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Food Sources of Saturated Fat and Cardiovascular Disease: A Systematic Review Protocol

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Introduction

To prepare for the development of the *Dietary Guidelines for Americans, 2025-2030*, the U.S. Departments of Health and Human Services (HHS) and Agriculture (USDA) identified a proposed list of scientific questions based on relevance, importance, potential federal impact, and avoiding duplication, which were posted for public comment.[*] The Departments appointed the 2025 Dietary Guidelines Advisory Committee (Committee) in January 2023 to review evidence on the scientific questions. The proposed scientific questions were refined and prioritized by the Committee for consideration in their review of the evidence. Their review forms the basis of their independent, science-based advice and recommendations to HHS and USDA, which is considered as the Departments develop the next edition of the *Dietary Guidelines*. As part of that process, the following systematic review question has been identified: What is the relationship between food sources of saturated fat consumed and risk of cardiovascular disease?

The Committee will conduct a systematic review to address this question, with support from USDA's Nutrition Evidence Systematic Review (NESR) team (**Table 1**).

Table 1. Review history

Date	Description	Citation
October 2023	Systematic review protocol for the 2025 Dietary Guidelines Advisory Committee published online	Hoelscher DM, Anderson C, Booth S, Deierlein A, Fung T, Gardner C, Giovannucci E, Raynor H, Stanford FC, Talegawkar S, Taylor C, Tobias D, Obbagy J, Kim JH, Kingshipp BJ, Raghavan R, Higgins M, Butera G, Terry N. Food Sources of Saturated Fat and Risk of Cardiovascular Disease: A Systematic Review Protocol. October 2023. U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, Nutrition Evidence Systematic Review. Available at: https://nesr.usda.gov/protocols
February 2024	Revisions to the systematic review protocol for the 2025 Dietary Guidelines Advisory Committee published online	Hoelscher DM, Anderson C, Booth S, Deierlein A, Fung T, Gardner C, Giovannucci E, Raynor H, Stanford FC, Talegawkar S, Taylor C, Tobias D, Obbagy J, Kim JH, Kingshipp BJ, Raghavan R, Higgins M, Butera G, Terry N. Food Sources of Saturated Fat and Risk of Cardiovascular Disease: A Systematic Review Protocol. October 2023. U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, Nutrition Evidence Systematic Review. Available at: https://nesr.usda.gov/protocols

Methods

The NESR methodology manual[†] has a detailed description of the NESR methodology as it will be applied in the systematic reviews for the Dietary Guidelines for Americans, 2025-2030 Project. This section presents an overview of the specific methods that will be used by the Committee to answer the systematic review question: What is the relationship between food sources of saturated fat consumed and risk of cardiovascular disease?

[*] Dietary Guidelines for Americans: Learn About the Process. 2022. Available at: https://www.dietaryguidelines.gov/work-under-way/learn-about-process

[†] USDA Nutrition Evidence Systematic Review Branch. USDA Nutrition Evidence Systematic Review: Methodology Manual. February 2023. U.S. Department of Agriculture, Food and Nutrition Service, Center for Nutrition Policy and Promotion, Nutrition Evidence Systematic Review. Available at: https://nesr.usda.gov/methodology-overview

Develop a protocol

A systematic review protocol is the plan for how NESR's methodology will be used to conduct a specific systematic review and is established by the Committee, *a priori*, before any evidence is reviewed. The protocol is designed to capture the most appropriate and relevant body of evidence to answer the systematic review question. Development of the protocol involves discussion of the strengths and limitations of various methodological approaches relevant to the question, which then inform subsequent steps of the systematic review process. The protocol describes all of the methods that will be used throughout the systematic review process. Additionally, the protocol includes the following components, which are tailored to each systematic review question: the analytic framework, the inclusion and exclusion criteria, and the synthesis plan.

The protocol for this systematic review was posted online (https://nesr.usda.gov/protocols) in October 2023. Revisions to the systematic review protocol were made during the review process. These revisions are documented in **Table 2**.

Table 2. Protocol revisions

Date	Protocol revision	Description
January 2024	Inclusion and exclusion criteria were added for sample size, specifying that only those intervention studies with ≥30 participants per study group or that report a power calculation indicating that the study is appropriately powered for the outcome(s) of interest will be included.	This revision was made to enable focus on a stronger body of evidence by including intervention studies with adequate statistical power to detect differences in the outcome(s) of interest. This edit also ensures consistency with the protocol for the systematic review on dietary patterns and cardiovascular disease. This revision was made before any evidence was synthesized.
January 2024	Inclusion and exclusion criteria for publication date were updated to document that the review will include studies published through January 2024.	This revision was made to document the final publication date range covered by the literature search.

Develop an analytic framework

An analytic framework visually represents the overall scope of the systematic review question and depicts the contributing elements that will be examined and evaluated. **Figure 1** is the analytic framework for the systematic review and shows that the intervention or exposure of interest is the consumption of food sources of saturated fatty acids (SFA) from: animal sources of saturated fat, such as dairy products (e.g., milk, cheese, yogurt, ice cream); meat (e.g., white meat, red meat, processed meat); solid fats (e.g., butter, ghee, tallow, lard); plant sources of saturated fat, such as tropical food sources/oils (e.g., palm oil, coconut oil, cocoa butter, coconut); and mixed/other food sources (e.g., shortening, baked goods) in children and adolescents (ages 2 up to 19 years), and adults and older adults (19 years and older). The comparators are consumption of different amounts of the same source (including no consumption), consumption of different food sources of SFA, consumption of similar food sources with different amounts of SFA (e.g., low fat dairy vs full-fat dairy), replacement with food sources of carbohydrate and/or protein, and consumption of food sources of monounsaturated fatty acids (MUFA), or polyunsaturated fatty acids (PUFA) (e.g., oils, nuts, fish). In children, adolescents, adults and older adults, the outcomes include LDL cholesterol, HDL cholesterol, triglycerides, hyperlipidemia, blood pressure (systolic and diastolic), and hypertension; and in adults and older adults, the outcomes also include cardiovascular disease (CVD) morbidity (e.g., myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease (PAD), stroke), or composite CVD morbidity and CVD mortality, and CVD-related mortality. The key confounders are sex, age, race and/or ethnicity, socioeconomic position, physical activity, anthropometry, smoking (adults), alcohol intake (adults), diet quality, and total energy intake. The key confounders may impact the relationships of interest.

Figure 1. Analytic framework for the systematic review question: What is the relationship between food sources of saturated fat consumed and risk of cardiovascular disease?

Population	***Intervention/ exposure***	***Comparator***	***Outcome***	***Key confounders***

Children and adolescents (2 up to 19 years)
 	
Adults and older adults (19 years and older)
	Consumption of food sources[1] of saturated fatty acids:
	• Animal sources of saturated fat
	  ○ Dairy products (e.g., milk, cheese, yogurt, ice cream)
	  ○ Meat (e.g., white meat, red meat, processed meat)
	  ○ Solid fats (e.g., butter, ghee, tallow, lard)
	• Plant sources of saturated fat
	  ○ Tropical food sources / oils (e.g., palm oil, coconut oil, cocoa butter, coconut)
	• Mixed/other food sources (e.g., shortening, baked goods)
		• Consumption of a different amount of the same food source (including no consumption)
		• Consumption of different food sources of saturated fatty acids
		• Consumption of similar food sources with different amounts of saturated fatty acids (e.g., low fat dairy vs full fat dairy)
		• Replacement with food sources of carbohydrate and/or protein
		• Consumption of food sources of monounsaturated, polyunsaturated fatty acids (e.g., oils, nuts, fish)
			In children and adolescents, adults and older adults
			• LDL cholesterol
			• HDL cholesterol
			• Triglycerides
			• Hyperlipidemia
			• Blood pressure (systolic, diastolic)
			• Hypertension
			In adults and older adults
			• CVD morbidity (e.g., myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease, stroke) or composite CVD morbidity and CVD mortality
			• CVD-related mortality
				• Sex
				• Age
				• Race and/or ethnicity
				• Socioeconomic position
				• Physical activity
				• Anthropometry
				• Smoking (adults)
				• Alcohol intake (adults)
				• Diet quality
				• Total energy intake

Synthesis organization:

I. ***Population:*** Children and adolescents; adults and older adults

  a. ***Intervention/exposure:*** Food sources of saturated fatty acids[1]

    i. ***Outcome:*** LDL cholesterol, HDL cholesterol, Triglycerides, Hyperlipidemia, Blood pressure (systolic, diastolic), Hypertension

II. ***Population:*** Adults and older adults

  a. ***Intervention/exposure:*** Food sources of saturated fatty acids[1]

    i. ***Outcome:*** CVD morbidity (e.g., myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease, stroke) or composite CVD morbidity and CVD mortality, CVD-related mortality

Key definitions:
[1]Food sources of saturated fatty acids considered include - Animal sources of saturated fat: meat (e.g., white meat, red meat, processed meat), dairy products (e.g., milk, cheese, yogurt, ice cream), solid fats (e.g., butter, ghee, tallow, lard); Plant sources of saturated fat: Tropical food sources/oils (e.g., palm oil, coconut oil, cocoa butter, coconut); Mixed/other food sources (e.g., shortening, baked goods)

Develop inclusion and exclusion criteria

The inclusion and exclusion criteria provide an objective, consistent, and transparent framework for determining which articles to include in the systematic review (see **Table 3**). These criteria ensure that the

most relevant and appropriate body of evidence is identified for the systematic review question, and that the evidence reviewed is:

- Applicable to the U.S. population of interest
- Relevant to Federal public health nutrition policies and programs
- Rigorous from a scientific perspective

Table 3. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Randomized controlled trials • Non-randomized controlled trials[*] • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies	• Uncontrolled trials[†] • Case-control studies • Cross-sectional studies • Ecological studies • Narrative reviews • Systematic reviews • Meta-analyses • Modeling and simulation studies
Publication date	• January 1990 – January 2024	• Before January 1990, after January 2024
Population: Study participants	• Human	• Non-human
Population: Life stage	• At intervention, exposure, and outcome: o Children and adolescents (2 up to 19 years) o Adults and older adults (19 years and older) o Individuals during pregnancy o Individuals during postpartum	

[*] Including quasi-experimental and controlled before-and-after studies

[†] Including uncontrolled before-and-after studies

Category	Inclusion Criteria	Exclusion Criteria
Population: Health status	• Studies that exclusively enroll participants not diagnosed with a disease* • Studies that exclusively enroll participants with elevated blood pressure or high cholesterol and are evaluating cardiovascular disease endpoint outcomes • Studies that enroll some participants: ○ diagnosed with a disease; ○ diagnosed with a disorder that affects feeding/eating or growth (e.g., autism spectrum disorder, attention-deficit/hyperactivity disorder, eating disorders); ○ with severe undernutrition, failure to thrive/underweight, stunting, or wasting; ○ hospitalized for an illness, injury, or surgery; ○ pre- or post-bariatric surgery; ○ receiving pharmacotherapy to treat obesity; ○ and/or with the outcome of interest.	• Studies that exclusively enroll participants: ○ diagnosed with a disease;† ○ diagnosed with a disorder that affects feeding/eating or growth (e.g., autism spectrum disorder, attention-deficit/hyperactivity disorder, eating disorders); ○ with severe undernutrition, failure to thrive/underweight, stunting, or wasting; ○ with elevated blood lipids or blood pressure levels that are or should be treated clinically/pharmacologically and only report on the specific outcome of blood lipids or blood pressure, respectively; ○ hospitalized for an illness, injury, or surgery;‡ ○ pre- or post-bariatric surgery; ○ and/or receiving pharmacotherapy to treat obesity.
Intervention/ exposure	• Consumption of food sources of saturated fatty acids: ○ Animal sources of saturated fat ▪ Dairy products (e.g., milk, cheese, yogurt, ice cream) ▪ Meat (e.g., white meat, red meat, processed meat) ▪ Solid fats (e.g., butter, ghee, tallow, lard) ○ Plant sources of saturated fat ▪ Tropical food sources / oils (e.g., palm oil, coconut oil, cocoa butter, coconut) ○ Mixed/other food sources (e.g., shortening, baked goods)	• Studies that do not assess consumption of food sources of saturated fat (e.g., studies that only examined biomarkers for consumption) • Studies that only assess total saturated fat intake, total fat intake or overall macronutrient composition • Studies that only examine % of total energy intake from or grams/day of saturated fatty acids • Studies that examine food sources not widely available to U.S. consumers • Multi-component interventions that do not isolate the impact of specific sources of saturated fat • Studies evaluating only non-fat dairy products
Comparator	• Consumption of a different amount of the same food source (including no consumption) • Consumption of different food sources of saturated fatty acids (e.g., dairy vs meat; butter vs chocolate) • Consumption of similar food sources with different amounts of saturated fatty acids (lean vs. non-lean beef; low-fat vs full-fat dairy; low-fat vs full-fat milk; low consumption vs high consumption of whole milk) • Replacement with food sources of carbohydrate (consider type e.g., simple or complex) and/or protein • Consumption of food sources of monounsaturated, and/or polyunsaturated fatty acids (e.g., oils, nuts, fish)	• No comparator • Studies that compare to food sources of *trans* fatty acids (e.g., partially hydrogenated oils)

* Studies that enroll participants who are at risk for chronic disease will be included

† Studies that exclusively enroll participants with obesity will be included

‡ Studies that exclusively enroll participants post-cesarean section will be included

Category	Inclusion Criteria	Exclusion Criteria
Outcomes	In children and adolescents, adults and older adults • LDL cholesterol • HDL cholesterol • Triglycerides • Hyperlipidemia • Blood pressure (systolic, diastolic) • Hypertension In adults and older adults • CVD morbidity (e.g., myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease, stroke) or composite CVD morbidity and CVD mortality • CVD-related mortality	• Studies that **only** assess post-prandial lipid levels (i.e., total, LDL-, and HDL-cholesterol, and/or triglycerides) • Studies that **only** assess serum/plasma lipid ratios (i.e., TC:HDL, LDL:HDL ratios) • Studies that **only** assess total cholesterol
Confounders	• Studies that control for at least one of the key confounders listed in the analytic framework	• Studies that do not control for any of the key confounders listed in the analytic framework
Study duration	• Intervention length ≥ 4 weeks	• Intervention length < 4 weeks
Size of study groups (not applied to pregnancy and postpartum studies)	• For intervention studies: ○ ≥30 participants per study group for between-subject analyses, ○ or a power calculation indicating that the study is appropriately powered for the outcome(s) of interest	• For intervention studies: ○ <30 participants per study group for between-subject analyses, ○ and no power calculation indicating that the study is appropriately powered for the outcome(s) of interest
Publication status	• Peer-reviewed articles published in research journals	• Non-peer-reviewed articles, unpublished data or manuscripts, pre-prints, reports, editorials, retracted articles, and conference abstracts or proceedings
Language	• Published in English	• Not published in English
Country*	• Studies conducted in countries classified as high or very high on the Human Development Index the year(s) the intervention/exposure data were collected	• Studies conducted in countries classified as medium or low on the Human Development Index the year(s) the intervention/exposure data were collected

* The classification of countries on the Human Development Index (HDI) is based on the UN Development Program Human Development Report Office (http://hdr.undp.org/en/data) for the year the study intervention occurred or data were collected. If the study does not report the year(s) in which the intervention/exposure data were collected, the HDI classification for the year of publication is applied. Studies conducted prior to 1990 are classified based on 1990 HDI classifications. If the year is more recent than the available HDI values, then the most recent HDI classifications are used. If a country is not listed in the HDI, then the current country classification from the World Bank is used (The World Bank Country and Lending Groups, available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-country-and-lending-groups)

Search for and screen studies

NESR librarians, in collaboration with NESR analysts and the Committee, will use the analytic framework and inclusion and exclusion criteria to develop a comprehensive literature search strategy. The literature search strategy will include selecting and searching the appropriate bibliographic databases, translating search using syntax appropriate for the databases being searched, and employing search refinements, such as search filters. The full literature search will be available upon request, and will be fully documented in the final review.

The results of all electronic database searches, after removal of duplicates, will be screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles meet the inclusion criteria. Manual searching will be conducted to find peer-reviewed published articles not identified through the electronic database search. These articles will also be screened independently by two NESR analysts at the abstract and full-text levels.

Extract data and assess the risk of bias

NESR analysts will extract all essential data from each included article to describe key characteristics of the available evidence, such as the author, publication year, cohort/trial name, study design, population life stage at intervention/exposure and outcome, intervention/exposure and outcome assessment methods, and outcomes. One NESR analyst will extract the data and a second NESR analyst will review the extracted data for accuracy. Each article included in the systematic review will undergo a formal risk of bias assessment, with two NESR analysts independently completing the risk of bias assessment using the tool that is appropriate for the study design.[*†‡]

Synthesize the evidence

The Committee will describe, compare, and combine the evidence from all included studies to answer the systematic review question. Synthesis of the body of evidence will involve identifying overarching themes or key concepts from the findings, identifying and explaining similarities and differences between studies, and determining whether certain factors impact the relationships being examined. The first level of synthesis organization will be by population. Then, within each of the population groups, the evidence will be organized by similar intervention/exposure based on the available evidence. Depending on the available evidence, the next level of organization will be according to similar outcomes.

Develop [a] conclusion statement[s] and grade the evidence

After the Committee synthesizes the body of evidence, they will draft a conclusion statement or conclusion statements. A conclusion statement is one or more summary statements carefully constructed to answer the systematic review question. It reflects the evidence reviewed, as outlined in the analytic framework (e.g., PICO elements) and synthesis plan, and does not take evidence from other sources into consideration. The Committee will review, discuss, and revise the conclusion statement until they reach agreement on wording that accurately reflect the body of evidence.

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[*] Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. Aug 28 2019;366:l4898.doi:10.1136/bmj.l4898

[†] Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. Oct 12 2016;355:i4919.doi:10.1136/bmj.i4919

[‡] ROBINS-E Development Group., Higgins J, Morgan R, et al. Bias In Non-randomized Studies - of Exposure (ROBINS-E). 2022. https://www.riskofbias.info/welcome/robins-e-tool

The Committee will then assign a grade to each conclusion statement (i.e., strong, moderate, limited, or grade not assignable). The grade communicates the strength of the evidence supporting a specific conclusion statement to decision makers and stakeholders. NESR has predefined criteria, based on five grading elements that the Committee will use to evaluate and grade the strength of the evidence supporting each conclusion statement. The five grading elements are: consistency, precision, risk of bias, directness and generalizability of the evidence. Study design will also be considered during the grading process.

Recommend future research

The Committee will identify and document research gaps and methodological limitations throughout the systematic review process. These gaps and limitations will be used to develop research recommendations that describe the research, data, and methodological advances that are needed to strengthen the body of evidence on a particular topic. Rationales for the necessity of additional or stronger research may also be provided with the research recommendations.

Acknowledgments and funding

The Committee members are involved in: establishing all aspects of the protocol, which presents the plan for how they are planning to examine the scientific evidence, including the inclusion and exclusion criteria; reviewing all studies that meet the criteria the Committee sets; deliberating on the body of evidence for each question; and writing and grading the conclusion statements. The NESR team, with assistance from Federal staff from HHS and USDA (Kara Beckman, PhD; Jessica Bluto, MS, RDN, LD, CDCES, CSOWM; Dana DeSilva, PhD, RD; Kevin Kuczynski, MS, RD; Emily Levin, MPH, RDN; TusaRebecca Pannucci, PhD, MPH, RD; Julia Quam, MSPH, RND; Elizabeth Rahavi, RD) and Project Leadership (HHS: Janet de Jesus, MS, RD; USDA: Eve Stoody, PhD), supports the Committee by facilitating, executing, and documenting the work necessary to ensure the reviews are completed in accordance with NESR methodology. Contractor support was also provided by Panum Telecom (Verena McClain, MSc).

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