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on liver cancer incidence. |
| Liver cancer mortality | 1 (37 453) | 6 | 1.89 (0.88 to 4.06) | 10 | 9 (−1 to 31) | Very low§ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on liver cancer mortality. |
| Ovarian cancer incidence | 1 (53 035) | 15 | 0.87 (0.62 to 1.22) | 7 | −1 (−3 to 2) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on ovarian cancer incidence. |

*Continued on following page*

*Table 2*–Continued

| Outcome | Studies (Participants), *n* | Follow-up, *y* | Relative Risk (95% CI) | Lifetime Population Risk per 1000 Persons* | Risk Difference per 1000 Persons (95% CI) | GRADE Certainty of Evidence | Plain-Language Summary |
|---|---|---|---|---|---|---|---|
| Ovarian cancer mortality | 1 (38 755) | 34 | 0.97 (0.62 to 1.52) | 4 | 0 (−2 to 2) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on ovarian cancer mortality. |
| Overall cancer incidence | 4 (158 087) | 4 to 15 | 0.90 (0.86 to 0.94) | 185 | −18 (−26 to −11) | Very low§ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on overall cancer incidence. |
| Overall cancer mortality | 18 (467 452) | 6 to 34 | 0.89 (0.83 to 0.96) | 105 | −12 (−18 to −4) | Very low‖ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on overall cancer mortality. |
| Pancreatic cancer incidence | 3 (104 069) | 14 to 16 | 0.89 (0.45 to 1.78) | 5 | −1 (−3 to 4) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on pancreatic cancer incidence. |
| Pancreatic cancer mortality | 1 (38 755) | 34 | 0.44 (0.26 to 0.76) | 4 | −2 (−3 to −1) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have a very small effect on pancreatic cancer mortality. |
| Prostate cancer incidence | 7 (137 597) | 4 to 15 | 0.93 (0.72 to 1.19) | 38 | −3 (−11 to 7) | Low | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on prostate cancer incidence. |
| Prostate cancer mortality | 6 (76 319) | 6 to 21 | 1.02 (0.63 to 1.65) | 6 | 0 (−2 to 4) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on prostate cancer mortality. |
| Stomach cancer incidence | 2 (56 798) | 10 to 15 | 0.60 (0.25 to 1.40) | 14 | −6 (−11 to 6) | Very low§¶ | We are uncertain of the effects of lower adherence to dietary patterns high in red and processed meat intake on stomach cancer incidence. |
| Stomach cancer mortality | 8 (145 474) | 6 to 21 | 0.89 (0.71 to 1.12) | 10 | −1 (−3 to 1) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on stomach cancer mortality. |
| Uterine cancer incidence | 1 (34 164) | 6 | 1.18 (0.80 to 1.73) | 10 | 2 (−2 to 7) | Low | Lower adherence to dietary patterns high in red and processed meat intake may have little or no effect on uterine cancer incidence. |

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* Baseline risk comes from lifetime cumulative risk estimate from GLOBOCAN 2012 (28).
† Downgraded due to inconsistency ($I^2$ = 60.5%).
‡ Downgraded due to inconsistency ($I^2$ = 53.4%).
§ Downgraded due to imprecision (CI around absolute effect includes both appreciable benefit and no appreciable benefit).
‖ Downgraded due to inconsistency ($I^2$ = 69.8%).
¶ Downgraded due to inconsistency ($I^2$ = 76.6%).

we used the GRADE approach to assess the certainty of evidence and to present absolute estimates of effect for all 30 outcomes.

One of the primary limitations of our work is the heterogeneity of dietary patterns across studies. Although all patterns discriminated between participants with low and high intake of red and processed meat, other food and nutrient characteristics of dietary patterns and the quantity of red and processed meat consumed varied widely across studies. Moreover, the quantity of red and processed meat consumed differed across dietary patterns and studies. For example, one study compared 1.4 versus 3.5 servings of processed meat per week (39), whereas another compared 0.7 versus 4.9 servings per week (40). Such inconsistencies may have increased heterogeneity of meta-analyses and potentially reduced the magnitude of observed associations. Also, analyses of extreme categories of adherence may artificially inflate effect estimates and may not be indicative of effects observed at typical levels of adherence. Second, we were unable to analyze the data separately for red and processed meat because authors typically combined them or did not distinguish between them in primary studies. Third, all eligible studies used observational designs and were thus prone to confounding. Although we minimized confounding by using the most adjusted analyses from each study in our meta-analyses, residual confounding remains a plausible explanation for all associations. Finally, eligible studies used recall-based methods for dietary measurement that are prone to measurement error, which can result in either an underestimate or an overestimate of observed associations (41, 42).

Although previous reviews have reported a positive association between red and processed meat intake and all-cause mortality, cardiovascular disease, stroke, myocardial infarction, and type 2 diabetes (4, 6, 10, 11), our systematic review is, to our knowledge, the first to address dietary patterns with respect to red and processed meat consumption and to include an assessment of the certainty of evidence. The 2010 Dietary Guidelines Advisory Committee of the U.S. Department of Agriculture conducted a project that summarized the evidence on dietary patterns and their effect on health, including obesity, cardiovascular disease, and type 2 diabetes (43). In general, although some dietary patterns, such as low-carbohydrate diets, were not considered, no single dietary pattern was associated with more favorable health outcomes. However, the Mediterranean-style diet, the DASH (Dietary Approaches to Stop Hypertension) diet, and Dietary Guidelines–related patterns were consistently associated with positive health outcomes (43).

Our work complements other systematic reviews performed to address NutriRECS recommendations on red and processed meat consumption. Although we found a small to very small decrease in risk for several adverse health outcomes, the effect sizes observed in our dose-response meta-analyses that directly addressed red and processed meat were, in general, only slightly smaller (16, 17). For example, studies directly addressing meat consumption suggested that a reduction of 3 servings per week resulted in 8 (red meat) and 9 (processed meat) fewer deaths per 1000 persons (16), whereas we found 15 fewer deaths per 1000 persons among those adhering to dietary patterns lower in red and processed meat consumption. Similarly, studies directly addressing meat consumption found that a reduction of 3 servings per week may decrease lifetime risk for cancer death by 7 (red meat) and 8 (processed meat) deaths per 1000 persons (17) versus 12 deaths per 1000 persons observed in this review. If red and processed meat were causally driving the association between diet and adverse health outcomes, we would anticipate finding stronger associations in our systematic reviews specific to red and processed meat intake (14, 22), but we did not. Our findings indicate the possibility that dietary components associated with red and processed meat intake may confound its association with health outcomes. However, inferences about causality should be interpreted with caution given the low- to very-low-certainty evidence.

Because of concerns about adverse health outcomes, recent dietary guidelines recommend limiting red and processed meat intake in cultures with traditionally high red meat consumption (1, 7–9). The results of our systematic review raise concerns about these recommendations. First, we identified only low-certainty (and often very-low-certainty) evidence linking dietary patterns lower in red and processed meat intake with small reductions in adverse cardiometabolic and cancer outcomes, making causal inferences tenuous. Second, our results suggest that dietary patterns lower in red or processed meat intake are associated with a small or, in most cases, very small reduction in risk for all-cause mortality, 3 cardiometabolic outcomes, and 5 cancer outcomes. Third, our findings of stronger associations in studies of dietary patterns high in red and processed meat intake compared with studies directly addressing red and processed meat consumption suggest the possibility of confounding by other dietary characteristics correlated with red and processed meat consumption.

In conclusion, adherence to dietary patterns lower in red or processed meat intake may result in decreased risk for all-cause mortality, cardiometabolic disease and mortality, and cancer morbidity and mortality. Nevertheless, the magnitude of these effects for all outcomes is small to very small, and the certainty of evidence is low to very low. Our results therefore raise questions about the plausibility of red and processed meat being causally related to adverse health outcomes.

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**Supplementary Material***

Vernooij RWM, Zeraatkar D, Han MA, et al. Patterns of red and processed meat consumption and risk for cardiometabolic and cancer outcomes. A systematic review and meta-analysis of cohort studies. Ann Intern Med. doi:10.7326/M19-1583



* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

**Supplement Table 1. Search Strategy**

**Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present
Search Strategy:

| # | Searches |
|---|---|
| 1 | meat/ or meat products/ or red meat/ |
| 2 | ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)).tw,kf. |
| 3 | 1 or 2 |
| 4 | limit 3 to "all adult (19 plus years)" |
| 5 | middle aged.sh. or "of age".tw,kf. |
| 6 | (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers).tw,kf. |
| 7 | 5 or 6 |
| 8 | 3 and 7 |
| 9 | 4 or 8 |
| 10 | 9 not (cattle or cow or cows or herd or herds or heifer or heifers or steers or bulls or bovines or calves or broiler or broilers or chickens or chicks or drakes or ducks or pigs or piglet or piglets or sow or sows or boars or porcine or swine or ewe or ewes or sheep or rabbit or rabbits or mouse or mice or canine or canines or cats).tw,kf. |
| 11 | randomized controlled trial.pt. |
| 12 | controlled clinical trial.pt. |
| 13 | randomized.ab. |
| 14 | placebo.ab. |
| 15 | clinical trials as topic.sh. |
| 16 | randomly.ab. |
| 17 | trial.ti. |
| 18 | Epidemiologic studies/ |
| 19 | exp case control studies/ |
| 20 | case control.tw,kf. |
| 21 | exp cohort studies/ |
| 22 | (cohort adj (study or studies)).tw,kf. |
| 23 | cohort analy*.tw,kf. |
| 24 | (follow up adj (study or studies)).tw,kf. |
| 25 | observational study/ |
| 26 | (observational adj (study or studies)).tw,kf. |

| | |
|---|---|
| 27 | longitudinal.tw,kf. |
| 28 | retrospective.tw,kf. |
| 29 | Cross-sectional studies/ |
| 30 | cross sectional.tw,kf. |
| 31 | or/11-30 |
| 32 | 10 and 31 |
| 33 | remove duplicates from 32 |

**Embase Classic+Embase** 1947 to 2017 Week 19
Search Strategy:

| # | Searches |
|---|---|
| 1 | red meat/ or meat/ or beef/ or lamb meat/ or mutton/ or pork/ or rabbit meat/ or veal/ or venison/ |
| 2 | ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)).tw,kw. |
| 3 | 1 or 2 |
| 4 | limit 3 to (adult <18 to 64 years> or aged <65+ years>) |
| 5 | middle aged.sh. or "of age".tw,kw. |
| 6 | (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers).tw,kw. |
| 7 | 5 or 6 |
| 8 | 3 and 7 |
| 9 | 4 or 8 |
| 10 | 9 not (cattle or cow or cows or herd or herds or heifer or heifers or steers or bulls or bovines or calves or broiler or broilers or chickens or chicks or drakes or ducks or pigs or piglet or piglets or sow or sows or boars or porcine or swine or ewe or ewes or sheep or rabbit or rabbits or mouse or mice or canine or canines or cats).tw,kw. |
| 11 | random*.tw. or placebo*.mp. or double-blind*.tw. |
| 12 | clinical study/ |
| 13 | case control study/ |
| 14 | family study/ |
| 15 | longitudinal study/ |
| 16 | retrospective study/ |
| 17 | prospective study/ |
| 18 | randomized controlled trials/ |
| 19 | 17 not 18 |
| 20 | cohort analysis/ |

| | |
|---|---|
| 21 | (cohort adj (study or studies)).mp. |
| 22 | (case control adj (study or studies)).tw. |
| 23 | (follow up adj (study or studies)).tw. |
| 24 | (observational adj (study or studies)).tw. |
| 25 | (epidemiologic* adj (study or studies)).tw. |
| 26 | (cross sectional adj (study or studies)).tw. |
| 27 | or/11-16,19-26 |
| 28 | 10 and 27 |

**Cochrane Central Register of Controlled Trials** March 2017
Search Strategy:

| # | Searches |
|---|---|
| 1 | meat/ or meat products/ or red meat/ |
| 2 | ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)).tw,kw. |
| 3 | 1 or 2 |
| 4 | middle aged.sh. or "of age".tw,kw. |
| 5 | (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers).mp. |
| 6 | 4 or 5 |
| 7 | 3 and 6 |
| 8 | remove duplicates from 7 |

[Web of Science]
**Science Citation Index Expanded (SCI-EXPANDED) --1900-present**
**Social Sciences Citation Index (SSCI) --1956-present**
**Conference Proceedings Citation Index- Science (CPCI-S) --1990-present**
**Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) --1990-present**

| # | Searches |
|---|---|
| 20 | #19 AND #5<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 19 | #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 18 | TS=("case control" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |

| | |
|---|---|
| 17 | TS=("cross sectional" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 16 | TS=("follow up" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 15 | TS=(comparative NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 14 | TS=(cohort NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 13 | TS=(correlation* NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 12 | TS=(epidemiologic* NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 11 | TS=(evaluation NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 10 | TS=("follow up" NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 9 | TS=(longitudinal NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 8 | TS=(observational NEAR(study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 7 | TS=(prospective NEAR (study or studies))<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 6 | TS=(random* or placebo* or "double-blind" or "single blind*" or "treble blind" or "triple blind" or "cross over*" or crossover* or "clinical trial*" or "controlled trial*")<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 5 | #3 NOT #4<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 4 | TS=(cattle or cow or cows or herd or herds or heifer or heifers or steers or bulls or bovines or calves or broiler or broilers or chickens or chicks or drakes or ducks or pigs or piglet or piglets or sow or sows or boars or porcine or swine or ewe or ewes or sheep or rabbit or rabbits or mouse or mice or canine or canines or cats)<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 3 | #2 AND #1<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |
| 2 | TS=(human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers)<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |

5

| | |
|---|---|
| 1 | TS=(meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and TS=(consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)<br>Indexes=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All years |

**CINAHL**

| # | Searches |
|---|---|
| S25 | S8 AND S24 |
| S24 | S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 |
| S23 | TI (observational N1 (study or studies)) OR AB (observational N1 (study or studies)) |
| S22 | TI (cohort N1 (study or studies)) OR AB (cohort N1 (study or studies)) |
| S21 | (MH "Correlational Studies") OR (MH "Case Control Studies+") OR (MH "Cross Sectional Studies") OR (MH "Prospective Studies") OR (MH "Nonconcurrent Prospective Studies") |
| S20 | TI allocat* random* OR AB allocat* random* |
| S19 | (MH "Quantitative Studies") |
| S18 | (MH "Placebos") |
| S17 | TI placebo* OR AB placebo* |
| S16 | TI random* allocat* OR AB random* allocat* |
| S15 | (MH "Random Assignment") |
| S14 | TI (randomi* control* trial*) OR AB (randomi* control* trial*) |
| S13 | AB ( (singl* N1 blind*) or (singl* N1 mask*) ) or AB ( (doubl* N1 blind*) or (doubl* N1 mask*) ) or AB ( (tripl* N1 blind*) or (tripl* N1 mask*) ) or AB ( (trebl* N1 blind*) or (trebl* N1 mask*) ) |
| S12 | TI ( (singl* N1 blind*) or (singl* N1 mask*) ) or TI ( (doubl* N1 blind*) or (doubl* N1 mask*) ) or TI ( (tripl* N1 blind*) or (tripl* N1 mask*) ) or TI ( (trebl* N1 blind*) or (trebl* N1 mask*) ) |
| S11 | TI (clinic* N1 trial*) OR TX clinic* N1 trial*) |
| S10 | PT Clinical trial |

| | |
|---|---|
| S9 | (MH "Clinical Trials+") |
| S8 | S4 AND S7 |
| S7 | S5 OR S6 |
| S6 | TI (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers) OR AB (human or humans or adult or adults or man or men or woman or women or patient or patients or person or persons or individuals or people or controls or participant or participants or subject or subjects or volunteer or volunteers) |
| S5 | (MH "Adult") OR (MH "Aged+") OR (MH "Middle Age") OR (MH "Young Adult") |
| S4 | S1 OR S2 OR S3 |
| S3 | AB ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)) |
| S2 | TI ((meat or meats or beef or lamb or mutton or pork or sausage or sausages or bacon) and (consum* or consumption or cooked or diet or diets or dietary or eat or eaters or eating or intake or intakes)) |
| S1 | (MH "Meat") |

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| # | Search |
|---|---|
| S1 | ((((TI(meat OR meats OR beef OR lamb OR mutton OR pork OR sausage OR sausages OR bacon) AND TI(consum* OR consumption OR cooked OR diet OR diets OR dietary OR eat OR eaters OR eating OR intake OR intakes)) OR (AB(meat OR meats OR beef OR lamb OR mutton OR pork OR sausage OR sausages OR bacon) AND AB(consum* OR consumption OR cooked OR diet OR diets OR dietary OR eat OR eaters OR eating OR intake OR intakes))) AND (TI(human OR humans OR adult OR adults OR man OR men OR woman OR women OR patient OR patients OR person OR persons OR individuals OR people OR controls OR participant OR participants OR subject OR subjects OR volunteer OR volunteers) OR AB(human OR humans OR adult OR adults OR man OR men OR woman OR women OR patient OR patients OR person OR persons OR individuals OR people OR controls OR participant OR participants OR subject OR subjects OR volunteer OR volunteers))) AND (TI(("case control" OR "cross sectional" OR "follow up" OR comparative OR cohort OR correlational OR epidemiologic* OR evaluation OR "follow up" OR longitudinal OR observational OR prospective) NEAR/5 (study OR studies)) OR AB(("case control" OR "cross sectional" OR "follow up" OR comparative OR cohort OR correlational OR epidemiologic* OR evaluation OR "follow up" OR longitudinal OR observational OR prospective) NEAR/5 (study OR studies)) OR TI(random* OR placebo* OR "double-blind" OR "single blind*" OR "treble blind" OR "triple blind" OR "cross over*" OR crossover* OR "clinical trial*" OR "controlled trial*") OR AB(random* OR placebo* OR "double-blind" OR "single blind*" OR "treble blind" OR "triple blind" OR "cross over*" OR crossover* OR "clinical trial*" OR "controlled trial*"))) NOT (TI(cattle OR cow OR cows OR herd OR herds OR heifer OR heifers OR steers OR bulks OR bovines OR calves OR broiler OR broilers OR chickens OR chicks OR drakes OR ducks OR pigs OR piglet OR piglets OR sow OR sows OR boars OR porcine OR swine OR |

| # | Search |
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| | ewe OR ewes OR sheep OR rabbit OR rabbits OR mouse OR mice OR canine OR canines OR cats) OR AB(cattle OR cow OR cows OR herd OR herds OR heifer OR heifers OR steers OR bulks OR bovines OR calves OR broiler OR broilers OR chickens OR chicks OR drakes OR ducks OR pigs OR piglet OR piglets OR sow OR sows OR boars OR porcine OR swine OR ewe OR ewes OR sheep OR rabbit OR rabbits OR mouse OR mice OR canine OR canines OR cats)) |

**Supplement Table 2. Baseline Characteristics of the Identified Articles**

| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Whichelow *et al.* (1996) | Health and Lifestyle survey | UK | 8 | 9003 | NR | 55 | Healthy | Principal component analysis | Dietary component 1 | NR | NR | NR | NR | 0.01 to 0.36 |
| Hu *et al.* (2000) | Health Professionals Follow-up Study | USA | 8 | 44875 | 53,8 | 0 | Healthy | Factor analysis | Western | NR | 0,1 vs 0,7 servings of times/day | NR | 0,2 vs 1 servings or times/day | 0,59 to 0,63 |
| Fung *et al.* (2001) | Nurses' Health Study | USA | 12 | 69017 | 50 | 100 | Healthy | Factor analysis | Western | NR | 0,1 vs 0,6 servings or times/day | NR | 0,3 to 1 servings or times/day | 0,56 |
| Terry *et al.* (2001) | Swedish Mammography Screening Cohort | Sweden | 10 | 61463 | 53 | 100 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,58 |
| van Dam *et al.* (2002) | Health Professionals Follow-up Study | USA | 12 | 42504 | 53,5 | 0 | Healthy | Factor analysis | Western | NR | 0,1 vs 0,7 servings or times/day | NR | 0,4 vs 0,9 servings or times/day | 0,60 to 0,67 |
| Fung *et al.* (2003) | Nurses' Health Study | USA | 12 | 76399 | NR | 100 | Healthy | Factor analysis | Western | NR | 0,1 vs 0,6 servings or times/day | NR | 0,3 vs 0,9 servings or times/day | 0,52 to 0,61 |
| Masaki *et al.* (2003) | Health Insurance Society of Tokyo Stockbrokerage | Japan | 10 | 5644 | 51,3 | 0 | Healthy | Principal component analysis | Meat | NR | NR | NR | NR | 0.26 to 0.52 |
| Dixon *et al.* (2004) | Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, the Netherlands Cohort Study on Diet and Cancer, and Swedish Mammography Cohort | Finland, the Netherlands, Sweden | 7 and 15 | 27111 and 120852 and 61463 | 57,2 and 61,4 and 53,7 | 0 and 51,8 and 100 | Healthy | Factor analysis | Pork, Processed Meats, Potatoes | NR | NR | NR | NR | 0,07 vs 0,60 |

| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Fung *et al.* (2004) | Nurses' Health Study | USA | 14 | 69554 | NR | 100 | Healthy | Factor analysis | Western | NR | 0,1 vs 0,6 servings or times/day | NR | 0,3 vs 1,0 servings or times/day | NR |
| Fung *et al.* (2004) | Nurses' Health Study | USA | 14 | 71768 | NR | 100 | Healthy | Factor analysis | Western | NR | 0,1 vs 0,6 servings of times/day | NR | 0,3 vs 1,0 servings or times/day | 0,56 to 0,61 |
| Sieri *et al.* (2004) | ORDET cohort | Italy | 10 | 8894 | NR | 100 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,30 to 0,46 |
| Tseng *et al.* (2004) | United States Health Examination Epidemiological Follow-up Study | USA | 7,6 | 3379 | NR | 0 | Healthy | Principal component analysis | Red meat-starch | NR | NR | NR | NR | 0.22 to 0.40 |
| Michaud *et al.* (2005) | Health Professionals Follow-Up Study and Nurses' Health Study | USA | 14 and 16 | 47493 and 77179 | 54,3 and 50,8 | 0 and 100 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,53 to 0,64 |
| Velie *et al.* (2005) | Breast Cancer Detection Demonstration Project | USA | 8 | 40559 | 62 | 100 | Healthy | Principal component analysis | Beef/pork-starch | NR | NR | NR | NR | 0,25 to 0,46 |
| Wu *et al.* (2006) | Health Professionals Follow-up Study | USA | 14 | 47725 | 54 | 0 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,60 to 0,66 |
| Cai *et al.* (2007) | Shanghai Women's Health Study | China | 5,7 | 74942 | 52,2 | 100 | Healthy | Principal component analysis | Meat-rich | NR | NR | NR | NR | 0.30 to 0.42 |
| Drogan *et al.* (2007) | European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort | Germany | 6 | 26238 | 50,3 | 61,4 | Healthy | Reduced Rank Regression | Food pattern score | NR | 37,7 vs 94,8 g/day | NR | 26,3 vs 63,8 g/day | NR |
| Harriss *et al.* (2007) | Melbourne Collaborative Cohort Study | Australia | 10 | 40653 | 54,6 | 59 | Healthy | Factor analysis | Meat | NR | NR | NR | NR | 0,29 to 0,40 |

| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Hodge *et al.*(2007) | Melbourne Collaborative Cohort Study | Australia | 4 | 36787 | 54,3 | 52,5 | Healthy | Factor analysis | Factor 3 | NR | NR | NR | NR | 0.20 to 0.41 |
| Masala *et al.* (2007) | European Prospective Investigation into Cancer and Nutrition | Italy | 6 | 5611 | 62,3 | 72,6 | Healthy | Factor analysis | Pasta and meat | NR | NR | NR | NR | 0,43 to 0,61 |
| Sant *et al.* (2007) | ORDET (Hormones and Diet in Etiology of Tumors (cohort) | Italy | 12 | 8861 | NR | 100 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,30 to 0,46 |
| Brunner *et al.* (2008) | Whitehall II study | UK | 15 | 7731 | 50 | 30,3 | Healthy | Cluster analysis | Healthy vs Unhealthy | NR | NR | NR | 75 vs 117 g/10 mJ | NR |
| Butler *et al.* (2008) | Singapore Chinese Health Study | Singapore | 10 | 61321 | NR | NR | Healthy | Principal component analysis | Meat- dim sum | NR | NR | NR | 5 vs 74 g/day | 0,33 to 0,40 |
| Flood *et al.* (2008) | National Institutes of Health-AARP Diet and Health Study | USA | 5 | 492382 | 62,2 | 40,4 | Healthy | Factor analysis | Factor 3 | NR | NR | NR | NR | 0,30 to 0,36 |
| Fung *et al.* (2008) | Nurses' Health Study | USA | 24 | 88517 | NR | 100 | Healthy | Index or scoring system | DASH | NR | NR | 0,5 vs 1 servings or times/day | NR | NR |
| Heidemann *et al.* (2008) | Nurses' Health Study | USA | 18 | 72113 | NR | 100 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,55 to 0,62 |
| Nettleton *et al.* (2008) | Multi-Ethnic Study of Atherosclerosis (MESA) | USA | 7 | 5011 | 61,7 | 47,4 | Healthy | Principal component analysis | Beans, tomatoes, and refined grains | NR | NR | NR | NR | 0,42 |
| Schulz *et al.* (2008) | European Prospective Investigation into Cancer rand Nutrition (EPIC)-Potsdam | Germany | 6 | 15351 | 49,0 | 100 | Healthy | Reduced rank regression | Simplified food pattern score | NR | 40,1 vs 76,6 g/day | NR | NR | NR |

| Study characteristics | | | Patient characteristics | | | | | Dietary pattern method | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Agurs-Collins *et al.* (2009) | Black Women's Health Study | USA | 12 | 50778 | 38,5 | 100 | Healthy | Factor analysis | Western | NR | 1 vs 5 servings/week | NR | NR | 0.62 |
| Cottet *et al.* (2009) | E3N-EPIC Cohort | France | 10 | 65374 | 53 | 100 | Healthy | Principal component analysis | Alcohol/Western | NR | NR | NR | NR | 0,31 to 0,59 |
| McNaughton *et al.* (2009) | Whitehall II study | UK | 15 | 7314 | NR | NR | Healthy | Reduced rank regression | Dietary pattern 2 | NR | NR | NR | 33,4 vs 60,9 g/day | 0,24 |
| Muller *et al.* (2009) | Melbourne Collaborative Cohort Study | Australia | 14 | 14627 | NR | 0 | Healthy | Factor analysis | Meat & Potatoes | NR | NR | NR | NR | 0,28 to 0,39 |
| Nettleton *et al.* (2009) | Multi-Ethnic Study of Atherosclerosis (MESA) | USA | 5 | 5316 | 61,3 | 53,0 | Healthy | Principal component analysis | Fats and processed meat pattern | NR | NR | NR | NR | 0,42 to 0,63 |
| Panagiotakos *et al.* (2009) | ATTICA study | Greece | 5 | 3042 | 45,4 | 55,5 | Mix (including hypertension & hypercholesterolemia patients) | Principal component analysis | Meat (red), pork, and margarine | NR | NR | NR | NR | 0,45 |
| Butler *et al.* (2010) | Singapore Chinese Health Study | Singapore | 11 | 34208 | 55 | 100 | Healthy | Principal component analysis | Meat-dim sum | NR | 0,06 vs 1,7 g/1000 kcal | NR | 11 vs 22 g/1000 kcal | 38 |
| Erber *et al.* (2010) | Multiethnic Cohort | USA | 14 | 75512 | NR | 52 | Healthy | Factor analysis | Fat and meat | NR | NR | NR | NR | 0.72 to 0.83 |
| Fung *et al.* (2010) | Nurses' Health Study and Health Professionals' Follow-Up study | USA | 20 and 26 | 85168 and 44548 | NR | 100 and 0 | Healthy | Index or scoring system | Animal low carbohydrate score | NR | NR | 0,5 vs 1,3 (female) and 0,3 vs 1,3 (male) servings of times/day | NR | NR |

| Study characteristics | | | | Patient characteristics | | | | | Dietary pattern method | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Héroux *et al.* (2010) | Aerobics Center Longitudinal Study | USA | 16 | 13621 | 47 | 24,3 | Healthy | Reduced rank regression | Unhealthy eating index | NR | NR | NR | NR | 0,25 to 0,50 |
| Pham *et al.* (2010) | Japan Collaborative Cohort Study | Japan | 15 | 63403 | 55,9 | 59,4 | Healthy | Factor analysis | Animal food | NR | NR | NR | NR | 0,35 to 0,57 |
| Anderson *et al.* (2011) | Health, Aging, and Body Composition Study | USA | 8 | 3075 | 74,1 | 52 | Healthy | Cluster analysis | Healthy foods vs Meat, fried foods, and alcohol vs refined grains | NR | 4.1% of total energy intake | NR | NR | NR |
| de Koning *et al.* (2011) | Health Professionals Follow-Up Study | USA | 20 | 40475 | NR | 0 | Healthy | Index or scoring system | Low-carbohydrate, high animal protein and fat score | NR | 0,2 vs 0,5 servings or times/day | 0,5 vs 1,5 servings or times/day | 0,3 vs 1 servings or times/day | NR |
| Bao *et al.* (2012) | Nurses' Health Study | USA | 12 | 55540 | 59,8 | 100 | Healthy | Index or scoring system | 'I eat anything I want, anytime I want' | NR | 0,07 vs 0,08 servings/day/1000 kcal | NR | 0,58 vs 0,64 servings/day/1000 kcal | NR |
| Fung *et al.* (2012) | Nurses' Health Study | USA | 20 | 66714 | NR | 100 | Healthy | Reduced rank regression | C-peptide dietary pattern | NR | NR | NR | 0,42 to 0,83 servings or times/day | NR |
| Fung *et al.* (2012) | Nurses' Health Study | USA | 22 | 67802 | NR | 100 | Healthy | Index or scoring system | Estrogen food pattern | NR | NR | NR | 0,3 vs 0,9 servings or times/day | NR |
| Guallar-Castillón *et al.* (2012) | European Prospective Investigation into cancer and Nutrition (EPIC)-Spain | Spain | 11 | 40757 | NR | 62.3 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,48 to 0,57 |
| Nilsson *et al.* (2012) | Västerbotten Intervention Program | Sweden | 10 | 77319 | NR | 51,3 | Healthy | Index or scoring system | Traditional Sami diet score | NR | NR | NR | 44.6 vs 77.6 (men) and 35.3 vs 54.4 g/day | NR |

| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Akbaraly *et al.* (2013) | Whitehall II cohort study | UK | 16 | 5350 | 51,3 | 29,4 | Healthy | Principal component analysis | Western | NR | NR | NR | NR | 0,41 to 0,52 |
| Chan *et al.* (2013) | - | China | 6 | 2735 | 72 | 51 | Healthy | Factor analysis | Meat-fish | NR | NR | NR | NR | 0,50 |
| Chen *et al.* (2013) | Health Effects of Arsenic Longitudinal Study (HEALS) | Bangladesh | 7 | 11116 | NR | NR | Healthy | Principal component analysis | Animal protein | NR | NR | NR | NR | 0,45 |
| Granic *et al.* (2013) | Swedish Twin Registry | Sweden | 27 | 12830 | 55 | 56,6 | Healthy | Cluster analysis | Low meat intake vs Moderate intake diet with low flour-based food | NR | NR | NR | NR | 0,32 to 0,97 |
| Kappeler *et al.* (2013) | Third National Health and Nutrition Examination Survey (NHANES III) | USA | 22 | 17611 | 41,4 | 53,2 | Healthy | Index or scoring system | HEI | NR | 3,2 vs 8,2 (men) and 1,0 vs 3,7 times/month | NR | 10,4 vs 16,4 (men) and 7,9 vs 13 times/month | NR |
| Link *et al.* (2013) | California Teachers Study cohort | USA | 14 | 91779 | 50 | 100 | Healthy | High-protein, high-fat | Factor analysis | NR | NR | NR | NR | 0,49 to 0,52 |
| Maruyama *et al.* (2013) | Japan Collaborative Cohort (JACC) study | Japan | 13 | 64037 | NR | 58,5 | Healthy | Factor analysis | Animal food | NR | NR | NR | NR | 0,34 to 0,53 |
| Ruano *et al.* (2013) | Seguimiento Universidad de Navarra (SUN) cohort) | Spain | 4 | 11128 | 40 | 54 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,58 |
| Zhang *et al.* (2013) | Shanghai Women's Health Study and Shanghai Men's Health study | China | 11 | NR | NR | 0 and 100 | Healthy | Factor analysis | Meat-based | NR | NR | NR | NR | 0,30 to 0,42 |

| Study characteristics | | | | Patient characteristics | | | | | Dietary pattern method | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| George *et al.* (2014) | Women's Health Initiative Observational Study | USA | 13 | 63805 | 62,8 | 100 | Healthy | Index | DASH | NR | 0,1 vs 0,4 servings or times/day | NR | 0,3 vs 0,9 servings or times/day | NR |
| Kumagai *et al.* (2014) | Ohsaki National Health Insurance Cohort Study | Japan | 11 | 44097 | 59,9 | 52,2 | Healthy | Factor analysis | Animal Food | NR | NR | NR | NR | 0,48 to 0,56 |
| Odegaard *et al.* (2014) | Singapore Chinese Health Study | Singapore | 18 | 52584 | 55,8 | 55,9 | Healthy | Principal component analysis | Dim Sum- and meat-rich | NR | NR | NR | 11,9 vs 26,2 g/1000 kcal | NR |
| Pastorino *et al.* (2014) | National Survey of Health and Development (NSHD) | UK | 34 | 1804 | 36 | 52,6 | Healthy | Reduced rank regression | High fat, high GI, low fiber | NR | NR | NR | NR | 0,1 to 0,2 |
| Yu *et al.* (2014) | Shanghai Men's Health Study and Shanghai Women's Health Study | China | 7 and 12 | 61239 and 73216 | 55,35 and 52,6 | 0 and 100 | Healthy | Index or scoring system | Chines Food Pagoda | NR | NR | NR | 46 vs 91 and 43 vs 83 g/day | NR |
| Yu *et al.* (2014) | Shanghai Men's Health Study and Shanghai Women's Health Study | China | 7 and 12 | 61239 and 73216 | NR | 0 and 100 | Healthy | Index or scoring system | Chinese Food Pagoda | NR | NR | NR | 46 vs 91 (men) and 43 vs 83 (women) g/day | NR |
| Zazpe *et al.* (2014) | Seguimiento Universidad de Navarra (SUN) Project | Spain | 7 | 16008 | 38,1 | 60 | Healthy | Factor analysis | Western | 52.5 vs 103.5 g/day | 28.0 vs 59.4 g/day | NR | NR | 0.47 to 0.50 |
| Boggs *et al.* (2015) | Black Women's Health study | USA | 16 | 37001 | NR | 100 | Healthy | Index or scoring system | DASH | NR | NR | 0,05 vs 1,7 servings or times/day | NR | NR |
| Catsburg *et al.* (2015) | Canadian Study of Diet, Lifestyle and Health and National Breast Screening Study | Canada | 12 and 23 | 39532 and 49410 | 67 | 100 | Healthy | Principal component analysis | Meat and potatoes | NR | NR | NR | NR | 0,09 to 0,50 |
| Lacoppidan *et al.* (2015) | Danish Diet, Cancer and Health cohort | Denmark | 15 | 55060 | 56 | 52,6 | Healthy | Index or scoring system | Healthy Nordic Food Index | NR | 17 vs 18 (women) and 33 vs 36 (men) g/day | NR | 59 vs 67 (women) and 93 vs 105 (men) g/day | NR |

| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Larsson *et al.* (2015) | Cohort of Swedish Men | Sweden | 10 | 11450 | 61 | 0 | History of hypertension, high cholesterol levels, diabetes, heart failure, or atrial fibrillation at baseline | Index or scoring system | Healthy lifestyle factors | NR | 17 vs 47 g/day | NR | NR | NR |
| Martinez-González *et al.* (2015) | PREvencion con DIeta MEDiterranea trial (PREDIMED) | Spain | 4 | 7216 | 67 | 57,4 | Type 2 diabetes or 3 or more cardiovascular risk factors | Principal component analysis | Western | NR | 1,8 vs 16,2 g/day | NR | 30,8 vs 72,2 g/day | 0,45 to 0,55 |
| Roswall *et al.* (2015) | Swedish Women's Lifestyle and Health Cohort | Sweden | 21 | 44961 | 39 | 100 | Healthy | Index or scoring system | Healthy Nordic food index score | NR | 21,6 vs 29,2 g/day | NR | 41,3 vs 52,1 g/day | NR |
| Shikany *et al.* (2015) | Reasons for Geographic and Racial Differences in Stroke (REGARDS) | USA | 6 | 17418 | NR | 55 | >50% suffers from hypertension and dyslipidemia. | Factor analysis | Southern | NR | NR | NR | NR | 0,26 to 0,45 |
| Akinyemiju *et al.* (2016) | The Reasons for Geographic and racial Differences in Stroke (REGARDS) Cohort | USA | 10 | 22041 | NR | NR | Healthy | Factor analysis | Convenience | NR | NR | NR | NR | 0,25to 0,45 |
| Bao *et al.* (2016) | Nurses' Health Study II Cohort | USA | 20 | 4502 | 38,0 | 100 | Women with a history of gestational diabetes mellitus | Index or scoring system | Overall low carbohydrate diet | NR | NR | NR | 0.8 vs 1.3 servings or times/day | NR |
| Nobbs *et al.* (2016) | Australian Longitudinal Study of Ageing (ALSA) | Australia | 8 | 2087 | NR | 50,5 | Healthy | Factor analysis | Red meat and protein alternatives | NR | NR | NR | NR | 0,51 |

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| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Larsson *et al.* (2016) | Cohort of Swedish Men and the Swedish Mammography Cohort | Sweden | 12 | 74404 | 60,2 | 46,3 | Healthy | Index or scoring system | Modified DASH score | NR | NR | 1,0 vs 1,4 servings or times/day | NR | NR |
| Moskal *et al.* (2016) | European Prospective Investigation into Cancer and Nutrition (EPIC) study) | 10 European countries | 11 | 477312 | 51,5 | 70,2 | Healthy | Principal component analysis | PC1 | NR | 13 vs 48 g/day | NR | 31 vs 51 g/day | NR |
| Okada *et al.* (2016) | The Japan Collaborative Cohort Study | Japan | 19 | 26562 | 56 | 0 | Healthy | Factor analysis | Animal Food | NR | NR | NR | NR | 0,34 to 0,53 |
| Shin *et al.* (2016) | Japan Public Health Center-based Prospective Study | Japan | 15 | 49552 | 57,3 | 100 | Healthy | Factor analysis | Western | NR | NR | NR | NR | 0,35 to 0,48 |
| Vargas *et al.* (2016) | Women's Health Initiative Observational Study | USA | 12 | 78273 | 63 | 100 | Healthy | Index or scoring system | AHEI 2010 and DASH | NR | 0,1 vs 0,4 servings or times/day | NR | 0,3 vs 0,9 servings/day | NR |
| Kojima *et al.* (2017) | Japan Collaborative Cohort Study | Japan | 17 | 23172 | 55,9 | 100 | Healthy | Factor analysis | Animal Food pattern | NR | NR | NR | NR | 0.40 to 0.52 |
| Larsson *et al.* (2017) | Swedish Mammography Cohort and Cohort of Swedish Men | Sweden | 13 | 32588 and 43426 | 60,6 | 0 and 100 | Healthy | Index or scoring system | mDASH diet and mMED diet | NR | NR | 1,1 vs 1,3 servings or times/day | NR | NR |
| Lv *et al.* (2017) | The China Kadoorie Biobank (CKB) study | China | 7 | 461211 | 50,7 | 59,0 | Healthy | Index | Less than daily fruit and vegetables, daily meat | NR | NR | NR | 1 vs 6 servings or times/week | NR |
| Mehta *et al.* (2017) | Health Professionals Follow-up Study and Nurses' Health Study | USA | 26 and 32 | 51529 and 121700 | 56,3 and 61,2 | 0 and 100 | Healthy | Principal component analysis | Western | 0,25 vs 0,94 and 0,31 vs 0,76 servings or times/day | 0,07 vs 0,54 and 0,09 vs 0,4 servings or times/day | NR | NR | NR |

| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Mertens *et al.* (2017) | Caerphilly Prospective Study | UK | 17 | 1838 | 56,7 | 0 | Mix (frequent hypertensive) | Factor analysis | Dietary Pattern 2 | NR | NR | NR | NR | 0.26 to 0.29 |
| Mirmiran *et al.*(2017) | Tehran Lipid and Glucose Study (TLGS) | Iran | 5 | 2276 | 38,2 | 57,2 | Healthy | Principal component analysis | Traditional | NR | NR | NR | NR | 0,3 |
| Kane-Diallo *et al.* (2018) | NutriNet-Santé | France | 4 | 42544 | 56,9 | 72,7 | Healthy | Index | Pro plant-based dietary score | NR | NR | 60,9 vs 94,9 g/day | NR | NR |
| Nazari *et al.* (2018) | Multi-Ethnic Study of Atherosclerosis | Iran | 5 | 5468 | 61,7 | 45,6 | Healthy | Principal component analysis | PCR1 | NR | NR | NR | NR | 0.48 |
| **Studies comparing vegetarian versus non-vegetarian dietary patterns** | | | | | | | | | | | | | | |
| Thorogood *et al.* (1994) | Oxford Vegetarian study | UK | 12 | 11130 | 38,7 | 62,1 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Key *et al.* (1996) | Health Food Shoppers study | UK | 17 | 10771 | 45,8 | 59.7 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Mann *et al.* (1997) | Oxford Vegetarian study | UK | 13 | 10802 | 34 (men) and 33 (women) | 62.0 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Key *et al.* (1999) | Adventist Mortality Study, Health Food Shopper Study, Adventist Health Study, German Vegetarian Study, Oxford Vegetarian Study | USA, UK, Germany | 6 - 18 | 24538, 9878, 28952, 17457, and 11047 | NR | 63.4, 59.7, 57.8, 55.4, and 62.2 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |

| Study characteristics | | | | Patient characteristics | | | | Dietary pattern method | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Fraser *et al.* (1999) | Adventist Health Study | USA | 6 | 34198 | 54,2 | 59,5 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Sanjoaquin *et al.* (2004) | Oxford Vegetarian Study | UK | 17 | 10998 | 33 | 62,2 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Chang-Claude *et al.* (2005) | German Vegetarian Study | Germany | 21 | 1904 | NR | 55.0 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Vang *et al.* (2008) | Adventist Mortality Study, Adventist Health Study | USA | 17 | 8401 | 64,5 | 38,4 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Key *et al.* (2009) | European Prospective Investigate into Cancer and Nutrition – Oxford | UK | 15 | 64234 | NR | 76,0 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Cade *et al.* (2010) | UK Women's Cohort Study | UK | 9 | 33725 | 52,6 | 100 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Tantamango-Bartley *et al.* (2013) | Adventist Health Study 2 | USA | 4 | 69120 | NR | NR | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Crowe *et al.* (2013) | European Prospective Investigate into Cancer and Nutrition-Oxford | UK | 12 | 44561 | 44,4 | 76,2 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Orlich *et al.* (2013) | Adventist Health Study 2 | USA | 6 | 73308 | 56,9 | 65,8 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Tonstad *et al.* (2013) | Adventist Health Study 2 | USA | 2 | 41387 | 57,9 | 63,3 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |

| Study characteristics | | | | Patient characteristics | | | | | Dietary pattern method | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Name of cohort | Country | Duration of follow-up (years) | Number of eligible participants at baseline | Age at baseline (years) | Proportion female (%) | Healthy population / patient population | Dietary pattern method | Name of dietary pattern | Quantity of unprocessed red meat intake | Quantity of processed meat intake | Quantity of mixed red meat intake | Quantity of unspecified red meat intake | Factor loadings |
| Key *et al.* (2014) | Oxford Vegetarian Study, European Prospective Investigate into Cancer and Nutrition-Oxford | UK | 15 | 61647 | 44,0 | 74,7 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Soret *et al.* (2014) | Adventist Health Study 2 | USA | 6 | 73308 | 56,8 | 67,8 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Orlich *et al.* (2015) | Adventist Health Study 2 | USA | 7 | 77659 | 57,1 | 64,9 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Appleby *et al.* (2016) | Oxford Vegetarian Study, European Prospective Investigate into Cancer and Nutrition-Oxford | UK | 34 | 60310 | 43,5 | 75,3 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Tantamango-Bartley *et al.* (2016) | Adventist Health Study 2 | USA | 8 | 27188 | NR | NR | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |
| Rada-Fernandez de Jauregui *et al.* (2018) | UK Women's Cohort Study | UK | 17,2 | 31681 | 52,0 | 100 | Healthy | Vegetarian vs non-vegetarian | NR | NR | NR | NR | NR | NR |

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**Studies comparing vegetarian versus non-vegetarian dietary patterns**

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**Supplement Table 3. Risk of Bias of the Included Studies**

| Reference | Outcome | 1. Was selection of exposed and non-exposed cohorts drawn from the same population? | 2. Can we be confident in the assessment of exposure? | 3. Can we be confident that the outcome of interest was not present at start of study? | 4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | 5. Can we be confident in the assessment of the presence or absence of prognostic factors? | 6. Can we confident in the assessment of outcome? | 7. Was the follow-up of cohorts adequate? |
|---|---|---|---|---|---|---|---|---|
| Thorogood *et al.* (1994) | All-cause mortality | Definitely no | Definitely no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular mortality | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| | Cancer | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Key *et al.* (1996) | All-cause mortality | Probably yes | Definitely no | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Probably yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Fatal stroke | Probably yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Probably yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Whichelow *et al.* (1996) | All-cause mortality | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Mann *et al.* (1997) | All-cause mortality | Definitely no | Definitely no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular mortality | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Fraser *et al.* (1999) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular disease | Definitely yes | Probably yes | Probably no | Definitely no | Probably yes | Definitely yes | Definitely yes |
| | Cancer | Definitely yes | Probably yes | Probably no | Definitely no | Definitely yes | Definitely yes | Definitely yes |
| Key *et al.* (1999) | All-cause mortality | Probably yes | Definitely no | Definitely yes | Probably yes | Probably yes | Probably yes | Probably yes |
| | Cardiovascular mortality | Probably yes | Definitely no | Definitely yes | Probably no | Probably yes | Definitely yes | Probably yes |
| | Fatal strokes | Probably yes | Definitely no | Definitely yes | Probably no | Probably yes | Definitely yes | Probably yes |
| | Cancer | Probably yes | Definitely no | Definitely yes | Probably no | Probably yes | Definitely yes | Probably yes |
| Hu *et al.* (2000) | Cardiovascular disease | Definitely yes | Probably yes | Definitely yes | Probably no | Probably yes | Definitely yes | Definitely yes |
| Fung *et al.* (2001) | Cardiovascular disease | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Terry *et al.* (2001) | Cancer | Definitely yes | Definitely no | Definitely yes | Definitely no | Definitely yes | Definitely yes | Probably yes |
| van Dam *et al.* (2002) | Type II diabetes | Definitely yes | Definitely yes | Definitely yes | Probably yes | Definitely yes | Probably yes | Definitely yes |
| Fung *et al.* (2003) | Cancer | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Masaki *et al.* (2003) | Cancer | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Dixon *et al.* (2004) | Cancer | Probably yes | Definitely no | Probably no | Definitely no | Probably yes | Definitely yes | Probably yes |
| Fung *et al.* (2004) | Type II diabetes | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes | Probably yes |
| Fung *et al.* (2004) | All stroke | Definitely yes | Definitely yes | Probably yes | Probably no | Definitely yes | Probably yes | Probably yes |
| Sanjoaquin *et al.* (2004) | Cancer | Definitely yes | Probably no | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |

| Reference | Outcome | 1. Was selection of exposed and non-exposed cohorts drawn from the same population? | 2. Can we be confident in the assessment of exposure? | 3. Can we be confident that the outcome of interest was not present at start of study? | 4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | 5. Can we be confident in the assessment of the presence or absence of prognostic factors? | 6. Can we confident in the assessment of outcome? | 7. Was the follow-up of cohorts adequate? |
|---|---|---|---|---|---|---|---|---|
| Sieri *et al.* (2004) | Cancer | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Tseng *et al.* (2004) | Cancer | Definitely yes | Probably no | Probably yes | Probably no | Definitely yes | Definitely yes | Definitely no |
| Chang-Claude *et al.* (2005) | All-cause mortality | Definitely no | Definitely no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Fatal stroke | Definitely no | Definitely no | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Definitely no | Definitely no | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes |
| Michaud *et al.* (2005) | Cancer | Definitely yes | Definitely yes | Definitely yes | Probably no | Definitely yes | Probably yes | Probably yes |
| Velie *et al.* (2005) | Cancer | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes |
| Wu *et al.* (2006) | Cancer | Definitely yes | Definitely no | Definitely yes | Probably yes | Definitely yes | Probably yes | Probably yes |
| Cai *et al.* (2007) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Probably yes | Definitely yes |
| | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Probably no | Definitely yes |
| | Fatal stroke | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Probably no | Definitely yes |
| | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Probably no | Definitely yes |
| Drogan *et al.* (2007) | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Non-fatal heart disease | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Harriss *et al.* (2007) | Cardiovascular mortality | Definitely yes | Definitely no | Definitely no | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular disease | Definitely yes | Definitely no | Definitely no | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Hodge *et al.*(2007) | Type II diabetes | Definitely yes | Definitely no | Definitely yes | Definitely no | Definitely yes | Probably yes | Probably yes |
| Masala *et al.* (2007) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Sant *et al.* (2007) | Cancer | Definitely yes | Definitely no | Probably no | Probably no | Definitely yes | Definitely yes | Probably yes |
| Brunner *et al.* (2008) | All-cause mortality | Probably yes | Definitely no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Probably yes | Definitely no | Probably no | Probably no | Definitely yes | Definitely yes | Probably yes |
| | Cancer | Probably yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Type II diabetes | Probably yes | Definitely no | Probably yes | Probably no | Definitely yes | Probably yes | Probably yes |
| Butler *et al.* (2008) | Cancer | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| Flood *et al.* (2008) | Cancer | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Fung *et al.* (2008) | Cardiovascular mortality | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | All stroke | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes | Definitely yes |
| | Cardiovascular disease | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes | Definitely yes |

| Reference | Outcome | 1. Was selection of exposed and non-exposed cohorts drawn from the same population? | 2. Can we be confident in the assessment of exposure? | 3. Can we be confident that the outcome of interest was not present at start of study? | 4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | 5. Can we be confident in the assessment of the presence or absence of prognostic factors? | 6. Can we confident in the assessment of outcome? | 7. Was the follow-up of cohorts adequate? |
|---|---|---|---|---|---|---|---|---|
| | Non-fatal heart disease | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes | Definitely yes |
| Heidemann *et al.* (2008) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Nettleton *et al.* (2008) | Type II diabetes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| Schulz *et al.* (2008) | Cancer | Definitely yes | Probably yes | Probably yes | Probably no | Probably yes | Probably yes | Probably no |
| Vang *et al.* (2008) | Type II diabetes | Definitely yes | Definitely no | Probably yes | Probably no | Definitely yes | Definitely no | Probably no |
| Agurs-Collins *et al.* (2009) | Cancer | Definitely yes | Probably yes | Probably no | Probably yes | Definitely yes | Definitely yes | Probably no |
| Cottet *et al.* (2009) | Cancer | Definitely yes | Probably no | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| Key *et al.* (2009) | All-cause mortality | Definitely no | Definitely no | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular mortality | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| | Fatal stroke | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| | Cancer | Definitely no | Definitely no | Definitely yes | Definitely no | Definitely yes | Definitely yes | Probably yes |
| McNaughton *et al.* (2009) | Cardiovascular disease | Definitely yes | Definitely no | Probably yes | Probably no | Definitely yes | Definitely yes | Probably no |
| Muller *et al.* (2009) | Cancer | Definitely yes | Definitely no | Definitely yes | Probably yes | Probably no | Definitely yes | Probably yes |
| Nettleton *et al.* (2009) | Cardiovascular disease | Definitely yes | Definitely yes | Probably yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Panagiotakos *et al.* (2009) | Cardiovascular disease | Definitely yes | Definitely yes | Probably yes | Probably yes | Definitely yes | Definitely yes | Definitely no |
| Butler *et al.* (2010) | Cancer | Definitely yes | Probably no | Definitely yes | Definitely no | Probably yes | Definitely yes | Definitely yes |
| Cade *et al.* (2010) | Cancer | Definitely yes | Probably yes | Probably yes | Definitely no | Definitely yes | Definitely yes | Probably yes |
| Erber *et al.* (2010) | Type II diabetes | Definitely yes | Definitely no | Probably yes | Definitely yes | Probably yes | Probably yes | Probably no |
| Fung *et al.* (2010) | All-cause mortality | Definitely yes | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Definitely yes | Definitely yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Definitely yes | Definitely yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Héroux *et al.* (2010) | All-cause mortality | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular mortality | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Pham *et al.* (2010) | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Anderson *et al.* (2011) | All-cause mortality | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably no |
| de Koning *et al.* (2011) | Type II diabetes | Definitely yes | Definitely yes | Probably yes | Probably yes | Probably yes | Probably yes | Definitely yes |
| Bao *et al.* (2012) | Cancer | Definitely yes | Definitely no | Probably yes | Definitely yes | Definitely yes | Probably no | Definitely yes |

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| Reference | Outcome | 1. Was selection of exposed and non-exposed cohorts drawn from the same population? | 2. Can we be confident in the assessment of exposure? | 3. Can we be confident that the outcome of interest was not present at start of study? | 4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | 5. Can we be confident in the assessment of the presence or absence of prognostic factors? | 6. Can we confident in the assessment of outcome? | 7. Was the follow-up of cohorts adequate? |
|---|---|---|---|---|---|---|---|---|
| Fung *et al.* (2012) | Cancer | Definitely yes | Definitely no | Probably yes | Definitely yes | Definitely yes | Probably yes | Probably no |
| Fung *et al.* (2012) | Cancer | Definitely yes | Definitely yes | Probably yes | Definitely no | Definitely yes | Probably yes | Probably yes |
| Guallar-Castillón *et al.* (2012) | Cardiovascular disease | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Nilsson *et al.* (2012) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably no |
| | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| Akbaraly *et al.* (2013) | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely no |
| | Cardiovascular disease | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely no |
| Chan *et al.* (2013) | Non-fatal stroke | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Probably yes | Probably yes |
| Chen *et al.* (2013) | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Fatal stroke | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Crowe *et al.* (2013) | Cardiovascular disease | Definitely no | Definitely no | Probably yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Granic *et al.* (2013) | All-cause mortality | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely no | Definitely yes | Probably yes |
| Kappeler *et al.* (2013) | All-cause mortality | Definitely yes | Definitely no | Definitely yes | Definitely yes | Probably yes | Definitely yes | Probably yes |
| | Cardiovascular mortality | Definitely yes | Definitely no | Definitely yes | Probably yes | Probably yes | Definitely yes | Probably yes |
| | Cancer | Definitely yes | Definitely no | Definitely yes | Probably yes | Probably yes | Definitely yes | Probably yes |
| Link *et al.* (2013) | Cancer | Definitely yes | Definitely no | Definitely yes | Definitely no | Definitely yes | Definitely yes | Probably yes |
| Maruyama *et al.* (2013) | Cardiovascular mortality | Definitely yes | Definitely no | Definitely yes | Probably no | Probably yes | Definitely yes | Probably yes |
| | Fatal stroke | Definitely yes | Definitely no | Definitely yes | Probably no | Probably yes | Definitely yes | Probably yes |
| Orlich *et al.* (2013) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Tonstad *et al.* (2013) | Type II diabetes | Definitely yes | Probably no | Probably yes | Probably no | Definitely yes | Definitely no | Probably no |
| Ruano *et al.* (2013) | Quality of life | Definitely yes | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely no |
| Tantamango-Bartley *et al.* (2013) | Cancer | Definitely yes | Probably yes | Probably yes | Probably yes | Definitely yes | Probably yes | Probably yes |
| Zhang *et al.* (2013) | Cancer | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| George *et al.* (2014) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |

| Reference | Outcome | 1. Was selection of exposed and non-exposed cohorts drawn from the same population? | 2. Can we be confident in the assessment of exposure? | 3. Can we be confident that the outcome of interest was not present at start of study? | 4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | 5. Can we be confident in the assessment of the presence or absence of prognostic factors? | 6. Can we confident in the assessment of outcome? | 7. Was the follow-up of cohorts adequate? |
|---|---|---|---|---|---|---|---|---|
| Key *et al.* (2014) | Cancer | Definitely yes | Definitely no | Probably yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Kumagai *et al.* (2014) | Cancer | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| Odegaard *et al.* (2014) | All-cause mortality | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Definitely yes | Probably no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Definitely yes | Probably no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Pastorino *et al.* (2014) | Type II diabetes | Definitely yes | Definitely no | Probably no | Probably no | Probably yes | Probably no | Probably no |
| Soret *et al.* (2014) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes | Probably no | Probably no |
| Yu *et al.* (2014) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Yu *et al.* (2014) | All-cause mortality | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes |
| | Cardiovascular mortality | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| | Cancer | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Zazpe *et al.* (2014) | All-cause mortality | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Boggs *et al.* (2015) | All-cause mortality | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Catsburg *et al.* (2015) | Cancer | Definitely yes | Definitely no | Probably no | Definitely no | Definitely yes | Definitely yes | Definitely yes |
| Lacoppidan *et al.* (2015) | Type II diabetes | Definitely yes | Definitely no | Definitely yes | Probably no | Probably yes | Definitely yes | Probably yes |
| Larsson *et al.* (2015) | All stroke | Definitely yes | Probably no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Martinez-González *et al.* (2015) | All-cause mortality | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular mortality | Definitely yes | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes |
| | All stroke | Definitely yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| | All MIs | Definitely yes | Definitely yes | Probably yes | Probably yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular disease | Definitely yes | Definitely yes | Probably yes | Probably yes | Definitely yes | Definitely yes | Probably yes |
| Orlich *et al.* (2015) | Cancer | Definitely no | Definitely yes | Definitely yes | Definitely no | Definitely yes | Definitely yes | Definitely no |
| Roswall *et al.* (2015) | All-cause mortality | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably no |
| | Cardiovascular mortality | Definitely yes | Definitely yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| | Cancer | Definitely yes | Definitely yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| Shikany *et al.* (2015) | Cardiovascular disease | Definitely yes | Probably yes | Probably yes | Probably no | Definitely yes | Probably yes | Probably no |
| Akinyemiju *et al.* (2016) | Cancer | Probably yes | Definitely no | Probably yes | Probably no | Probably yes | Probably no | Probably yes |

| Reference | Outcome | 1. Was selection of exposed and non-exposed cohorts drawn from the same population? | 2. Can we be confident in the assessment of exposure? | 3. Can we be confident that the outcome of interest was not present at start of study? | 4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables? | 5. Can we be confident in the assessment of the presence or absence of prognostic factors? | 6. Can we confident in the assessment of outcome? | 7. Was the follow-up of cohorts adequate? |
|---|---|---|---|---|---|---|---|---|
| Appleby *et al.* (2016) | All-cause mortality | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| | Cardiovascular mortality | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| | Fatal stroke | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| | Cancer | Definitely no | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| Bao *et al.* (2016) | Type II diabetes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Definitely yes | Probably yes | Definitely yes |
| Nobbs *et al.* (2016) | Cardiovascular mortality | Definitely yes | Definitely yes | Probably yes | Probably no | Probably yes | Definitely no | Definitely no |
| | Cancer | Definitely yes | Definitely yes | Probably yes | Probably no | Probably yes | Definitely yes | Definitely no |
| Larsson *et al.* (2016) | Non-fatal stroke | Definitely yes | Probably no | Definitely yes | Probably yes | Definitely yes | Definitely yes | Probably yes |
| Moskal *et al.* (2016) | Cancer | Definitely yes | Definitely no | Probably yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Okada *et al.* (2016) | All-cause mortality | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| Shin *et al.* (2016) | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Tantamango-Bartley *et al.* (2016) | Cancer | Definitely yes | Probably no | Probably yes | Probably no | Definitely yes | Definitely yes | Definitely yes |
| Vargas *et al.* (2016) | Cancer | Definitely yes | Definitely yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably no |
| Mehta *et al.* (2017) | Cancer | Definitely yes | Definitely yes | Probably yes | Probably yes | Probably yes | Probably yes | Definitely yes |
| Kojima *et al.* (2017) | Cancer | Definitely yes | Definitely yes | Probably yes | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Larsson *et al.* (2017) | Cancer | Definitely yes | Probably yes | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Lv *et al.* (2017) | All stroke | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular disease | Definitely yes | Definitely no | Definitely yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Mertens *et al.* (2017) | All stroke | Definitely yes | Definitely yes | Probably yes | Probably yes | Definitely yes | Definitely yes | Probably yes |
| | Cardiovascular disease | Definitely yes | Definitely yes | Probably yes | Probably no | Definitely yes | Definitely yes | Probably yes |
| Mirmiran *et al.* (2017) | Cardiovascular disease | Definitely yes | Probably no | Probably yes | Definitely no | Definitely yes | Definitely yes | Definitely yes |
| Kane-Diallo *et al.* (2018) | Cancer | Probably yes | Probably no | Probably no | Definitely yes | Definitely yes | Definitely yes | Probably yes |
| Nazari *et al.* (2018) | All stroke | Definitely yes | Probably yes | Probably yes | Probably no | Probably yes | Probably no | Probably no |
| Rada-Fernandez de Jauregui *et al.* (2018) | Cancer | Definitely yes | Definitely no | Probably no | Definitely yes | Definitely yes | Definitely yes | Probably no |

**Guidance and criteria on the risk of bias assessment.**

| | |
|---|---|
| **1. Was selection of exposed and non-exposed cohorts drawn from the same population?** | This field queries whether participants consuming different amounts of red meat and/or processed meat were drawn from the same population.<br><br>1=Definitely yes |

| | |
|---|---|
| | 2=Probably yes<br>3=Probably no<br>4=Definitely no<br>5=Unclear |

| | |
|---|---|
| Definitely yes | Studies in which selection for participation is not dependent on exposure level. For example, the New York University Women's Health Study recruited women 34 to 65 years old from the Guttman Breast Diagnostic Institute in New York City or the Strax Breast Cancer Institute. Enrolment in the study was independent of dietary characteristics. |
| Probably yes | Studies in which methods for recruitment of the cohort is not adequately described to be able to determine whether recruitment into the study was dependent on intake of red meat and/or processed meat. |
| Probably no | |
| Definitely no | A study that recruits participants with high adherence to Western dietary pattern from the US and those with low adherence to the Western dietary pattern from Greece is at high risk of bias. |

| | |
|---|---|
| Justification for question 1 | Copy and paste the text in the article that supports your response to the previous field. This will usually include a brief description of the cohort(s). |
| **2. Can we be confident in the assessment of exposure?** | This field queries how confident we are about the quantification of intake of red meat and/or processed meat.<br><br>1=Definitely yes<br>2=Probably yes<br>3=Probably no<br>4=Definitely no<br>5=Unclear |

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| Definitely yes | Participants complete a dietary measure at least once every five years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has undergone validation against a multiday weighed food record. A weighed food record is a record of food consumption over one or more days where an individual or investigator weighs each item of food before consumption. Some studies may provide a citation to the study validating the dietary measure and other studies may simply say that the measure has been validated against a weighed food record. The correlation coefficient between the dietary measure and the majority of food items and nutrients evaluated should generally be equal to 0.4. |
| Probably yes | Participants complete a dietary measure at least once every six to eight years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has undergone validation against a dietary measure other than a weighed food record (e.g., 24 h food record, biomarker). Some studies may provide a citation to the study validating the dietary measure and other studies may simply say that the measure has been validated against another dietary measure. |
| Probably no | Participants complete a dietary measure at least once every nine to 10 years. The dietary measure has not been validated or validation is not reported.<br><br>If the measure has been validated, the correlation coefficient of the dietary measure against another measure for validation is less than 0.40 for the majority of nutrients and food items evaluated. |
| Definitely no | Participants complete a dietary measure only at baseline or the dietary measure is repeated less frequently than once every 10 years. The dietary measure (in most cases, this is a semi-quantitative food frequency questionnaire (FFQ)) has not undergone any validation.<br><br>Some studies may report that diet was assessed at multiple timepoints throughout the study but only baseline dietary data is used for analysis. |

| | |
|---|---|
| | Please note that if a study provides a citation to another paper that reports on the validation of the dietary measure, you **MUST** retrieve and read the paper to complete this field. |
| Justification for question 2 | Copy and paste the text in the article that supports your response to the previous field. |
| **3. Can we be confident that the outcome of interest was not present at start of study?** | 1=Definitely yes<br>2=Probably yes<br>3=Probably no<br>4=Definitely no<br>5=Unclear |

| | |
|---|---|
| Definitely yes | The outcome of interest is fatal. In that case, we can be certain that participants did not have the outcome at baseline.<br><br>Continuous outcomes (i.e., hemoglobin, quality of life, and satisfaction with diet) should be specified as 'definitely yes'.<br><br>For dichotomous outcomes, authors have made an effort to exclude participants with the outcome of interest at baseline. The outcome may be self-reported with some external validation (e.g., validation against medical records). |
| Probably yes | The authors have made an effort to exclude participants with the outcome of interest at baseline. The outcome is self-reported and there is no external validation.<br><br>The authors have made an effort to exclude participants with the outcome of interest at baseline. The authors do not report how the outcome at baseline was ascertained. |
| Probably no | |
| Definitely no | The authors have made no effort to exclude participants with the outcome of interest at baseline. |

| | |
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| Justification for question 3 | Copy and paste the text in the article that supports your response to the previous field. |
| **4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?** | This field queries how confident we are that the reported association or lack thereof is not due to confounding.<br><br>1=Definitely yes<br>2=Probably yes<br>3=Probably no<br>4=Definitely no<br>5=Unclear |

| | |
|---|---|
| Definitely yes | The study adjusts at a minimum for age, sex, smoking, at least one measure of socioeconomic status such as level of income or education or occupation, family history (of cancer for cancer outcomes, cardiovascular disease for cardiovascular outcomes, and diabetes for the outcome of diabetes), aspirin use (necessary only for colon cancer), diabetes (necessary only for cardiovascular outcomes, excluding diabetes), alcohol consumption (only for cancers of the mouth, pharynx, larynx, esophagus, colorectum, and breast), weight or BMI (only for cancers of the esophagus, pancreas, liver, breast, endometrium) and physical activity (only for cardiovascular outcomes) in the analysis. |
| Probably yes | Adjusts at a minimum for age, sex, smoking, family history (of cancer for cancer outcomes, coronary heart disease for cardiovascular outcomes, and diabetes for the outcome of diabetes), and diabetes (only for cardiovascular outcomes, excluding diabetes). |
| Probably no | Adjusts at a minimum for age, sex, and smoking. |
| Definitely no | The study does not adjust for any prognostic variables relevant to the outcome or does not adjust for age, sex, or smoking. |

Note that if a study excludes a group of participants (e.g., women), then adjusting for that variable (e.g., sex) is not necessary.

<table>
<tr><td></td><td>If age is used as the time scale of a survival model (e.g., Cox proportional hazards model), additional adjustment for age is not necessary since analyses will be age-adjusted.</td></tr>
<tr><td>Justification for question 4</td><td>Copy and paste the text in the article that supports your response to the previous field. This should include a list of the variables that were adjusted for in the analysis.</td></tr>
<tr><td>5. Can we be confident in the assessment of the presence or absence of prognostic factors?</td><td>This field queries whether we are confident in the measurement or ascertainment of prognostic factors that were used either for matching or were adjusted for in the model.<br><br>1=Definitely yes<br>2=Probably yes<br>3=Probably no<br>4=Definitely no<br>5=Unclear<br><br>
<table>
<tr><td>Definitely yes</td><td>Typically, prognostic factors are self-reported by participants. This is considered acceptable.</td></tr>
<tr><td>Probably yes</td><td>Some studies may not report how prognostic variables were measured. Most of the time we can assume they were self-reported. These studies should be classified as ‘probably yes’.</td></tr>
<tr><td>Probably no</td><td>Some studies may make assumptions regarding various prognostic factors. For example, a study may assume that all participants who did not answer the question on diabetes disease at baseline did not have diabetes.</td></tr>
<tr><td>Definitely no</td><td></td></tr>
</table>
<br>Note that for this item, we are only concerned with the measurement of the prognostic factors listed in question four of the risk of bias assessment tool. We are not concerned with the measurement of any additional prognostic factors the authors choose to consider.<br><br>If there is a significant proportion of the study population (>10%) that is missing data on an important prognostic factors or if missing prognostic factors are inappropriately handled in data analysis, we would consider rating the study at higher risk of bias only if the prognostic factor is essential to the rating in question 4.</td></tr>
<tr><td>Justification for question 5</td><td>Copy and paste the text in the article that supports your response to the previous field. Make sure to copy and paste all the variables that were adjusted for in the final model.</td></tr>
<tr><td>6. Can we be confident in the assessment of outcome?</td><td>This field queries our confidence in the accuracy of the measurement of the outcome.<br><br>1=Definitely yes<br>2=Probably yes<br>3=Probably no<br>4=Definitely no<br>5=Unclear<br><br>
<table>
<tr><td>Definitely yes</td><td>All-cause mortality based on a government registry (e.g., National Death Index) with or without review by study physician or study staff<br><br>National or local registries (e.g., National Program of Cancer Registries (NPCR)) with review by a study physician or study staff<br><br>Medical records reviewed by a study physician or study staff<br><br>Measurement of hemoglobin by trained medical professionals or by a qualified medical facility (e.g., medical lab)<br><br>Measurement of a lab value indicative of the outcome by trained medical professionals or by a qualified medical facility</td></tr>
</table>
</td></tr>
</table>

| | | |
|---|---|---|
| | | Measurement of quality of life and satisfaction with diet with previously validated instruments |
| | Probably yes | Self-report with external validation by medical records. For example, a study may ask participants whether they have been diagnosed with breast cancer every two years. Medical records may be retrieved for participants who indicate a diagnosis of breast cancer. The authors may report that medical records confirmed self-report breast cancer for over 98% of cases. A minimum of 80% agreement must be reached.<br><br>External validation may only be done for a subsample of participants. This is acceptable as long as the rate of concordance between self-report and medical records is high (>95%).<br><br>Active follow-up with no external validation for all-cause mortality.<br><br>Active follow-up with external validation for cause-specific mortality (a minimum of 80% of events must be correctly classified in validation) |
| | Probably no | Medical records without review by study physician or study staff.<br><br>The authors do not specify how outcomes were measured.<br><br>Active follow-up without external validation for cause-specific mortality.<br><br>Self-report with external validation by medical records where the rate of agreement between self-report and medical records is low (<80%). |
| | Definitely no | Self-report with no external validation. |
| Justification for question 6 | Copy and paste the text in the article that supports your response to the previous field. | |
| **7. Was the follow-up of cohorts adequate?** | This field queries the risk of bias associated with loss to follow-up and missing outcome data.<br><br>1=Definitely yes<br>2=Probably yes<br>3=Probably no<br>4=Definitely no<br>5=Unclear | |
| | Definitely yes | At least 90% retention for the duration of the study. |
| | Probably yes | 80 to 89% retention for the duration of the study with loss to follow-up unlikely to be related to outcomes.<br><br>If rate of follow-up is not reported but the study is likely to have low rates of loss to follow-up through government or local databases and registries. |
| | Probably no | 80 to 89% retention for the duration of the study with loss to follow-up likely to be related to outcomes. For example, if the study requires participants to make special clinic visits for ascertainment of outcomes, participants who are more ill with more comorbidities may be less likely to be able to attend these clinics.<br><br>Loss to follow-up is not reported or cannot be estimated from information provided in the paper. |
| | Definitely no | Less than 80% follow-up. |
| Justification for question 7 | Copy and paste the text in the article that supports your response to the previous field. | |
| Funding source | Select the source of funding for the study. | |

| | |
|---|---|
| | 1=Private, for profit (e.g., cattle industry)<br>2=Public or private, not for profit (e.g., hospitals, universities, government)<br>3=Mix of public or private, for profit and not for profit<br><br>NR=not reported |
| Funding source – details | Enter the source(s) of funding. If more than one source, please separate with a comma.<br><br>Report if any for-profit organizations or companies provided materials for the conduct of the study (e.g., Bertolli Co. supplied olive oil for the study).<br><br>NR=not reported<br><br>Ex: Australian Pork Ltd., Pork Co-operative Research Centre |
| Conflicts of interest – financial | Do the authors declare any financial conflicts of interest?<br><br>For this review, financial conflicts of interest include having received or receiving money from any industry that may be relevant to the topic of the study.<br><br>0=no (the reference includes a conflicts of interest section but no financial conflicts of interest are declared)<br>1=yes<br>NR=not reported (there is no general conflicts of interest section or there is no conflicts of interest section particular to financial conflicts of interest) |
| Conflicts of interest – intellectual | Do the authors declare any intellectual conflicts of interest?<br><br>For this review, intellectual conflicts of interest include having led or been involved in previous work that is relevant to the topic of the study.<br><br>0=no (the reference includes a conflicts of interest section but no intellectual conflicts are declared)<br>1=yes<br>NR=not reported (there is no general conflicts of interest section or there is no conflicts of interest section particular to intellectual conflicts of interest) |
| Conflicts of interest – personal | Do the authors declare any personal conflicts of interest?<br><br>For this review, personal conflicts of interest are defined as other relevant conflicts related to dietary behaviors or beliefs about dietary behaviors due to personal, family, religious, social, or cultural reasons.<br><br>0=no (the reference includes a conflicts of interest section but no personal conflicts are declared)<br>1=yes<br>NR=not reported (there is no general conflicts of interest section or there is no conflicts of interest section particular to personal conflicts of interest) |
| Conflicts of interest justification | Copy and paste the authors' statement of conflicts of interest from the paper. |

**Supplement Table 4. Results of the Subgroup Analysis Regarding Method of Dietary Pattern Assessment**

| Outcome | Effect estimate | All methods | Factor analyses / principal component analyses | Indices | Vegetarian versus non-vegetarian |
|---|---|---|---|---|---|
| All-cause mortality | Relative effect: | 0.87 | 0.96 | 0.79 | 0.92 |
| | | (0.82 to 0.92) | (0.78 to 1.19) | (0.74 to 0.84) | (0.82 to 1.03) |
| | Absolute effect: | 15 fewer per 1,000 | 5 fewer per 1,000 | 24 fewer per 1,000 | 9 fewer per 1,000 |
| | | (from 20 fewer to 9 fewer) | (from 25 fewer to 21 more) | (from 29 fewer to 18 fewer) | (from 20 fewer to 3 more) |
| Cardiovascular mortality | Relative effect: | 0.86 | 0.96 | 0.81 | 0.83 |
| | | (0.79 to 0.94) | (0.81 to 1.15) | (0.69 to 0.94) | (0.71 to 0.96) |
| | Absolute effect: | 6 fewer per 1,000 | 2 fewer per 1,000 | 8 fewer per 1,000 | 7 fewer per 1,000 |
| | | (from 9 fewer to 2 fewer) | (from 8 fewer to 6 more) | (from 13 fewer to 2 fewer) | (from 12 fewer to 2 fewer) |
| Stroke (fatal and non-fatal) | Relative effect: | 0.75 | 0.81 | < 3 studies | < 3 studies |
| | | (0.53 to 1.05) | (0.57 to 1.14) | | |
| | Absolute effect: | 5 fewer per 1,000 | 4 fewer per 1,000 | - | - |
| | | (from 9 fewer to 1 more) | (from 8 fewer to 3 more) | | |
| Fatal stroke | Relative effect: | 1.00 | 1.09 | < 3 studies | 0.94 |
| | | (0.88 to 1.14) | (0.93 to 1.28) | | (0.73 to 1.22) |
| | Absolute effect: | 0 fewer per 1,000 | 0 fewer per 1,000 | - | 0 fewer per 1,000 |
| | | (from 0 more to 0 fewer) | (from 0 more to 0 fewer) | | (from 0 more to 0 fewer) |
| Non-fatal stroke | Relative effect: | 0.86 | < 3 studies | < 3 studies | < 3 studies |
| | | (0.81 to 0.92) | | | |
| | Absolute effect: | 3 fewer per 1,000 | - | - | - |
| | | (from 3 fewer to 1 fewer) | | | |
| Myocardial infarction (fatal and non-fatal) | Relative effect: | 1.04 | < 3 studies | < 3 studies | < 3 studies |
| | | (0.78 to 1.39) | | | |
| | Absolute effect: | 1 more per 1,000 | - | - | - |
| | | (from 8 fewer to 14 more) | | | |
| Cardiovascular disease (fatal and non-fatal) | Relative effect: | 0.87 | 0.90 | < 3 studies | < 3 studies |
| | | (0.75 to 1.01) | (0.76 to 1.06) | | |
| | Absolute effect: | 10 fewer per 1,000 | 8 fewer per 1,000 | - | - |
| | | (from 19 fewer to 1 more) | (from 18 fewer to 5 more) | | |
| Non-fatal coronary heart disease | Relative effect: | 0.85 | < 3 studies | < 3 studies | < 3 studies |
| | | (0.17 to 4.27) | | | |
| | Absolute effect: | 4 fewer per 1,000 | - | - | - |
| | | (from 20 fewer to 78 more) | | | |

| Outcome | Effect estimate | All methods | Factor analyses / principal component analyses | Indices | Vegetarian versus non-vegetarian |
|---|---|---|---|---|---|
| Type II diabetes | Relative effect: | 0.76 | 0.84 | 0.75 | < 3 studies |
| | | (0.68 to 0.86) | (0.65 to 1.09) | (0.68 to 0.83) | |
| | Absolute effect: | 13 fewer per 1,000 | 9 fewer per 1,000 | 14 fewer per 1,000 | - |
| | | (from 18 fewer to 8 fewer) | (from 20 fewer to 5 more) | (from 18 fewer to 10 fewer) | |
| Breast cancer incidence | Relative effect: | 0.95 | 0.94 | < 3 studies | 0.96 |
| | | (0.88 to 1.02) | (0.87 to 1.02) | | (0.73 to 1.27) |
| | Absolute effect: | 2 fewer per 1,000 | 3 fewer per 1,000 | - | 2 fewer per 1,000 |
| | | (from 6 fewer to 1 more) | (from 6 fewer to 1 more) | | (from 12 fewer to 12 more) |
| Breast cancer mortality | Relative effect: | 1.04 | < 3 studies | < 3 studies | 0.97 |
| | | (0.63 to 1.73) | | | (0.52 to 1.82) |
| | Absolute effect: | 1 more per 1,000 | - | - | 0 fewer per 1,000 |
| | | (from 5 fewer to 10 more) | | | (from 7 fewer to 11 more) |
| Colorectal cancer incidence | Relative effect: | 0.94 | 0.93 | < 3 studies | 1.08 |
| | | (0.85 to 1.05) | (0.85 to 1.01) | | (0.56 to 2.07) |
| | Absolute effect: | 1 fewer per 1,000 | 1 fewer per 1,000 | - | 2 more per 1,000 |
| | | (from 3 fewer to 1 more) | (from 3 fewer to 0 fewer) | | (from 9 fewer to 21 more) |
| Colorectal cancer mortality | Relative effect: | 0.96 | < 3 studies | < 3 studies | 1.02 |
| | | (0.76 to 1.21) | | | (0.84 to 1.24) |
| | Absolute effect: | 0 fewer per 1,000 | - | - | 0 fewer per 1,000 |
| | | (from 2 fewer to 2 more) | | | (from 1 fewer to 2 more) |
| Endometrial cancer incidence | Relative effect: | 0.99 | < 3 studies | < 3 studies | < 3 studies |
| | | (0.68 to 1.45) | | | |
| | Absolute effect: | 0 fewer per 1,000 | - | - | - |
| | | (from 3 fewer to 5 more) | | | |
| Esophageal cancer mortality | Relative effect: | 0.87 | < 3 studies | < 3 studies | < 3 studies |
| | | (0.49 to 1.54) | | | |
| | Absolute effect: | 1 fewer per 1,000 | - | - | - |
| | | (from 3 fewer to 3 more) | | | |
| Extrahepatic cancer incidence | Relative effect: | 0.41 | < 3 studies | < 3 studies | < 3 studies |
| | | (0.26 to 0.64) | | | |
| | Absolute effect: | 6 fewer per 1,000 | - | - | - |
| | | (from 8 fewer to 4 fewer) | | | |
| Gallbladder cancer incidence | Relative effect: | 0.36 | < 3 studies | < 3 studies | < 3 studies |
| | | (0.20 to 0.64) | | | |

| Outcome | Effect estimate | All methods | Factor analyses / principal component analyses | Indices | Vegetarian versus non-vegetarian |
|---|---|---|---|---|---|
| | Absolute effect: | 1 fewer per 1,000 (from 2 fewer to 1 fewer) | - | - | - |
| Liver cancer incidence | Relative effect: | 0.79 (0.32 to 1.94) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 2 fewer per 1,000 (from 7 fewer to 10 more) | - | - | - |
| Liver cancer mortality | Relative effect: | 1.89 (0.88 to 4.06) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 9 more per 1,000 (from 1 fewer to 31 more) | - | - | - |
| Ovarian cancer incidence | Relative effect: | 0.87 (0.62 to 1.22) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 1 fewer per 1,000 (from 3 fewer to 2 more) | - | - | - |
| Ovarian cancer mortality | Relative effect: | 0.97 (0.62 to 1.52) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 0 fewer per 1,000 (from 2 fewer to 2 more) | - | - | - |
| Overall cancer incidence | Relative effect: | 0.90 (0.86 to 0.94) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 18 fewer per 1,000 (from 26 fewer to 11 fewer) | - | - | - |
| Overall cancer mortality | Relative effect: | 0.89 (0.83 to 0.96) | 0.90 (0.69 to 1.17) | 0.85 (0.78 to 0.92) | 0.97 (0.82 to 1.15) |
| | Absolute effect: | 12 fewer per 1,000 (from 18 fewer to 4 fewer) | 18 fewer per 1,000 (from 57 fewer to 31 more) | 28 fewer per 1,000 (from 41 fewer to 15 fewer) | 6 fewer per 1,000 (from 33 fewer to 28 more) |
| Pancreatic cancer incidence | Relative effect: | 0.89 (0.45 to 1.78) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 1 fewer per 1,000 (from 3 fewer to 4 more) | - | - | - |
| Pancreatic cancer mortality | Relative effect: | 0.44 (0.26 to 0.76) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 2 fewer per 1,000 (from 3 fewer to 1 fewer) | - | - | - |

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| Outcome | Effect estimate | All methods | Factor analyses / principal component analyses | Indices | Vegetarian versus non-vegetarian |
|---|---|---|---|---|---|
| Prostate cancer incidence | Relative effect: | 0.93 (0.72 to 1.19) | 1.02 (0.78 to 1.33) | < 3 studies | 0.93 (0.32 to 2.68) |
| | Absolute effect: | 3 fewer per 1,000 (from 11 fewer to 7 more) | 1 fewer per 1,000 (from 8 fewer to 13 more) | - | 3 fewer per 1,000 (from 26 fewer to 64 more) |
| Prostate cancer mortality | Relative effect: | 1.02 (0.63 to 1.65) | < 3 studies | < 3 studies | 1.02 (0.63 to 1.65) |
| | Absolute effect: | 0 fewer per 1,000 (from 2 fewer to 4 more) | - | - | 0 fewer per 1,000 (from 2 fewer to 4 more) |
| Stomach cancer incidence | Relative effect: | 0.60 (0.25 to 1.40) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 6 fewer per 1,000 (from 11 fewer to 6 more) | - | - | - |
| Stomach cancer mortality | Relative effect: | 0.89 (0.71 to 1.12) | 0.88 (0.58 to 1.32) | < 3 studies | 0.92 (0.55 to 1.53) |
| | Absolute effect: | 1 fewer per 1,000 (from 3 fewer to 1 more) | 1 fewer per 1,000 (from 4 fewer to 3 more) | - | 1 fewer per 1,000 (from 5 fewer to 5 more) |
| Uterine cancer incidence | Relative effect: | 1.18 (0.80 to 1.73) | < 3 studies | < 3 studies | < 3 studies |
| | Absolute effect: | 2 more per 1,000 (from 2 fewer to 7 more) | - | - | - |

**Supplement Table 5. Results of the Subgroup Analysis on Risk of Bias**

| Outcome | Effect estimate | All | Low risk of bias | High risk of bias |
|---|---|---|---|---|
| All-cause mortality | Relative effect: | 0.87 | 0.85 | 0.93 |
| | | (0.82 to 0.92) | (0.80 – 0.91) | (0.82 – 1.07) |
| | Absolute effect: | 15 fewer per 1,000 | 17 fewer per 1,000 | 8 fewer per 1,000 |
| | | (from 20 fewer to 9 fewer) | (from 23 fewer to 10 fewer) | (from 20 fewer to 8 more) |
| Cardiovascular mortality | Relative effect: | 0.86 | 0.79 | 0.92 |
| | | (0.79 to 0.94) | (0.70 – 0.89) | (0.81 – 1.04) |
| | Absolute effect: | 6 fewer per 1,000 | 9 fewer per 1,000 | 3 fewer per 1,000 |
| | | (from 9 fewer to 2 fewer) | (from 12 fewer to 5 fewer) | (from 8 fewer to 2 more) |
| Stroke (fatal and non-fatal) | Relative effect: | 0.75 | < 3 studies | 0.64 |
| | | (0.53 to 1.05) | | (0.29 – 1.38) |
| | Absolute effect: | 5 fewer per 1,000 | - | 7 fewer per 1,000 |
| | | (from 9 fewer to 1 more) | | (from 13 fewer to 7 more) |
| Fatal stroke | Relative effect: | 1.00 | < 3 studies | 1.00 |
| | | (0.88 to 1.14) | | (0.86 – 1.16) |
| | Absolute effect: | 0 fewer per 1,000 | - | 0 fewer per 1,000 |
| | | (from 0 more to 0 fewer) | | (from 0 more to 0 fewer) |
| Non-fatal stroke | Relative effect: | 0.86 | < 3 studies | < 3 studies |
| | | (0.81 to 0.92) | | |
| | Absolute effect: | 3 fewer per 1,000 | - | - |
| | | (from 3 fewer to 1 fewer) | | |
| Myocardial infarction (fatal and non-fatal) | Relative effect: | 1.04 | < 3 studies | < 3 studies |
| | | (0.78 to 1.39) | | |
| | Absolute effect: | 1 more per 1,000 | - | - |
| | | (from 8 fewer to 14 more) | | |
| Cardiovascular disease (fatal and non-fatal) | Relative effect: | 0.87 | 0.79 | 0.93 |
| | | (0.75 to 1.01) | (0.62 – 1.01) | (0.75 – 1.16) |
| | Absolute effect: | 10 fewer per 1,000 | 16 fewer per 1,000 | 5 fewer per 1,000 |
| | | (from 19 fewer to 1 more) | (from 29 fewer to 1 more) | (from 19 fewer to 12 more) |
| Non-fatal coronary heart disease | Relative effect: | 0.85 | < 3 studies | < 3 studies |
| | | (0.17 to 4.27) | | |
| | Absolute effect: | 4 fewer per 1,000 | - | - |
| | | (from 20 fewer to 78 more) | | |

| Outcome | Effect estimate | All | Low risk of bias | High risk of bias |
|---|---|---|---|---|
| Type II diabetes | Relative effect: | 0.76 | 0.71 | 0.78 |
| | | (0.68 to 0.86) | (0.66 – 0.73) | (0.65 – 0.93) |
| | Absolute effect: | 13 fewer per 1,000 | 16 fewer per 1,000 | 12 fewer per 1,000 |
| | | (from 18 fewer to 8 fewer) | (from 19 fewer to 15 fewer) | (from 20 fewer to 4 fewer) |
| Breast cancer incidence | Relative effect: | 0.95 | 0.94 | 0.93 |
| | | (0.88 to 1.02) | (0.75 – 1.18) | (0.85 – 1.03) |
| | Absolute effect: | 2 fewer per 1,000 | 3 fewer per 1,000 | 3 fewer per 1,000 |
| | | (from 6 fewer to 1 more) | (from 12 fewer to 8 more) | (from 7 fewer to 1 more) |
| Breast cancer mortality | Relative effect: | 1.04 | < 3 studies | 1.04 |
| | | (0.63 to 1.73) | | (0.63 to 1.73) |
| | Absolute effect: | 1 more per 1,000 | - | 1 more per 1,000 |
| | | (from 5 fewer to 10 more) | | (from 5 fewer to 10 more) |
| Colorectal cancer incidence | Relative effect: | 0.94 | 0.97 | 0.88 |
| | | (0.85 to 1.05) | (0.88 – 1.07) | (0.65 – 1.21) |
| | Absolute effect: | 1 fewer per 1,000 | 1 fewer per 1,000 | 2 fewer per 1,000 |
| | | (from 3 fewer to 1 more) | (from 2 fewer to 1 more) | (from 7 fewer to 4 more) |
| Colorectal cancer mortality | Relative effect: | 0.96 | < 3 studies | 0.96 |
| | | (0.76 to 1.21) | | (0.76 to 1.21) |
| | Absolute effect: | 0 fewer per 1,000 | - | 0 fewer per 1,000 |
| | | (from 2 fewer to 2 more) | | (from 2 fewer to 2 more) |
| Endometrial cancer incidence | Relative effect: | 0.99 | < 3 studies | < 3 studies |
| | | (0.68 to 1.45) | | |
| | Absolute effect: | 0 fewer per 1,000 | - | - |
| | | (from 3 fewer to 5 more) | | |
| Esophageal cancer mortality | Relative effect: | 0.87 | < 3 studies | < 3 studies |
| | | (0.49 to 1.54) | | |
| | Absolute effect: | 1 fewer per 1,000 | - | - |
| | | (from 3 fewer to 3 more) | | |
| Extrahepatic cancer incidence | Relative effect: | 0.41 | < 3 studies | < 3 studies |
| | | (0.26 to 0.64) | | |
| | Absolute effect: | 6 fewer per 1,000 | - | - |
| | | (from 8 fewer to 4 fewer) | | |
| Gallbladder cancer incidence | Relative effect: | 0.36 | < 3 studies | < 3 studies |
| | | (0.20 to 0.64) | | |

| Outcome | Effect estimate | All | Low risk of bias | High risk of bias |
|---|---|---|---|---|
| | Absolute effect: | 1 fewer per 1,000 (from 2 fewer to 1 fewer) | - | - |
| Liver cancer incidence | Relative effect: | 0.79 (0.32 to 1.94) | < 3 studies | < 3 studies |
| | Absolute effect: | 2 fewer per 1,000 (from 7 fewer to 10 more) | - | - |
| Liver cancer mortality | Relative effect: | 1.89 (0.88 to 4.06) | < 3 studies | < 3 studies |
| | Absolute effect: | 9 more per 1,000 (from 1 fewer to 31 more) | - | - |
| Ovarian cancer incidence | Relative effect: | 0.87 (0.62 to 1.22) | < 3 studies | < 3 studies |
| | Absolute effect: | 1 fewer per 1,000 (from 3 fewer to 2 more) | - | - |
| Ovarian cancer mortality | Relative effect: | 0.97 (0.62 to 1.52) | < 3 studies | < 3 studies |
| | Absolute effect: | 0 fewer per 1,000 (from 2 fewer to 2 more) | - | - |
| Overall cancer incidence | Relative effect: | 0.90 (0.86 to 0.94) | < 3 studies | 0.89 (0.82 to 0.96) |
| | Absolute effect: | 18 fewer per 1,000 (from 26 fewer to 11 fewer) | - | 20 fewer per 1,000 (from 33 fewer to 7 fewer) |
| Overall cancer mortality | Relative effect: | 0.89 (0.83 to 0.96) | 0.88 (0.81 – 0.95) | 0.94 (0.78 – 1.15) |
| | Absolute effect: | 12 fewer per 1,000 (from 18 fewer to 4 fewer) | 13 fewer per 1,000 (from 20 fewer to 5 fewer) | 6 fewer per 1,000 (from 23 fewer to 16 more) |
| Pancreatic cancer incidence | Relative effect: | 0.89 (0.45 to 1.78) | < 3 studies | < 3 studies |
| | Absolute effect: | 1 fewer per 1,000 (from 3 fewer to 4 more) | - | - |
| Pancreatic cancer mortality | Relative effect: | 0.44 (0.26 to 0.76) | < 3 studies | < 3 studies |
| | Absolute effect: | 2 fewer per 1,000 (from 3 fewer to 1 fewer) | - | - |

| Outcome | Effect estimate | All | Low risk of bias | High risk of bias |
|---|---|---|---|---|
| Prostate cancer incidence | Relative effect: | 0.93 | < 3 studies | 0.99 |
| | | (0.72 to 1.19) | | (0.69 – 1.41) |
| | Absolute effect: | 3 fewer per 1,000 | - | 0 fewer per 1,000 |
| | | (from 11 fewer to 7 more) | | (from 12 fewer to 16 more) |
| Prostate cancer mortality | Relative effect: | 1.02 | < 3 studies | 1.02 |
| | | (0.63 to 1.65) | | (0.63 to 1.65) |
| | Absolute effect: | 0 fewer per 1,000 | - | 0 fewer per 1,000 |
| | | (from 2 fewer to 4 more) | | (from 2 fewer to 4 more) |
| Stomach cancer incidence | Relative effect: | 0.60 | < 3 studies | < 3 studies |
| | | (0.25 to 1.40) | | |
| | Absolute effect: | 6 fewer per 1,000 | - | - |
| | | (from 11 fewer to 6 more) | | |
| Stomach cancer mortality | Relative effect: | 0.89 | < 3 studies | 0.87 |
| | | (0.71 to 1.12) | | (0.59 – 1.29) |
| | Absolute effect: | 1 fewer per 1,000 | - | 1 fewer per 1,000 |
| | | (from 3 fewer to 1 more) | | (from 4 fewer to 3 more) |
| Uterine cancer incidence | Relative effect: | 1.18 | < 3 studies | < 3 studies |
| | | (0.80 to 1.73) | | |
| | Absolute effect: | 2 more per 1,000 | - | - |
| | | (from 2 fewer to 7 more) | | |

# CHAPTER 6: CONCLUSION TO THE THESIS

This thesis compiles a series of investigations focused on the synthesis and evaluation of evidence in nutrition. This concluding chapter summarizes key findings and implications, lists strengths and limitations, and discusses opportunities and challenges for future research.

**Key findings and implications**

We began this thesis by describing important methodological issues in dietary guideline development—many of which had not been previously acknowledged or discussed in the nutrition literature—and offering novel insight on how to improve the quality of future dietary guidelines, in chapter 2.

In chapter 3, we presented a cross-sectional descriptive analysis of a sample of recently published systematic reviews and meta-analyses of nutritional epidemiology studies. We found that reviews of nutritional epidemiology studies often have important limitations related to the search for and selection of studies, the collection and appraisal of data, the synthesis of results, and the evaluation of findings. Based on our findings, we developed a series of recommendations that address common deficiencies and errors in reviews of nutritional epidemiology studies, and which, if implemented by review authors, may improve the credibility of future reviews. The most important finding that emerged from this chapter, however, was that reviews of nutritional epidemiology studies will seldom produce evidence of sufficient certainty to allow confident application to guide dietary recommendations and policies because estimated effects of dietary exposures on health outcomes are nearly always small or very small and primary studies are usually at high risk of bias due to confounding, errors in the measurement of nutritional exposures, and selective reporting. This finding has important implications for guideline developers and policymakers who may need to prioritize the types of evidence that they consider to inform recommendations or policy decisions.

In chapters 4 and 5, we presented two systematic reviews that were used to inform dietary recommendations addressing red and processed meat consumption. These reviews serve as

examples of the application of rigorous systematic review methodology in nutrition—methods that are aligned with standards used across other health fields. In addition, these reviews contain several innovative features. For example, while many reviews to date have addressed the relationship between red and processed meat and adverse health outcomes, we were the first to review the evidence on patterns of red and processed meat consumption—an approach that overcomes the limitations of studying single foods and nutrients (1-3). Further, we conducted dose-response meta-analysis, which, compared to conventional meta-analysis that compares extreme categories of exposure, has higher statistical power and is less likely to produce misleading results (4-7). We were also the first to apply the GRADE approach to assess the certainty of the evidence on the relationship between red and processed meat and adverse health outcomes, including the first to systematically and transparently account for all critical factors that bear on the decision to consume red and processed meat for health reasons, such as the certainty of evidence, the magnitude of suspected health effects, and public values and preferences (8). The broader application of these methods to other nutrition topics has the potential to substantially improve the transparency and validity of future reviews, recommendations, and policies in nutrition and to align their methods with standards that have already been adopted in other health fields. For example, the consideration of absolute effects—as was done in these two chapters and is routinely done across nearly all fields—will enhance the interpretation of the balance of benefits and harms of alternative dietary advice and will moderate strong recommendations on many dietary exposures since the evidence typically suggests that most dietary exposures have very modest absolute effects on health, if any (9).

**Strengths and limitations**

The major strength of this thesis is its appraisal of current methods for evidence synthesis and evaluation in nutrition and its application of rigorous methods for evidence synthesis and evaluation—which are consistent with standards used across other health fields—to a nutrition topic.

Beyond the limitations described in the individual chapters, a limitation of this work is the lack of a knowledge translation strategy. This limitation is significant because there are considerable barriers to the adoption of alternative methods in nutrition. Notably, the adoption of alternative methods challenges established nutritional dogmas and contradicts decades of research on which many esteemed nutrition researchers have built long and illustrious careers. Future work should explore opportunities for the uptake of methods in nutrition that are consistent with standards used in other health fields, such as the GRADE approach and the consideration of absolute effects and public and/or patient values and preferences in developing recommendations.

**Opportunities and challenges for future research**

This thesis produced several novel methods that may have broader applications in both nutrition research and in other areas. A notable example is our approach to evaluating the plausibility of causal relationships using dietary pattern studies. We applied this approach in chapters 4 and 5, whereby we compared the magnitude of association between adverse health outcomes and i) dietary patterns of red and processed meat consumption and ii) red and processed meat consumption directly. Since we found the magnitude of association to be similar across these two comparisons, we concluded that the association between red and processed meat with adverse health outcomes is likely confounded by other correlated dietary factors (10). Our work illustrates that comparing the magnitude of association of indices composed of highly correlated and potentially confounding exposures with the outcome of interest to the magnitude of association between the exposure and the outcome directly may be useful to evaluate the plausibility of causal relationships (11).

Since we were among the first to apply the GRADE approach to produce dietary recommendations, we also identified several areas in which additional guidance for the application of GRADE to nutritional questions may be useful. One such area is the appropriateness of rating up the certainty of evidence in the presence of a dose-response gradient. In situations in which there are dense networks of correlations among exposures, such as in nutritional

epidemiology, a dose-response effect may be less convincing of a causal relationship and rating up of the certainty of evidence for a dose-response gradient is usually not appropriate (12).

In this thesis, we showed that current research in nutrition, which has largely been dominated by non-randomized studies, is unlikely to generate evidence of sufficient certainty (according to well-established standards across health fields) to allow confident application to guide dietary recommendations and policies—a critical insight with important implications for the design of future nutrition research. One plausible approach to generating higher certainty evidence is large dietary trials (13). Though conducting such trials is challenging due to poor adherence from participants and the need for long follow-up, dietary trials may still be the only plausible way to ultimately offer higher certainty evidence on the health effects of dietary exposures if they include sufficient safeguards against bias, such as the provision of controlled feeding environments and the implementation of strategies to minimize loss to follow-up. Although the cost of such trials will be high, they may nevertheless prove cost effective in comparison to the hundreds of conflicting and misleading non-randomized studies that are regularly published (9, 13).

The application of novel analytic methods that can identify more robust relationships between exposures and health outcomes may be an alternative approach to generate higher certainty evidence in nutrition. Examples of these approaches include the 'environment-wide association study', which involves running a series of models that simultaneously regress all exposures (for which data is available) on the health outcome of interest, controlling for multiple testing, and validating findings in an independent dataset (14), and 'vibration of effects' methods that can be used to identify exposure-outcome relationships that are most robust to the choice of confounders included in analytic models (15). Such analytic methods may be able to identify nutritional exposures with the most compelling statistical evidence of exerting an important effect on the outcome of interest (usually the exposures with the largest effects), while also overcoming other common problems, such as multiple testing.

Collectively, the application of the principles and methods for evidence synthesis and evaluation outlined in this thesis, combined with efforts to produce higher certainty evidence either via

randomized controlled trials or the application of novel analytic methods, represent promising approaches to advance nutrition research, recommendations, and policies.

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