

## Red and processed meat: more with less?

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Nutrition scientists have a major responsibility to provide evidence-based dietary recommendations for health promotion and disease prevention to clinicians and their patients, policymakers, and the public. Evidence-based dietary guidance is particularly crucial because well over half of all Americans have 1 or more preventable diet-related chronic diseases or their precursor, such as hypertension, obesity, or hyperlipidemia (1–6). Public Law 101–445, 7 U.S.C. 5341 et seq stipulates that every 5 y the USDA and the Department of Health and Human Services jointly appoint an advisory committee of experts to review the state-of-the-science for nutrition and chronic disease risk and to generate a scientific report, which forms the basis for the policy document—The Dietary Guidelines for Americans (7).

In its 2015 scientific report, the Dietary Guidelines Advisory Committee (DGAC) emphasized the importance of the totality of the diet – or *dietary patterns* – for health promotion and prevention of the major preventable diseases crippling the US population and overburdening the healthcare system (8, 9). The 2015 DGAC relied on existing and de-novo systematic reviews adhering to a stringent review and evaluation process. Both observational cohort studies and randomized controlled trials were evaluated with respect to a priori healthy dietary patterns, such as the Healthy Eating Index and the Mediterranean Diet, and their associations with risks of obesity, cardiovascular disease, type 2 diabetes, and some cancers (8, 9). These healthy dietary patterns have the following commonalities: higher intake of fruit, vegetables, whole grains, low-fat and nonfat dairy, seafood, legumes, and nuts; moderate intake of alcohol (for adults only who choose to drink alcohol); lower intake of red and processed meat; and low intake of added sugars and refined grains (8, 10). Similar healthy dietary patterns are also recommended by professional groups such as the American Heart Association and the American College of Cardiology (11).

Despite considerable evidence supporting the wholistic, overall dietary pattern approach for optimal health, the intake of red and processed meat is a pattern component that may merit attention on its own. The USDA defines *red meat* as any red animal muscle tissue; the source of the red pigment is the myoglobin protein that delivers oxygen to the tissue (12). Most red meat retains some amount of red upon cooking, but even meats that become lighter in color after cooking are still considered red meat and include beef, veal, lamb, and pork. Venison and other game meats are also classified as red meat.

Poultry, wild fowl, and fish are not considered red meat due to the lower concentration of myoglobin. The USDA defines *processed meat* as “any meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavor or improve preservation” (12). Processed meat may include both red meat and white meat (fish and poultry) in products such as sausage, bacon, and cold cuts. Each of the prominent a priori dietary patterns [e.g. Healthy Eating Index 2015, Alternative Healthy Eating Index, Mediterranean Diet, and the Dietary Approaches to Stop Hypertension Trial (DASH) eating plan] recommend a low intake of red and processed meat, but acknowledge that meat provides protein, iron, zinc, and other essential nutrients. In practical terms, the 2015 DGAC recommended no more than 12.5 oz-equivalents per week (354 g/wk or 50 g/d) of meat on an average 2000 kcal/d intake (8, 9). Other scientific groups reviewing the evidence base have issued more stringent red and processed meat recommendations. In 2015, the International Agency for Cancer Research (IARC)/WHO expert review panel classified red meat as a probable carcinogen (Group 2A) and processed meat as a carcinogen (Group 1) (13). Similarly, in its 2018 Third Expert Report, the World Cancer Research Fund concluded in its evidence review that there was “strong evidence that consumption of processed meat is a *convincing* cause of colorectal cancer” and that consumption of red meat was a *probable* cause of colorectal cancer (14). Despite the recommendations to consume red and processed meat in moderation, a recent report using US nutrition surveillance data (NHANES) indicated a decline in red meat consumption from a mean of 340 g/wk to 284 g/wk between 1999 and 2016, but relatively constant intake of processed meat over the same time period with an estimated mean intake of 187 g/wk in 2016 (15).

Controversy and confusion regarding red and processed meat arose recently because in October 2019 a group of authors published a series of papers wherein they declared a new and opposing set of dietary recommendations based on their own de-novo systematic reviews (16–21). This author group suggested

The author reported no funding received for this work.

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Received October 26, 2019. Accepted for publication October 31, 2019.

First published online November 19, 2019; doi: <https://doi.org/10.1093/ajcn/nqz294>.

that “adults continue current unprocessed red meat consumption and processed meat consumption” (17). They further declared that diets “restricted in meat may have little or no effect on major cardiometabolic outcomes and cancer mortality and morbidity” (21) or on “all-cause mortality” (20).

How can such conclusions, which differ so vastly from numerous other evidence-based guidelines, arise and be published in a peer-reviewed journal? In addressing this question, it is important to recognize that most diet-related chronic diseases take years to develop and manifest clinical symptoms. With a few exceptions of dietary modification trials yielding key findings applicable to health promotion and disease prevention (22–25), many randomized trials are short-term with insufficient follow-up time for enough outcome accrual to detect intervention effects. For this reason, observational cohort studies are an important research design for the study of risk factors involved in chronic disease risk. In this type of study design, individuals free of specified disease endpoints are recruited into the cohort and exposures (in this example – usual diet) are assessed. Large amounts of other data are also rigorously and uniformly collected such as demographic characteristics, weight, weight history, health history, medication use, education, occupation, smoking and alcohol habits, physical activity, and other pertinent variables. Blood, DNA, and other biospecimens are often collected, archived, and used later in nested case-control studies. The cohort is followed over time, often many years or decades, for disease occurrence that is assessed by self-report, medical records, Medicare–Medicaid linkage, or the National Death Index. Several important study design elements should be noted. First, enrolling cohort participants who are disease-free at baseline allows investigators to test the relations between the assessed exposure (e.g. diet) and the outcome. Second, the temporal relation is critical. As diet-related chronic diseases take many years to develop, the lengthy follow-up in cohort studies allows investigators to establish the temporal sequence between the dietary exposure and the outcome. Finally, because multiple risk factors in addition to diet are associated with chronic disease risk (26), carefully collected data on potential confounding variables enable analyses that estimate the independent contribution of diet after controlling for body weight, family history of the disease, and physical activity, and other potential confounding variables. Observational studies have been critical to major nutrition- and health-related success stories and subsequent public policies, including establishing the relation between folic acid and neural tube defect affected pregnancies and fortifying the US food supply (27), and the link between industrially produced *trans* fatty acids and cardiovascular disease risk and subsequent removal of these fats from the US food supply (28).

Epidemiologists recognize the limitations of observational cohorts. First, measurement error in dietary assessment is common (29–31). In recent years, this limitation has begun to be addressed by using objective biomarkers of diet from baseline stored bloods that are used to calibrate the self-report (32, 33). Other limitations include loss to follow-up and missing data, some of which can be rectified through multiple imputation procedures. Despite the limitations of observational cohorts, they remain a crucial component of nutrition research. Epidemiologists have developed methods for assessing the strength of the evidence from observational studies. Criteria evaluated include assessing the magnitude of the observed

associations (effect size), biological plausibility, dose–response, temporal associations, and consistency of findings across cohorts. In addition, the risk of bias and ability to control for confounding are assessed.

Certainty of the evidence to establish causal associations is not taken lightly, but when rigorous criteria for evaluating evidence are followed, public benefit is achieved. Herein is one reason that the recent reports on red and processed meat may fall short and, quite naturally, cause confusion. The authors used a system called GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) wherein observational studies begin the process with a rating of low and may be downgraded even further to very low should evidence for bias or other limitations arise during the course of the evaluation (16, 17, 19–21). Although a standardized system has some merits, GRADE ignores some of the well-tested criteria used by epidemiologists for drawing causal inference as described above.

Regarding red and processed meat, 3 important aspects were not considered or applied in a manner consistent with methodology used by nutritional epidemiologists:

- 1) Biological plausibility is critical to assess: short-term randomized controlled trials and controlled feeding studies, and the use of biospecimens from large cohort studies provide critically important data on biological mechanisms and surrogate endpoint biomarkers that relate red and processed meat causal pathways to chronic disease. Multiple studies have tested, via short-term trials or controlled feeding trials, red and processed meat and biomarkers of risk including lipids and lipid peroxidation, DNA damage via exposure to heterocyclic amines, *N*-nitroso compounds and polycyclic aromatic hydrocarbons, and effects on the gut microbial community composition (13, 34–37). Notably, the 2015 IARC Monograph (13) reviewed both human and preclinical animal model data with regard to biological mechanisms that support the observational data demonstrating greater health benefits when red and processed meat are consumed in moderation. Biological plausibility and supporting biomarker studies were not considered in the recent reports suggesting that red and processed meat consumption should not be reduced.
- 2) Consistency of the evidence: as described above, epidemiologists are well aware of the limitations of observational research and are very cautious regarding causal inference. Yet, when there is a body of evidence testing similar exposures and outcomes across multiple cohorts in varied populations, then the confidence in the results rises to a higher level (e.g. “moderate” or “probable”). This approach has been used and endorsed by many expert groups in evidence reviews (8, 14, 38), but was not employed by the authors of the recent papers.
- 3) Effect size: the recent reports allowed observational studies to rise to “moderate” or “high certainty” only when “a large effect size is observed, when all plausible biases would work in an opposite direction to the observed effect”; they explicitly did not upgrade when dose–response gradients were present (16, 20, 21). This meant that results were dismissed as “very low evidence” that had shown significantly reduced risk of certain outcomes (type 2 diabetes, stroke, fatal stroke, cardiovascular mortality, for

example) (20), even though the 95% CIs around the RR estimates did not include the null value of 1.0. From a population health perspective, any lifestyle modification that could significantly reduce risk by 6–10% is noteworthy and provides population benefit. The risk estimates in the original studies were meant to be RRs, not absolute risks as was interpreted in the recent reports (20). Such misinterpretation is unfortunate and confuses both the nutrition science community and the public.

Earlier this year, the *American Journal of Clinical Nutrition* published an important piece that was years in the making (39). The report provided several recommendations for best practices in conducting and publishing nutrition science research. The recent publications about red and processed meat suggest that we as a nutrition science community still have a long way to go to ensure both the trust of the scientific community as well as clinicians and their patients and the public. The stakes are high; most of the chronic diseases facing Americans are preventable. We have a responsibility and duty to conduct high-quality science, to properly interpret the data, and to communicate our findings through a rigorous process. The recent reports on red and processed meat fell short on several of these points.

The author reports no conflicts of interest.

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## Update

# The American Journal of Clinical Nutrition

Volume 111, Issue 2, February 2020, Page 488

DOI: <https://doi.org/10.1093/ajcn/nqz320>

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Corrigendum for S. Smajis et al. Metabolic effects of a prolonged, very-high-dose dietary fructose challenge in healthy subjects. *Am J Clin Nutr* 2020;111:369–77. The name of co-author Chiara Barbieri was spelled incorrectly; the name should read Chiara Barbieri instead of Chiara Barbierri. The authors apologize for the mistake.

doi: <https://doi.org/10.1093/ajcn/nqz341>

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Corrigendum for Marian L. Neuhouser. Red and processed meat: more with less? *Am J Clin Nutr* 2020;111:252–5. Page 1 of the published paper, column 2, last sentence at the end of the paragraph should state: “Despite... 340g/wk to 284 g/wk... 187 g/wk in 2016” instead of per day as is currently states. The author apologizes for this error and for any confusion it may have caused.

doi: <https://doi.org/10.1093/ajcn/nqz320>

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Corrigendum for Porter J et al. Total energy expenditure measured using doubly-labelled water compared with estimated energy requirements in older adults (65 years and over): analysis of primary data. *Am J Clin Nutr* 2019;110:1353–61.

An error between the results and discussion due to a sentence omitted from the methods has been identified. This corrigendum adds the missing sentence, and also adds footnotes to tables to ensure correct interpretation of the findings, and to amend inaccuracies in the interpretation of the results.

On page 2, second column and second full paragraph of the PDF, a third sentence should be added after “...gold standard measures” to read “The difference between measured and predicted RMR and TEE was calculated as “measured minus predicted,” therefore a negative difference means the equation overestimated measured RMR or TEE and a positive difference means the equation underestimated measured RMR or TEE.

In Table 1, the last value in the column (WHO) “Lower LOA” should be -2031 not -2013 and the last column of Table 1 all should be “yes.”

A second footnote should be added to Table 1: “A negative “mean of the difference” means the equation overestimated measured RMR and a positive “mean of the difference” means the equation underestimated measured RMR.”

On page 4, second column and first full paragraph of the PDF, 86 should be -86, 175 should be -175 and -24 should be 24

The words “underestimated” should be changed to “overestimated” (2 occasions) on page 6, first column, first full paragraph.

A second footnote should be added to Table 3: “A negative “mean of the difference” means the equation overestimated measured TEE and a positive “mean of the difference” means the equation underestimated measured TEE.”

In Supplementary Table 4, last column, third row down (Korth) should be a “yes.”

The authors apologize for the errors.

doi: <https://doi.org/10.1093/ajcn/nqz321>

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Corrigendum for Shih et al. Changes in blood lipid concentrations associated with changes in intake of dietary saturated fat in the context of a healthy low-carbohydrate weight-loss diet: a secondary analysis of the Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) trial. *Am J Clin Nutr* 2019;109:433–41.

The authors would like to add a source of support that was not included in the original publication. The study received support from The European Union’s Horizon 2020 Research and Innovation Programme (grant/award number 701,944).

The Authors apologize for this error.

doi: <https://doi.org/10.1093/ajcn/nqz324>