PART D. CHAPTER 9: DIETARY FATS AND SEAFOOD

INTRODUCTION

Since its inception in 1980, the *Dietary Guidelines for Americans* has offered evidence-based recommendations on dietary fats due to their well-documented influence on cardiometabolic disease risk, including weight regulation. This chapter updates and expands the review conducted by the 2015 Dietary Guidelines Advisory Committee, which focused on saturated fat and replacement with other fatty acids or carbohydrates.[1] Seafood is also a high priority dietary exposure of interest, due both to its unique nutrient contributions, particularly the omega-3 fatty acids, and its role as a food component within dietary patterns. The reviews undertaken by the Committee examined these topics with a life course approach, beginning with pregnancy, lactation, and early childhood and continuing throughout adulthood.

Past reviews of the scientific literature on the relationship between dietary fat intake and cardiovascular disease (CVD) risk have included research from Federally-funded, longitudinal, multi-site studies going back to the 1960s. These landmark studies, both clinical trials and prospective cohort studies (PCSs), continue to guide clinical practice for advancing cardiovascular health of Americans. For the current review on dietary fats, the 2020 Dietary Guidelines Advisory Committee examined evidence from studies conducted in adults published since the 2015 Committee's review of saturated fat and risk of CVD. This Committee's review considered fat types, amounts, proportions, and replacement. The types of fat considered in the systematic review included saturated fat, omega-3 and omega-6 polyunsaturated fats, monounsaturated fat, and dietary cholesterol. Additionally, the Committee examined evidence on dietary fat intake and risk of CVD in children from 1990 to present.

Although the Committee initially sought to conduct its dietary fats review on a range of health outcomes including CVD, all-cause mortality, certain types of cancer, and neurocognitive health, it ultimately chose to focus on CVD outcomes. However, two of these outcomes—all-cause mortality and cancer—were included in the Committee's reviews of dietary patterns, which took into account not only the dietary fat component of the diet but all other food components (see ***Part D. Chapter 8: Dietary Patterns***).

Seafood intake also is of public health interest due to its association with reduced CVD risk[2] as well as with potentially beneficial neurocognitive outcomes. The Committee reviewed the current literature pertaining to seafood consumption during childhood and adolescence and risk of CVD and neurocognitive outcomes that present in both childhood and adulthood. The

childhood neurocognitive outcomes explored included the developmental domains, academic performance, attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anxiety, and depression. The adulthood outcomes included cognitive decline, mild cognitive impairment, dementia, anxiety, and depression. For purposes of these reviews, seafood was defined as marine animals that live in the sea and in freshwater lakes and rivers. Seafood includes fish (e.g., salmon, tuna, trout, tilapia) and shellfish (e.g., shrimp, crabs, oysters).[3]

The Committee also reviewed seafood intake during pregnancy and lactation and neurocognitive development of the infant. These topics are discussed in ***Part D. Chapter 2: Food, Beverage, and Nutrient Consumption During Pregnancy*** and in ***Part D. Chapter 3: Food, Beverage, and Nutrient Consumption During Lactation***.

Diet and neurocognitive health is an emerging and complex topic reviewed by this Committee, which sought to expand upon the reviews of the 2015 Committee examining dietary patterns and neurological and psychological illnesses. Although still a relatively under-researched area of scientific inquiry, the study of this relationship is expanding and could offer additional insight into how to promote optimal brain health and/or reduce the risk of neurocognitive diseases.

Current Intakes of Dietary Fat

The *2015-2020 Dietary Guidelines for Americans* encourage replacement of saturated fat with unsaturated fat while keeping saturated fat intake to less than 10 percent of calories per day,[2] however only 23 percent of the U.S. population report intakes aligned with this guidance (see ***Part D. Chapter 1: Current Intakes of Foods, Beverages, and Nutrients).*** Saturated fats are found in the highest amounts in tropical oils (i.e., coconut, palm kernel and palm), butter, and animal (beef, pork, and chicken) fats. Common food sources of saturated fat are mixed dishes containing cheese and/or meat, pizza, full fat dairy products (cheese, cream and ice cream, and whole milk), and baked goods and sweets. Both the 2015 Committee and this 2020 Committee identified saturated fat as a nutrient of concern for overconsumption because saturated fat intakes exceed current recommendations (see ***Chapter 1*** and the 2015 Dietary Guidelines Advisory Committee report).[3]

Mean saturated fat intake in the U.S. population ages 2 years and older in 2015-2016 was approximately 12 percent of total daily calories (2 percentage points higher than guidance), regardless of sex and age, according to National Health and Nutrition Examination Survey.[4] By race and ethnicity, non-Hispanic whites had the highest intake (12.2 percent daily calories) and

non-Hispanic Asians had the lowest intake (9.7 percent daily calories). Non-Hispanic whites had the highest prevalence (83 percent) of those exceeding the recommended limit of less than 10 percent energy contribution from saturated fat, followed by Hispanics (70 percent), non-Hispanic blacks (69 percent), and non-Hispanic Asians (43 percent) based on the NHANES 2013-2016 data analysis (Energy contribution from NHANES 2013-2016; see ***Part D. Chapter 1***).[5]

In contrast, saturated fat intake and its energy contribution varied little by family income as a percentage of poverty level.[4] No significant trends in saturated fat intake by meal patterns, snack occasions, or place of consumption were noted.[4]

The food category called "solid fat" includes a variety of fats, but predominantly saturated fat and to a small extent, *trans* fat. This category includes the saturated fats naturally found in animal products (e.g., meats, dairy) as well as vegetable sources with high saturated fat content, like tropical oils, e.g., coconut oil and hydrogenated vegetable shortenings. Although as a category, solid fat intake has decreased in recent years, as shown in NHANES data between 2003-2004 and 2015-2016, this appears to be largely attributable to the reduction of *trans* fat in the food supply. No significant change in the percentage of energy from saturated fat has occurred since the 1999-2000 NHANES.[6]

The top food subcategory sources of solid fats among American adults and children include burgers and sandwiches (12 to 22 percent) and desserts and sweet snacks (14 to 19 percent). Higher-fat milk/yogurt provide 19 percent of solid fats in the diets of children ages 2 to 5 years and 11 percent of solid fats among those ages 6 to 11 years. Similar to sources of solid fats, burgers and sandwiches are the top food subcategory source of oils across all age groups (15 to 20 percent). The next most common food subcategory source of oils is chips, crackers, and savory snacks for individuals ages 2 to 49 years, and vegetables for individuals ages 51 years and older (see ***Part D. Chapter 1***).

Additionally, the *2015-2020 Dietary Guidelines for Americans* recommend keeping dietary cholesterol intake to a minimum while consuming a healthy eating pattern. In general, only animal foods contain dietary cholesterol and some, such as fatty meats and full-fat cheese, are also higher in saturated fats. The exceptions to this are eggs and shellfish (e.g., shrimp), which are high in dietary cholesterol, but are not high in saturated fat. Currently, the mean intake of dietary cholesterol is 282 mg per day for the general population ages 2 and older. Males have a higher mean dietary cholesterol intake of 321 mg per day compared to 245 mg per day for females.[4] This represents an increase in mean dietary cholesterol consumption compared to 4 years prior when the mean population intake was 267 mg per day.[7]

Current Intakes of Seafood

Current guidance on seafood encourages consumption of 8 ounces or more per week of a variety of seafood for the general population,[2] with more specific guidance for women who are pregnant. However, recent intake data document that most people do not meet this recommendation, and, in fact, among both children and adults, seafood intake has decreased since 2005-2006 (see ***Part D. Chapter 1***).

Data from two 24-hour dietary recalls conducted as part of the What We Eat in America component of NHANES 2013-2016 reported that among children (ages 1 to 18 years), usual seafood intake was less than 0.3 ounce-equivalents per day and among adults, intake was 0.5 to 0.7 ounce-equivalents per day.[8] Given the episodic nature of seafood consumption in the United States, a non-quantitative food-frequency questionnaire (FFQ) focusing on fish and shellfish consumption during the previous 30 days was also administered as part of the same NHANES survey. Based on these supplemental data, approximately 20 percent of adults consumed seafood at least two times per week. Non-Hispanic Asian adults (41 percent) report a higher frequency of consuming seafood at least two times per week, when compared to non-Hispanic white (19 percent), non-Hispanic black (23 percent), and Hispanic (15 percent) adults. Among youths ages 2 to 19 years, about 5 percent report consuming seafood at least two times per week, with little variation by age group. Non-Hispanic Asian youth report a significantly higher frequency of consuming seafood at least two times per week (20 percent), compared to non-Hispanic white (4.1 percent), non-Hispanic black (7.5 percent), and Hispanic (4.8 percent) youth.

This chapter will discuss the findings, limitations, and recommendations from the Committee's review of these important topics.

LIST OF QUESTIONS

Dietary Fats

1. What is the relationship between types of dietary fat consumed and risk of cardiovascular disease?

Seafood

2. What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and risk of cardiovascular disease?
3. What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and neurocognitive development?

METHODOLOGY

All questions discussed in this chapter were answered using systematic reviews conducted with support from USDA's Nutrition Evidence Systematic Review (NESR) team. NESR's systematic review methodology provided a rigorous, consistent, and transparent process for the Committee to search for, evaluate, analyze, and synthesize evidence.

The Committee developed a systematic review protocol for each question, which described how the Committee would apply NESR's methodology to answer the question. The protocol included an analytic framework and inclusion and exclusion criteria to guide identification of the most relevant and appropriate body of evidence to use in answering each systematic review question. Each analytic framework outlined core elements of the systematic review question (i.e., population, intervention and/or exposure and comparator [i.e., the alternative being compared to the intervention or exposure], and outcomes), and included definitions for key terms, key confounders, and other factors to be considered when reviewing the evidence. The inclusion and exclusion criteria were selected, up front, to operationalize the elements of the analytic framework, and specify what made a study relevant for each systematic review question.

Next, a literature search was conducted to identify all potentially relevant articles, and those articles were screened by two NESR analysts independently, based on the criteria selected by the Committee. For each included article, data were extracted and risk of bias assessed. The Committee qualitatively synthesized the body of evidence to inform development of a conclusion statement(s), and graded the strength of evidence using pre-established criteria for risk of bias, consistency, directness, precision, and generalizability. Finally, recommendations for future research were identified. A detailed description of NESR's systematic review methodology is provided in ***Part C. Methodology***, including standard inclusion and exclusion criteria applied in many of the Committee's systematic reviews. Complete documentation of each systematic review is available on the following website: nesr.usda.gov/2020-dietary-guidelines-advisory-

committee-systematic-reviews. Below is a summary of the unique elements of the protocols developed to answer the dietary fats and seafood questions addressed in this Chapter and in ***Part D. Chapter 2: Food, Beverage, and Nutrient Consumption During Pregnancy*** and ***Part D. Chapter 3: Food, Beverage, and Nutrient Consumption During Lactation***.

Dietary Fats

Question 1 was answered using a new systematic review conducted with support from USDA's NESR team to build on evidence reviewed by the 2015 Committee. A description of the process the 2020 Committee used when existing systematic reviews were available is provided in ***Part C. Methodology***. In addition, detailed information about the 2015 Committee's review of the evidence can be found in their report, which is available at the following website: dietaryguidelines.gov/current-dietary-guidelines/process-develop-2015-2020-dg/advisory-committee.

For the current review, the intervention or exposure of interest was types of dietary fat, including saturated fat, omega-3 and omega-6 polyunsaturated fats, monounsaturated fat, and dietary cholesterol. The comparators of interest were consumption of different types, sources, amounts, and/or proportions of dietary fats, or replacement with other dietary fats, carbohydrates, and/or protein. To maintain the focus of the review on types of dietary fat, the Committee established criteria for the intervention and exposure to exclude studies that:

- Did not assess consumption of type(s) of dietary fats (e.g., studies that examined only biomarkers for consumption),
- Assessed only total fat intake or overall macronutrient composition; *trans* fat; intake of fat from supplements or fish oils; or human milk and/or infant formula,
- Examined food products not widely available to U.S. consumers, or
- Examined multi-component interventions that do not isolate the impact of type of fat.

The population of interest for the intervention or exposure was infants and toddlers (birth to age 24 months, children and adolescents (age 2 to 18 years), adults (ages 19 to 64 years), and older adults (ages 65 years and older).

Outcomes of interest included both CVD intermediate and endpoint health outcomes, and the types of outcomes examined varied by population (i.e., children or adults) and study design. Intermediate outcomes included blood pressure (systolic and diastolic; in children only), and blood lipids (i.e., total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides in children and adults). The original protocol

also included lipid ratios (e.g., LDL-C:HDL-C) and blood pressure in adults, but these were later removed to focus on the strongest predictors of CVD and due to the lack of evidence on the effect of types of dietary fat on blood pressure, respectively. Endpoint CVD health outcomes included CVD (i.e., myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, and peripheral artery disease), stroke, venous thrombosis, and CVD-related mortality.

To focus on the strongest available evidence, additional criteria were employed to specify which study designs were eligible for inclusion depending on the outcomes being examined. For adults (ages 19 years and older), only evidence on intermediate outcomes from controlled trials, both randomized controlled trials (RCTs) and non-randomized controlled trials, was included, whereas evidence on endpoint outcomes was considered from all included study designs. For children (birth to age 18 years), evidence on intermediate and endpoint outcomes was considered from all included study designs (i.e., RCTs and certain types of observational studies). Furthermore, the Committee established inclusion and exclusion criteria for intervention duration. For all experimental studies (RCTs and non-RCTs), studies were included if the intervention duration was equal to or greater than 4 weeks; studies were excluded if the intervention duration was less than 4 weeks. Interventions shorter than 4 weeks were considered inadequate in length to assess change in blood lipids.

When establishing other inclusion and exclusion criteria, the Committee used standard NESR criteria for publication status, language of publication, country, study participants, and health status of study participants. The inclusion and exclusion criteria for date of publication was selected to build on the evidence previously reviewed by the 2015 Committee, which reviewed evidence only on adults, and therefore, the inclusion and exclusion criteria varied by the age of study participants. Specifically, the publication date range for studies in children was January 1990 to October 2019, and the date range for studies in adults was January 2010 to October 2019.

Two literature searches were conducted to identify all potentially relevant articles for this question on risk of CVD. The first search identified articles published between January 1990 and December 2009 on types of dietary fat consumed by children and adolescents. The second search identified articles published between January 2010 and October 2019 on types of dietary fat consumed by children, adolescents, and adults. After the two searches were conducted, duplicate articles were removed, and the total number of articles were combined for screening.

Seafood

Questions 2 and 3 in this chapter and questions on seafood consumption during pregnancy (see ***Part D. Chapter 2: Food, Beverage, and Nutrient Consumption During Pregnancy***) and lactation (see ***Part D. Chapter 3: Food, Beverage, and Nutrient Consumption During Lactation***) were answered by conducting new NESR systematic reviews. The intervention or exposure of interest was consumption of seafood. Studies that assessed only biomarkers of seafood consumption (e.g., blood levels of omega-3 polyunsaturated fatty acids and environmental pollutants) were excluded. The comparators of interest included different amounts, frequency, timing, types, or sources of seafood. When evaluating whether a study's results represented a true effect of seafood consumption, the Committee considered multiple factors such as 1) nutrients in seafood (e.g., omega-3 polyunsaturated fatty acids, iodine, selenium, iron, fish protein, vitamin D), 2) environmental chemicals within seafood (e.g., methylmercury, persistent organic pollutants, and polychlorinated biphenyls), 3) blood and human milk biomarkers of seafood intake (e.g., omega-3 polyunsaturated fatty acids, and environmental pollutants), and 4) infant feeding mode. These factors, along with key confounders, were considered while evaluating study findings and synthesizing evidence.

For Questions 2 and 3, the population of interest at intervention or exposure was children and adolescents from birth to age 18 years. Seafood consumption in women during pregnancy and lactation and neurocognitive development of the infant also was examined; results are reported in ***Part D. Chapter 2*** and ***Part D. Chapter 3***.

For Question 2, the outcomes of interest included both CVD intermediate outcomes, including blood pressure (systolic and diastolic) and blood lipids (i.e., TC, LDL-C and HDL-C [including TC:HDL-C and LDL-C:HDL-C ratios], triglycerides), and CVD endpoint health outcomes, including CVD (i.e., myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease), stroke, venous thrombosis, and CVD-related mortality. The population of interest for CVD intermediate outcomes included children and adolescents (ages 2 to 18 years), adults (ages 19 to 64 years) and older adults (ages 65 years and older). The populations of interest for CVD endpoint health outcomes were adults (ages 19 to 64 years) and older adults (ages 65 years and older).

For Question 3, and the questions regarding seafood consumption in women during pregnancy and lactation and neurocognitive development of the child reported in Chapters 2 and 3, the outcome of interest was neurocognitive development. Neurocognitive development included developmental domains, academic performance, ADD or ADHD, anxiety, depression, and ASD. Developmental domains (including developmental milestones) were examined

individually, as seafood intake may have different influences on different developmental domains, and included cognitive, language and communication, movement and physical, and social-emotional and behavioral development. In the questions regarding seafood consumption in women during pregnancy or lactation, these outcomes were assessed in infants and toddlers (birth to age 24 months), and in children and adolescents (ages 2 to 18 years). In Question 3 of this chapter, these outcomes were assessed in children and adolescents (ages 2 to 18 years). An existing systematic review previously conducted by USDA's Nutrition Evidence Systematic Review (NESR) team as part of the Pregnancy and Birth to 24 Months Project reviewed evidence on seafood intake as a component of complementary feeding and neurocognitive outcomes (developmental milestones). These findings are discussed in ***Part D Chapter 5: Foods and Beverages Consumed During Infancy and Toddlerhood***.[9] Question 3 also examined neurocognitive health outcomes, including cognitive decline, mild cognitive impairment, and dementia (including Alzheimer's disease), anxiety, and depression assessed in adults (ages 19 to 64 years) and older adults (age 65 years and older).

When establishing inclusion and exclusion criteria, the Committee used standard NESR criteria for study design, publication status, language of publication, country, study participants, and health status of study participants. One literature search from January 2000 to July 2019 was conducted to answer Question 2. Another literature search was conducted to identify studies published from January 2000 to October 2019 to answer questions on seafood consumption by children (Question 3) and women during pregnancy and lactation and neurocognitive outcomes.

REVIEW OF THE SCIENCE

Dietary Fats

Question 1. What is the relationship between types of dietary fat consumed and risk of cardiovascular disease?

Approach to Answering Question: NESR systematic review

Conclusion Statements and Grades

Cardiovascular Disease Intermediate Outcomes: Children

Strong evidence demonstrates that diets lower in saturated fatty acids and cholesterol during childhood result in lower levels of total blood and low-density lipoprotein cholesterol throughout childhood, particularly in boys. Grade: Strong

Moderate evidence indicates that diets higher in polyunsaturated fatty acids during childhood result in lower levels of total blood cholesterol throughout childhood, particularly in boys. Grade: Moderate

Insufficient evidence is available to determine the relationship between monounsaturated fatty acid intake during childhood and total blood and low-density lipoprotein cholesterol throughout childhood. Grade: Grade Not Assignable

Insufficient evidence is available to determine the relationship between intake of types of dietary fat during childhood and blood pressure throughout childhood. Grade: Grade Not Assignable

Cardiovascular Disease Endpoint Outcomes: Children

Insufficient evidence is available to determine the relationship between intake of types of dietary fat during childhood and cardiovascular disease health outcomes during adulthood. Grade: Grade Not Assignable

Cardiovascular Disease Intermediate Outcomes: Adults

Strong and consistent evidence from randomized controlled trials demonstrates that replacing saturated fatty acids with unsaturated fats, especially polyunsaturated fatty acids, in adults

significantly reduces total and low-density lipoprotein cholesterol. Replacing saturated fatty acids with carbohydrates (sources not defined) also reduces total and low-density lipoprotein cholesterol, but significantly increases triglycerides and reduces high-density lipoprotein cholesterol. Since the 2015 Dietary Guidelines Advisory Committee review, evidence remains inadequate to differentiate among sources of carbohydrate and their impact on blood lipids. Grade: Strong

Insufficient evidence is available to determine an independent relationship between dietary cholesterol intake in adults and blood lipids, given the co-occurrence of cholesterol with saturated fats in foods. Grade: Grade Not Assignable

Cardiovascular Disease Endpoint Outcomes: Adults

Strong evidence demonstrates that replacing saturated fatty acids with polyunsaturated fatty acids in adults reduces the risk of coronary heart disease events and cardiovascular disease mortality. Grade: Strong

Insufficient evidence is available to determine whether replacing saturated fatty acids with polyunsaturated fatty acids in adults affects the risk of stroke or heart failure. Grade: Grade Not Assignable

Insufficient evidence is available to determine whether replacing saturated fatty acids with different types of carbohydrates (e.g., complex, simple) in adults affects the risk of cardiovascular disease. Grade: Grade Not Assignable

Limited evidence is available regarding whether replacing saturated fatty acids with monounsaturated fatty acids in adults confers overall cardiovascular disease endpoint health benefits. Main sources of monounsaturated fatty acids in a typical American diet are animal fats, with co-occurrence of saturated fatty acids and monounsaturated fatty acids in these foods thereby obscuring the independent association of monounsaturated fatty acids with cardiovascular disease. Evidence reviewed from randomized controlled trials and prospective studies demonstrated benefits of plant sources of monounsaturated fats, including olive oil and nuts on cardiovascular disease risk. Grade: Limited

Moderate evidence indicates that total intake of omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid and docosahexaenoic acid from food sources, by adults is associated with lower risk of cardiovascular disease. Grade: Moderate

Limited evidence suggests that intake of linoleic acid, but not arachidonic acid, during adulthood may be associated with lower risk of cardiovascular disease, including cardiovascular disease mortality. Grade: Limited

Insufficient evidence is available from randomized controlled trials to quantify an independent relationship between dietary cholesterol intake in adults and overall risk of cardiovascular disease. Grade: Grade Not Assignable

Summary of the Evidence

Children

- This systematic review included 37 articles,[10-46] 22 articles from 7 RCTs and 16 articles from 14 prospective cohort studies (PCSs), published between January 1990 and October 2019 that examined the relationship between intake of types of dietary fat during childhood and CVD risk. (Note: One article from an RCT also was analyzed as a PCS.)
    - The RCTs modified child fat intake either through dietary counseling that focused primarily on reducing saturated fat and dietary cholesterol intake, with additional encouragement to increase polyunsaturated fat intake, or through provision of food products (i.e., eggs, extra virgin olive oil, or oily fish) that differed in types of fat including saturated fat, monounsaturated fat, polyunsaturated fat, and/or dietary cholesterol.
    - The PCSs primarily assessed saturated fat or polyunsaturated fat intake, with fewer studies on monounsaturated fat or dietary cholesterol intake; only two studies modeled replacement between different types of fat or macronutrients.
- Most included studies assessed the relationship between intake of types of dietary fat during childhood and blood lipids.
    - Evidence from RCTs predominantly indicated that consuming less saturated fat and dietary cholesterol resulted in lower blood total cholesterol and LDL-C throughout childhood, particularly in boys; evidence from PCSs was consistent with the RCTs.
    - Although reduction of saturated fat intake was the primary focus of most RCTs,

evidence from these RCTs also showed that higher polyunsaturated fat intake resulted in decreased total blood cholesterol, particularly in boys; evidence from PCSs was broadly consistent with the RCTs.
    - Few studies, RCTs or PCSs, focused on the relationship between monounsaturated fat intake and blood lipids and the results were predominantly null.
    - The majority of studies assessed blood lipids during childhood; few assessed intake of types of fat during childhood and blood lipids into early adulthood.
- Fewer studies assessed the relationship between intake of types of dietary fat during childhood and blood pressure.
    - It was difficult to discern the effect of consuming different types of fat in the RCT that contributed the most evidence due to additional advice to reduce sodium consumption.
    - Few PCSs were conducted on this topic and results were predominantly null.
- Only 1 study included in this review assessed the relationship between intake of types of dietary fat during childhood and CVD endpoint outcomes and methodological limitations related to the dietary assessment confounded interpretation of results. Therefore, no conclusion could be drawn.
- Limitations of this body of evidence:
    - Most articles did not report race and ethnicity, but those that did included predominantly White or Caucasian participants.
    - Some studies specifically recruited children with elevated or higher than average blood lipid levels, reducing generalizability.
    - RCTs had predominantly low risk of bias, but few pre-registered their analysis intentions and several RCTs did not provide information on allocation of randomization sequences.
    - Although many PCSs accounted for most or many key confounders, all PCSs did not account for at least one key confounder.
    - Approximately half of the diet assessment methods used in the PCSs were not validated; many PCSs had high attrition rates and did not provide information on those lost to follow-up.

Adults

<u>Adults: CVD Intermediate Outcomes</u>

- This systematic review included 97 articles[47-143] that examined the relationship between intake of types of dietary fat during adulthood and CVD intermediate outcomes, published

between January 2010 and October 2019. Of these, 47 were from 47 parallel design RCTs, 46 were from 44 crossover design RCTs, and 5 were from non-RCT designs. (Note: One parallel design RCT was also analyzed as a crossover design RCT.)
    - The articles examined intake of saturated fat, monounsaturated fat, polyunsaturated fat, and dietary cholesterol.
    - The majority of articles specifically examined types of fat from different food sources, including food sources that were predominantly fat (e.g., butter and olive oil).
- The relationship between types of dietary fat and blood lipids varied by the type of fat examined and the comparator.
    - Saturated fat intake: Predominantly null effects were reported for saturated fat intake when replacement was not considered or when saturated fat was partially replaced by carbohydrates. However, among the studies that detected significant effects, all reported significantly higher total cholesterol, LDL-C, and HDL-C with higher intake of saturated fat, compared to either lower intake of saturated fat or substitution with carbohydrate.
    - Replacement of saturated fat with monounsaturated fat: More than half of articles reported a beneficial effect of replacing a portion of saturated fat intake with monounsaturated fat intake on total cholesterol and LDL-C. Predominantly null effects were reported for HDL-C and triglycerides.
    - Replacement of saturated fat with polyunsaturated fat: More than half of articles reported a beneficial effect of replacing a portion of saturated fat intake with polyunsaturated fat intake on total and LDL-C. Predominantly null effects were reported for HDL-C and triglycerides.
    - Monounsaturated fat intake: Predominantly null effects were reported for monounsaturated fat intake when replacement was not considered or when monounsaturated fat was partially replaced with carbohydrates.
    - Replacement of monounsaturated fat with polyunsaturated fat: Predominantly null effects were reported in articles that examined partial replacement of monounsaturated fat intake with polyunsaturated fat intake.
        - Among the studies that found significant effects, the majority detected significantly lower levels of or significant decreases in total cholesterol and LDL-C when polyunsaturated fat intake replaced a portion of monounsaturated fat intake.
        - Studies replacing a portion of monounsaturated fat intake with polyunsaturated fat intake predominantly detected significant decreases or greater decreases in HDL-

C and significantly higher levels of, smaller decreases in, or greater increases in triglycerides.

  - Polyunsaturated fat intake: The vast majority of articles that assessed the effect of polyunsaturated fat intake (without considering replacement) on total cholesterol, LDL-C, or HDL-C and triglycerides were null. However, among the few articles that detected significant effects, total cholesterol and LDL-C were significantly lower with greater polyunsaturated fat intake, compared with lower polyunsaturated fat intake; HDL-C significantly increased or had smaller decreases with greater polyunsaturated fat intake; and triglycerides were significantly lower or had greater decreases with greater polyunsaturated fat intake.
- Few articles published during the search years of the present review assessed the relationship between dietary cholesterol intake and blood lipids
  - Predominantly null effects were reported for dietary cholesterol. However, among the few articles that found significant results, higher intake of dietary cholesterol, compared to lower intake, significantly increased or resulted in higher levels of total cholesterol, LDL-C, and HDL-C.
  - In several articles, it was not possible to isolate the independent effect of dietary cholesterol on blood lipids due to simultaneous changes in the total amount of fat or proportion of different types of fat in the study diet.
- Limitations of this body of evidence:
  - Several articles involved small sample sizes and lacked sufficient power.
  - Race or ethnicity was not consistently reported, but among those studies that provided this information, the majority included participants who were predominantly White or Caucasian.
  - It was not possible to isolate the independent effect of saturated fat, monounsaturated fat, polyunsaturated fat, or dietary cholesterol on blood lipids in several articles due to simultaneous changes of those three types of fat.
  - The majority of articles did not control for other dietary components beyond the intervention or test meal.
- This systematic review builds and expands on the work of the 2015 Committee, which answered the question “What is the relationship between intake of saturated fat and risk of cardiovascular disease?” and considered evidence from RCTs and PCSs from the 1960s to 2010. This systematic review concurs with and updates the conclusions drawn by the 2015 Committee.

Adults: CVD Endpoint Outcomes

- This systematic review included 94 articles[144-237] that examined the relationship between intake of types of dietary fat during adulthood and CVD endpoint outcomes, published between January 2010 and October 2019. Of these, 90 were from 47 PCSs and 4 were from 3 nested case-control studies.
    - The articles primarily examined saturated fat, total polyunsaturated fat, omega-3 polyunsaturated fat (including alpha-linolenic acid [ALA], eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], or docosapentaenoic acid [DPA]), or monounsaturated fat intake. Fewer articles examined omega-6 polyunsaturated fat (including linoleic acid [LA] or arachidonic acid [AA]) or dietary cholesterol intake.
    - Several articles modeled replacement between different types of fats or macronutrients or, in some cases, between different sources of the same type of fat. Few articles specifically assessed food sources that are predominantly fat (i.e., butter and olive oil) or types of fat from different food sources.
- The relationship between types of dietary fat and CVD endpoint outcomes varied by the type of fat examined and the specific outcome assessed, with the most consistent results observed when replacement was modeled.
    - Replacement of saturated fat with polyunsaturated fat: In this review, replacement of saturated fat with polyunsaturated fat (predominantly total polyunsaturated fat) in many studies was associated with significantly lower risk of CVD mortality and/or coronary heart disease (CHD) or associations were null. Fewer articles in this review reported data regarding the relationship between replacement of saturated fat with polyunsaturated fat and other specific types of CVD including heart failure or stroke, and results were predominantly null.
    - Replacement of saturated fat with carbohydrates: In this review, replacement of saturated fat with carbohydrates and CVD outcomes were predominantly null. Most articles did not specify or differentiate between the types of carbohydrate replacing saturated fat (e.g., complex or simple carbohydrates/sugar).
    - Replacement of saturated fat with monounsaturated fat: In this review, predominantly null associations were observed between replacement of saturated fat with monounsaturated fat and total CVD and CHD. However, among the few articles that differentiated plant and animal sources, monounsaturated fat from plants tended to be associated with lower risk.
- In addition to articles that reported on total polyunsaturated fat intake, many specifically

assessed omega-3 polyunsaturated fat and some assessed omega-6 polyunsaturated fat.
    - Total omega-3 polyunsaturated fat: Predominantly null or beneficial associations were observed between total omega-3 polyunsaturated fat intake and CVD outcomes.
    - Types of omega-3 polyunsaturated fat: When "long chain" omega-3 polyunsaturated fat (EPA, DHA, and sometimes DPA), primarily from marine sources, were assessed separately from ALA, more consistent associations with lower risk of CVD were observed.
    - Total omega-6 polyunsaturated fat: Associations between total omega-6 polyunsaturated fat intake and CVD were predominantly null.
    - Types of omega-6 polyunsaturated fat: In the few articles specifically assessing LA and AA separately, beneficial associations were more often observed for LA as compared to AA.
- Few articles, with inconsistent results, assessed the independent relationship between dietary cholesterol intake and CVD endpoint outcomes, thereby further confounding meaningful conclusions. Due to the co-occurrence of dietary cholesterol and saturated fat in animal source foods, disentangling independent associations between dietary cholesterol and CVD endpoint outcomes in these observational studies is challenging.
- Limitations of this body of evidence:
    - Many articles did not report race or ethnicity, but the majority of those that did involved participants who were predominantly White or Caucasian. Other important characteristics of participants in some included articles did not mirror those of the U.S. population, such as BMI and diet at baseline.
    - Although many articles accounted for the majority of key confounders, few accounted for all key confounders.
    - Some studies did not use validated dietary assessment methods or were limited by high attrition.
    - Although most studies included in this body of evidence were specifically designed to evaluate the relationship between diet and CVD, several articles were less direct as a result of being secondary analyses of RCTs or cohorts originally designed to assess outcomes other than CVD.
- This systematic review builds upon the work of the 2015 Committee, which answered the question "What is the relationship between intake of saturated fat and risk of cardiovascular disease?" and considered evidence from RCTs and PCSs from the 1960s to 2010.
    - Regarding the relationships between replacement of saturated fat with polyunsaturated

fat or carbohydrate, this systematic review concurs with and updates the conclusions drawn by the 2015 Committee, providing additional context regarding specific CVD endpoint outcomes and the type of carbohydrate replacing saturated fat.

- Regarding the relationship between replacement of saturated fat with monounsaturated fat, this systematic review concurs with and updates the conclusions drawn by the 2015 Committee.

For additional details on this body of evidence, visit: nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/dietary-fats-and-seafood-subcommittee/dietary-fat-cardiovascular-disease

Discussion: Dietary Fats

Background

CVD remains the leading cause of death in the United States, currently totaling 647,000 deaths per year.[238,239] This 2020 Committee updated and expanded the 2015 Committee's review of the evidence on dietary fats and CVD risk in children and adults. This Committee conducted a systematic review of more recent studies, including those examining the effects of dietary saturated fat intake and its replacement by other types of fats, specifically polyunsaturated fat, monounsaturated fat, and carbohydrates as they relate to intermediate (e.g., blood lipids, blood pressure) or endpoint CVD outcomes (e.g., incidence of, or mortality from, CVD). Previous research has found that RCTs that reduced dietary saturated fat or replaced saturated fat with polyunsaturated fat from vegetable oil reduced CVD by approximately 30 percent, similar to the reduction achieved by statin treatment.[240] Likewise, cross-cultural PCSs report that reduced saturated fat intake, along with higher polyunsaturated fat or monounsaturated fat intake, are associated with reduced incidence of CVD and all-cause mortality.[240] Conversely, replacement of saturated fat with refined carbohydrates and/or added sugars is not consistently associated with lower rates and may cause higher rates of CVD. Replacement of saturated fat with unsaturated fat lowers LDL cholesterol (LDL-C), a known cause of atherosclerosis, also called Atherosclerotic Cardiovascular Disease (ASCVD). ASCVD is distinct from stroke, heart failure or other components commonly included more broadly within CVD terminology.

The following sections will discuss the Committee's findings about the relationship of dietary fat with various outcomes in children and in adults and will highlight areas in which additional research is needed. These areas are described in greater detail in ***Part E. Future Directions***.

Studies in Children

Dietary fat contributes energy (calories) to the diet of growing children and is especially important in infants and young children because they are not able to consume very large quantities of food at one time. Therefore, the higher caloric density of fat (9 calories/gram, compared to protein and carbs, which have 4 calories/gram) is important because it helps to meet the energy demands of the rapid growth that occurs during this life stage. Fatty acids also play a major role in brain development and other important physiological functions. Before the age of 12 months, approximately 40 percent of energy intake comes from dietary fats, with a reduction to about 30 percent from age 24 months throughout preschool years (see ***Part D. Chapter 1: Current Intakes of Foods, Beverages, and Nutrients***).

Studies examined in this review demonstrated strong evidence that diets lower in saturated fat and cholesterol during childhood, primarily after 24 months of age, result in lower levels of total blood and LDL cholesterol throughout childhood, particularly in boys. Additionally, the Committee found moderate evidence suggesting that diets higher in polyunsaturated fat during childhood result in lower levels of total blood cholesterol throughout childhood, particularly in boys. The dominant sources of evidence for these conclusions are the Special Turku Coronary Risk Factor Intervention Project (STRIP) and Dietary Intervention Study in Children (DISC) studies.

The STRIP study, a widely cited population-based RCT conducted in Finland, which had the highest CVD mortality rate worldwide at baseline, randomized more than 1,000 participants to reduce saturated fat and dietary cholesterol intake while increasing polyunsaturated fat intake beginning at age 7 months. For participating infants who were consuming human milk or formula, the saturated fat reduction applied only to complementary foods and beverages. Participants were followed over a period of 20 years.[17,19,20,23,24,30-33,37-40] This dietary counseling-based intervention resulted in lower total cholesterol, LDL-C, and triglycerides in boys, providing longitudinal evidence of cardiovascular benefit. At different ages, favorable blood lipid responses appeared to occur in both males and females but at other times only boys appeared to have reduced LDL-C levels, thus demonstrating male-female differences in blood lipid response to dietary intervention, possibly attributed to changes in hormones during and throughout puberty.

The U.S.-based DISC study randomized more than 650 preadolescent children with elevated levels of LDL-C (80th to 90th percentile) to test the efficacy, safety and feasibility of reducing saturated fat within the context of a heart healthy diet in growing children, especially during puberty.[15,22,34,41] The DISC counseling intervention, which continued for approximately 7

years, reduced total cholesterol and LDL-C at 1- and 3-year follow-up, with no adverse impact on growth and development, but these differences in blood lipids were not sustained at 5- and 7-year follow-up. The study ended prior to all children reaching age 18 years or Tanner Stage 5, thereby limiting the ability to determine post-pubertal impact of dietary intervention on CVD risk in adulthood. The study also did not find significant influences on blood pressure, but sodium intake was not addressed in this study.[15,22,34,41] Both the STRIP and DISC studies provide important longitudinal evidence of the influences of dietary modification starting in childhood through adulthood.

Five RCTs conducted in children more recently provided food products to modulate dietary cholesterol, saturated fat, and monounsaturated fat and/or polyunsaturated fat intake. Consistent with the studies described above, LDL-C and total cholesterol were increased or were higher following consumption of food products higher in saturated fat and dietary cholesterol, compared to alternatives that replaced saturated fat with other types of fat or reduced dietary cholesterol.

Most of the 14 PCSs included in the Committee's review were conducted in the United States and primarily reported intermediate outcomes during childhood. The results were broadly consistent with those of the RCTs, either reporting predominantly null findings or reporting that higher intakes of saturated fat were associated with higher levels of total cholesterol or LDL-C.

This review found insufficient evidence to draw conclusions about the relationship between dietary fat during childhood and blood pressure throughout childhood. Studies varied considerably in their design and age-ranges and whether salt intake, a known mediator of blood pressure, was assessed. In addition, insufficient evidence was available to determine how monounsaturated fat intake during childhood affects total blood and LDL-C throughout childhood. All associations between monounsaturated fat intake, including those that modeled replacement, and blood lipids were non-significant. Lastly, only one article studying the association between saturated fat consumed during childhood and CHD mortality or stroke mortality in adulthood was included in this review.[28] Although the study reported results after approximately 60 years of follow-up, the Committee identified significant flaws with the dietary assessment method employed, and determined insufficient evidence was available to determine the relationship between dietary fat during childhood and CVD endpoint outcomes during adulthood.

Dietary studies in children are difficult to conduct not only due to ethical concerns, but also because of issues with compliance, follow-up, accuracy in assessing dietary adherence and confounders. Despite these challenges, dietary intervention studies in children are of critical

importance, particularly given the growing evidence that poor nutrition in childhood heavily contributes to poor health outcomes—both chronic and acute—and subsequently poorer quality of life in adulthood.[241-244] Inadequate research meeting systematic review criteria was available to draw meaningful conclusions regarding outcomes of interest within this review. Additional longitudinal RCTs involving dietary intervention among growing children with a focus on separating male and female data are needed to provide more definitive preventive recommendations, particularly regarding food sources of dietary fats and replacement with unsaturated fats and carbohydrates, with a focus on type of carbohydrate. See additional recommendations for future research in ***Part E. Future Directions***.

Because there is no biological requirement for saturated fat or dietary cholesterol, diets lower in these components that also contain foods consistent with the recommended dietary patterns, can be applied to children age 2 years and older. This approach appears to be safe and promotes dietary adherence useful for establishing healthy lifelong eating behaviors and potential cardiovascular benefits across the life course.[243,244]

Studies in Adults

Intermediate Outcomes

This Committee concurs with the conclusion from the 2015 Committee's review, which stated**:** Strong and consistent evidence from RCTs shows that replacing saturated fat with unsaturated fats, especially polyunsaturated fat, significantly reduces total and LDL-C.

The 2015 Committee reviewed evidence from existing systematic reviews and meta-analyses published between 2009 and 2014, including the American Heart Association/American College of Cardiology (AHA/ACC) Lifestyle Guidelines and associated National Heart, Lung, and Blood Institute (NHLBI) Lifestyle Report,[238] which included primarily RCTs on intermediate risk factors. The evidence reviewed included the landmark studies and RCTs from the 1960s, which first identified the relationship between saturated fat and CVD risk. In their report, the 2015 Committee found a high consistency of the evidence from PCSs and RCTs in supporting the benefits of replacing saturated fat with unsaturated fats, especially polyunsaturated fat, in reducing CVD risk.

The 2020 Committee's systematic review added 97 articles—all from RCTs—to the evidence reviewed by the 2015 Committee and found this new evidence to be broadly consistent with the conclusions drawn by the 2015 Committee. In articles that examined replacement of saturated fat with monounsaturated fat or polyunsaturated fat, the intervention

predominantly resulted in lower levels of, or larger decreases in, LDL-C and total blood cholesterol or null effects. Within the group of articles assessing the effect of polyunsaturated fat intake replacing a portion of saturated fat, the majority reported a statistically significant, beneficial effect of polyunsaturated fat on LDL-C or total cholesterol. Likewise, of the studies that examined the effect of monounsaturated fat intake replacing a portion of saturated fat, approximately half reported a beneficial effect of monounsaturated fat on LDL-C or total cholesterol, with the remaining studies reporting null effects.

Consistent with this Committee's findings, a World Health Organization review found that replacing dietary saturated fat with unsaturated fats decreases LDL-C levels and replacement with omega-6 polyunsaturated fatty acids reduces LDL-C more than does replacement with monounsaturated fat.[245] More specifically, based on regression analyses, it has been estimated that decreasing saturated fat intake by 1 percent of total daily calories with a corresponding 1 percent increase in polyunsaturated fat, monounsaturated fat, or carbohydrate results in reductions in LDL-C of 2.1 mg/dL, 1.6 mg/dL and, 1.3 mg/dL, respectively.[245]

When evaluating replacement of saturated fat with carbohydrates, the Committee concurs with the conclusion from the 2015 Committee: Replacing saturated fat with carbohydrates (sources not defined) also reduces LDL-C and total cholesterol, but significantly increases triglycerides and reduces HDL-C. Relative to studies reporting results on replacement of SFA with unsaturated fats, far fewer (only 2 articles) studies within the 2020 Committee's body of evidence examined the effect of replacing saturated fat with carbohydrates. Results from these articles were null or showed lower LDL-C, and HDL-C and total cholesterol when saturated fat was replaced with carbohydrates. The new evidence the Committee reviewed remains inadequate to differentiate among types and food sources of carbohydrates and their impact on blood lipids. However, in the context of dietary patterns, benefits in CVD risk factors were shown in dietary patterns that include whole grains and are lower in refined carbohydrates (See ***Part D. Chapter 8: Dietary Patterns)***.

The mechanism by which different types of carbohydrates influence blood lipids is not yet fully understood and evidence reviewed by the Committee did not provide insight into this relationship. Diets high in refined carbohydrates are often associated with elevated levels of triglycerides and very low-density lipoprotein (VLDL) cholesterol, especially among individuals with overweight and obesity.[240] Some research suggests that this may shift the distribution of LDL-C particles to smaller, cholesterol-depleted LDL-C particles. Researchers are studying whether atherogenicity differs by LDL-C particle size. However, measures of overall LDL-C that do not differentiate between particle size are currently considered sufficient to monitor

atherogenic risk and response to therapeutic intervention.[246,247] More research is needed on biomarkers with increased specificity compared to LDL-C regarding intermediate and endpoint cardiovascular risk.[248]

This review focused on types rather than sources of dietary fats. However, the Committee recognizes the importance of and growing body of research on the specific fatty acids, food matrix and sources of fats, explicitly saturated fat. Differences in the effects of specific saturated fatty acids on CVD are important to examine. Based on meta-regression analysis,[245] replacement of carbohydrates with specific saturated fat sources including lauric, myristic, palmitic, and stearic acids increased LDL-C and HDL-C while decreasing triglycerides. Because pure stearic acid does not increase LDL-C, but represents approximately 20 percent of the fat in beef, 30 percent of the fat in pure cocoa (chocolate), and 10 to 15 percent of the fat in lard (pork fat) and lamb, it remains challenging to quantify the impact of saturated fat on LDL-C without dietary assessment data that distinguishes between specific fatty acids.[240] Likewise, the health effects of the different fatty acids may vary also according to their proportion on specific foods and other components within the food matrix.

CVD Endpoint Outcomes

The Committee reviewed 94 articles from PCSs that provided assessment of dietary fat intake and endpoint cardiovascular outcomes. Compared with RCTs, PCSs typically include large populations that report self-selected dietary intake over longer duration and often, periodically during a follow-up period. Although observational studies, including PCSs, cannot demonstrate causality, they do identify associations between dietary intake and long-term health outcomes that would be difficult to assess through RCTs, and therefore, are critical to include in the evidence base for determining dietary recommendations for public health purposes (i.e., health promotion and chronic disease risk reduction).

This Committee's review found strong evidence demonstrating that replacing saturated fat with polyunsaturated fat in adults reduces the risk of CHD events and CVD mortality. (Note: This outcome is distinctly different from risk of stroke or heart failure, about which the Committee found insufficient evidence to draw a meaningful conclusion; see below.) The vast majority (71 of 94) of the articles included in this review of endpoint outcomes assessed the relationship between polyunsaturated fat intake—either total polyunsaturated fat intake, polyunsaturated fat as replacement for saturated fat, or specific polyunsaturated fatty acids (e.g., EPA, DHA, LA)—during adulthood and CVD outcomes. Studies that examined the relationship of total polyunsaturated fat intake and CVD without consideration of replacement, had null results or

showed associations with lower risk of CVD. When polyunsaturated fat was studied as a replacement for saturated fat, results were more consistent, predominantly reporting associations with lower risk of CVD.

One illustrative study is the National Institutes of Health (NIH)-AARP cohort, which included more than 500,000 men and women. At baseline, higher saturated fat intake at a mean age of 63 years was associated with higher risk of CVD mortality over 16 years of follow up and lower risk when saturated fat was replaced with total and omega-3 polyunsaturated fatty acids, as well as plant-sourced monounsaturated fat.[235] Likewise, the National Health and Nutrition Examination Survey (NHANES) cohort similarly reported that substitution of saturated fat with polyunsaturated fat was associated with reduced CVD mortality.[210] Studies conducted outside the United States found similar results. A small study in Finland[222] with isocaloric substitution of saturated fat with polyunsaturated fat showed reduced fatal and nonfatal CHD. In the PREDIMED (Prevención con Dieta Mediterránea) cohort, substitution of saturated fat with polyunsaturated fat showed significantly reduced risk of CVD.[172,173]

In addition to total polyunsaturated fat intake, studies further investigated intake of types of polyunsaturated fats: omega-3, omega-6, and specific fatty acids (i.e., EPA, DHA, DPA, LA, AA) on CVD outcomes.

The Committee found moderate evidence suggesting that total intake of omega-3 polyunsaturated fatty acids, particularly EPA and DHA from food sources, in adults is associated with lower risk of CVD. In articles studying the relationship between long chain omega-3 polyunsaturated fatty acids (EPA, DHA, with or without DPA) and CVD endpoint health outcomes, most focused on CHD, coronary artery disease, and myocardial infarction or CVD and showed predominantly beneficial associations.

Less evidence was available from this review to determine associations between intake of the omega-6 polyunsaturated fatty acids during adulthood and CVD, including CVD mortality. Omega-6 polyunsaturated fatty acids (e.g., LA, AA) are more prevalent than omega-3 polyunsaturated fatty acids in the diet as they are found widely in vegetable oils. Studies that evaluated the intake of LA, an essential omega-6 polyunsaturated fatty acid, reported predominantly beneficial or null associations. Relatively few studies assessed the relationship between AA and CVD endpoint outcomes. Results from these studies were inconsistent and resulted in inconclusive findings.

Similar to the 2015 Committee's review, this updated review did not provide clear evidence on whether replacing saturated fat with monounsaturated fat confers CVD benefits because of the co-occurrence of saturated fat and monounsaturated fat in animal fats, which are the main

sources of monounsaturated fat in the typical American diet. Within this review, many of the same cohorts reporting on substitution of saturated fat with polyunsaturated fat also reported substitution effects with monounsaturated fat. Compared to replacement of saturated fat with polyunsaturated fat, associations between risk of CVD and replacement of saturated fat with monounsaturated fat were predominantly null. However, differences between monounsaturated fat from plant-based (e.g., olive oil and nuts) vs animal sources were noted, suggesting benefits from plant sources of monounsaturated fat.

With growing research interest in the health effects of olive oil and specifically extra virgin olive oil and nuts as used in the PREDIMED trial, additional studies are needed to differentiate the effects of specific forms of monounsaturated fat from plant-source vs animal-source foods and to compare the effects of different forms of monounsaturated fat with polyunsaturated fat as part of well-characterized dietary patterns. Few studies to date include diet assessment methodology or nutrient biomarkers that permit such specificity and that could further allow evidence-based conclusions to be drawn.

As noted above, insufficient evidence was available from studies examining the replacement of saturated fat with polyunsaturated fat in adults and risk of stroke or heart failure. Among the few studies examining the relationship between saturated fat intake and stroke, most reported null associations between saturated fat intake and incident total stroke or subtypes of stroke such as ischemic stroke or hemorrhagic stroke. Only two articles assessed the relationship between saturated fat intake and heart failure and both reported null associations.

Lastly, in reviewing studies that examined replacing saturated fat with different types of carbohydrates (e.g., complex vs simple), insufficient evidence was available to determine how the exposures affected the risk of CVD. Associations between replacement of saturated fat with carbohydrate and risk of CVD, including total CVD and CHD, were predominantly null. Although 12 articles examined this relationship, only 6 articles reported results specifying different types of carbohydrates. Of these, the comparisons between types of carbohydrates in the interventions varied, making it difficult to arrive at a conclusive finding.

Recent analyses assessing replacement of saturated fat with carbohydrates have suggested beneficial effects when saturated fat is replaced with complex carbohydrates vs refined carbohydrates. As reported by Sacks et al.,[240] and based on calculations developed by Willet et al.,[249] replacing 5 percent of energy intake from saturated fat with equivalent energy intake from complex carbohydrates from whole grains was significantly associated with a 9 percent lower risk of CHD. However replacing saturated fat with refined carbohydrates (e.g., starches, added sugars) was associated with a slight increase in CHD risk.[240]

Not all recently published studies have arrived at conclusions consistent with this Committee's systematic review findings regarding the relationship between saturated fat intake and CVD risk. Some of the disparate findings relate to differences in methodology, including non-validated dietary assessment techniques; differences in study design; small sample sizes; distinctly different population characteristics, especially high body mass index; outcome measures; and cross-cultural differences in background dietary intake, such as in findings in those consuming diets vastly different from typical U.S.-style diets. One example of differences in methodology leading to findings inconsistent with the Committee's review is shown in meta-analyses that compare diets higher or lower in saturated fat, yet do not examine the replacement of saturated fat when it is reduced.[250,251] As summarized by Sacks et al., comparing disease rates between people in a population who have low compared with high intake of saturated fat—without defining the usual dietary pattern, i.e. types of carbohydrates consumed—leads to the potential for misinterpretation of the role saturated fat plays in relation to risk of CVD.[240]

Dietary Cholesterol

The Committee found insufficient evidence published since 2010 to determine an independent relationship between dietary cholesterol and blood lipids given the co-occurrence of cholesterol and saturated fat in foods. Nine articles from 4 parallel design and 5 cross-over design RCTs assessed the relationship between dietary cholesterol intake and blood lipids. Eight of the 9 studies provided whole eggs as the source of dietary cholesterol and 1 study provided prawns. Comparators varied, including egg whites, egg substitutes, or carbohydrate foods. Across this small body of evidence, higher dietary cholesterol intake, compared to lower dietary cholesterol intake, had mainly null effects on blood lipids. Among the few studies that reported significant effects, higher dietary cholesterol intake resulted in higher levels of, or greater increases in, total blood cholesterol, LDL-C, and HDL-C. No studies found a significant effect on triglycerides. However, because several studies concurrently modulated intake of total fat or other types of fat through the dietary intervention, it was difficult to evaluate the independent effect of dietary cholesterol.

Likewise, insufficient evidence published since 2010 was available to determine an independent relationship between dietary cholesterol intake in adults and overall risk of CVD. Eleven articles met inclusion criteria and results were inconsistent, with most studies reporting null associations, some reporting detrimental associations with higher intake of dietary cholesterol, and fewer reporting beneficial associations with higher intake. One article, a pooled

analysis of 6 large PCSs from the United States, found that higher consumption of dietary cholesterol was significantly associated with higher risk of incident CVD mortality, incident CVD, and incident stroke in a dose-response manner; this article did not detect significant associations between dietary cholesterol intake and heart failure or CHD.[233] Other articles that assessed CVD incidence or mortality reported null associations or significant associations between higher intake of dietary cholesterol and lower risk.[149,177,193] Among other articles that examined stroke, some did not detect associations with dietary cholesterol intake, whereas 1 additional study detected significant associations between higher dietary cholesterol intake and higher risk of stroke.[144,188,229,233] Results also were inconsistent for heart failure outcomes. All articles that assessed the relationship between dietary cholesterol intake and CHD or MI reported null associations.[196,204,223,233] As mentioned above, the co-occurrence of dietary cholesterol and saturated fat in animal-source foods as well as relatively lower population-wide dietary cholesterol intake (compared to the mean intake of the U.S. population) reported in several studies, made it difficult to evaluate independent associations between dietary cholesterol and CVD endpoint outcomes in this body of evidence. Well-designed PCSs and RCTs with long-term follow-up are required to better quantify the impact of dietary cholesterol on overall CVD and CHD incidence and mortality.

The lack of studies evaluating a number of outcomes in this review highlights the need for additional research, which is further discussed in ***Part E. Future Directions***.

Conclusions

Based on the totality of the scientific evidence, including the rigorous systematic reviews considered by the 2015 Committee and further examined by the 2020 Committee, it remains evident that reducing saturated fat intake and replacing it with unsaturated fats, specifically polyunsaturated fat, reduces the incidence of CVD.

Conversely, evidence to differentiate among sources of carbohydrate (e.g., sugars, refined vs complex) and their impact on blood lipids and CVD outcomes remains inadequate to draw clear conclusions. Although some evidence indicates that replacing saturated fat with complex carbohydrates may reduce CVD risk, replacing saturated fat with mostly refined carbohydrates and sugars shows no change or slightly increased risk of CVD.

Because dietary cholesterol is found only in animal-source foods that are typically also sources of saturated fat, the independent effects on blood lipids and CVD are difficult to assess. Nevertheless, because dietary patterns associated with reduced risk of CVD are characterized

by lower levels of both saturated fat and dietary cholesterol, it seems prudent to recommend lower intake of foods high in dietary cholesterol as well.[240]

Seafood

Question 2. What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and risk of cardiovascular disease?

Approach to Answering Question: NESR systematic review

Conclusion Statement and Grade

Insufficient evidence is currently available to accurately determine the relationship between seafood consumption during childhood and adolescence and risk of developing cardiovascular disease. Grade: Grade Not Assignable

Summary of the Evidence

- Four articles,[28,252-254] 2 RCTs and 2 PCSs, met inclusion criteria for this systematic review.
- Few articles were identified that examined the relationship between seafood intake during childhood and adolescence and blood pressure, lipid levels, and cardiovascular-related mortality, and no articles examined the relationship with incidence of CVD.
- Studies had serious methodological limitations that made interpretation of the results difficult.
- Evidence was insufficient, and no conclusion could be drawn.

For additional details on this body of evidence, visit: nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/dietary-fats-and-seafood-subcommittee/seafood-childhood-adolescence-cardiovascular-disease

Question 3. What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and neurocognitive development?

Approach to Answering Question: NESR systematic review

Conclusion Statements and Grades

Developmental Domains

Cognitive development: Insufficient evidence is available to determine whether there is a favorable relationship between seafood intake during childhood and adolescence and measures of cognitive development in children and adolescents. However, no unfavorable relationships were found between seafood consumption during childhood and adolescence and measures of cognitive development. Grade: Grade Not Assignable

Language and communication development: Insufficient evidence is available to determine whether there is a favorable relationship between seafood intake during childhood and adolescence and measures of language and communication development in children and adolescents. However, no unfavorable relationships were found between seafood consumption during childhood and adolescence and measures of language and communication development. Grade: Grade Not Assignable

Movement and physical development: Insufficient evidence is available to determine the relationship between seafood intake during childhood and movement and physical development in children. Grade: Grade Not Assignable

Social-emotional and behavioral development: Insufficient evidence is available to determine the relationship between seafood intake during childhood and adolescence and social-emotional and behavioral development in children and adolescents. Grade: Grade Not Assignable

Attention Deficit Disorder or Attention Deficit/Hyperactivity Disorder

Insufficient evidence is available to determine the relationship between seafood consumption during childhood and adolescence and attention deficit disorder or attention-deficit/hyperactivity disorder-like traits or behaviors. Grade: Grade Not Assignable

Autism Spectrum Disorder

No evidence is available to determine the relationship between seafood intake during childhood and adolescence and autism spectrum disorder-like traits or behaviors or autism spectrum disorder diagnosis. Grade: Grade Not Assignable

Academic Performance

Insufficient evidence is available to determine the relationship between seafood intake during adolescence and academic performance in adolescents. Grade: Grade Not Assignable

Anxiety and Depression

Insufficient evidence is available to determine the relationship between seafood consumption during childhood and adolescence and anxiety and depression. Grade: Grade Not Assignable

Summary of the Evidence

- This review included 13 articles,[255-267] 6 articles from 3 RCTs and 7 articles from 6 PCSs, published between January 2000 and October 2019.
- The majority of studies addressed developmental domain outcomes - cognitive development (7 articles), language and communication development (5 articles), movement and physical development (2 articles), and social-emotional and behavioral development (3 articles).
- No conclusion regarding the relationship between seafood intake during childhood and adolescence and developmental domains could be drawn due to an inadequate number of studies, inconsistency in results, risk of bias in classification of exposures, and heterogeneity of outcome assessments.
    - Seafood intake during childhood and adolescence was predominantly beneficial or null across all domains, and had a few detrimental relationships, primarily in social-emotional and behavioral development.
        - Results from 3 RCTs found that 3 fatty fish meals per week (about 50 to 80 grams per meal) compared to meat meals for 12 weeks in adolescents or 16 weeks in children had a predominantly null effect on developmental domain outcomes.
        - Results from 3 PCSs generally found a beneficial association between fish intake in children and adolescents and development outcomes.

  - The vast majority of analyses showed no detrimental relationship between seafood intake during childhood and adolescence and cognitive, language and communication, and movement and physical development.
- No conclusion regarding the relationship between seafood consumption during childhood and adolescence and academic performance, ADD or ADHD, anxiety and depression, and ASD could be drawn due to an inadequate number of studies and variation in outcome assessment and child age.

For additional details on this body of evidence, visit: nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews/dietary-fats-and-seafood-subcommittee/seafood-childhood-adolescence-neurocognitive-development

Discussion: Seafood

The scientific literature supports the health benefits of seafood consumption alone or as part of an overall dietary pattern across life stages. However, for young children, the potential for negative health consequences raises concerns due to possible contamination with heavy metals, mainly methylmercury. Seafood is the primary sources of methylmercury exposure for humans. Methylmercury is not naturally found within seafood, but rather it results from a complex interplay of environmental factors that culminate in its accumulation in the water column resulting in methylmercury accumulation in the flesh of fish. Although all seafood contains some level of methylmercury, the amount varies by species, as described by the Environmental Protection Agency.[268] Exposure to methylmercury is considered detrimental to the cognitive development and performance of infants and children, especially during critical windows of neurocognitive development in the first 1,000 days of life, though the risks have not been entirely characterized.[269]

Two previous Dietary Guidelines Advisory Committees (2010 and 2015) examined the topic of seafood. The 2010 Committee conducted an extensive safety analysis of seafood consumption and the 2015 Committee reviewed seafood in the context of an overall dietary pattern. The 2010 Committee concluded that the health benefits from consuming seafood outweigh the risks associated with potential toxins, including exposure to methylmercury and persistent organic pollutants. Because seafood is an important source of many nutrients and food components that are of public health relevance, the 2015 Committee found the role of seafood in dietary patterns was associated with lower risk of CVD (Grade: Strong), lower risk of overweight and obesity (Grade: Moderate), lower risk of colorectal cancer (Grade: Moderate).

However, the 2015 Committee found no clear associations with other cancer types or neurocognitive factors in adulthood (Grade: Limited). The 2020 Committee reviewed seafood by focusing on specific populations and health outcomes.

The Committee's review of seafood consumption during childhood and risk of CVD found insufficient evidence to make a conclusion about the relationship. Four articles, which reported on 2 RCTs and 2 PCSs, met inclusion criteria for this systematic review. Three studies evaluated intermediate markers of CVD risk, including blood pressure, total cholesterol, HDL-C, LDL-C, and triglycerides. Findings were predominantly insignificant with a few favorable associations. Only 1 study reported an association between fish consumption during childhood and CVD health outcomes in adulthood. However, this study's design had multiple flaws, including a lack of rigorous diet assessment methodology, serious risk of bias, and a failure to account for key confounders. All of these limitations likely affected the outcome. For the reasons outlined above, the Committee found insufficient evidence to make a conclusion about the relationship between seafood consumption during childhood and risk of CVD.

The systematic review of seafood consumption during childhood and neurocognitive development and neurocognitive health yielded 13 studies, including 6 articles from 3 RCTs. Due to inconsistency in the results and a variety of limitations among the studies, the Committee determined that insufficient evidence was available to draw a meaningful conclusion about this relationship. A few studies reported results suggesting favorable associations in measures of cognitive development and language and communication development. However, studies that focused on other domains, including movement and physical development and social and behavioral development, resulted in inconclusive findings.

Although the Committee's questions did not specifically focus on safety, a few studies reported an unfavorable association between seafood intake and measures of social-emotional and behavioral development, while none found a detrimental impact on cognitive, language and communication, and movement and physical development. The overwhelming majority of studies showed a null or favorable association between seafood intake during childhood and measures of neurocognitive development.

Additionally, insufficient data were available to grade evidence for the outcomes of academic performance, anxiety, and depression as well as ADD/ADHD. No studies reported on the relationship between seafood consumption during childhood and ASD or between seafood consumption during childhood and neurocognitive health outcomes in adulthood.

Although the scientific literature on the topic of seafood consumption during childhood and health outcomes has recently expanded, our synthesis of the literature was limited due to the

number of challenges with the body of evidence. The following discussion highlights a number of areas in which the current literature base is lacking and where additional research is needed. These are described further in ***Part E. Future Directions***.

First, while all seafood contains some level of methylmercury, substantial heterogeneity in the methylmercury content of seafood exists by the type, age, geographic location, and source (i.e., farm raised vs wild caught) of the fish. Local departments of natural resources or fish and game boards are sources of information specific to the mercury content in the fish from local communities and municipalities.

Second, few studies with high-quality data exist to inform decisions about seafood intake during childhood and neurocognitive development. RCTs with appropriate sample size and robust assessment of exposures and outcomes are used to infer causality, but are limited in part by ethical issues. In the absence of RCTs, the scientific and policy communities rely on well-designed observational studies, which are weaker in quality due to confounding and selection-bias but are often large, diverse in relevant characteristics (e.g., exposure of interest, ages), and typically have longer duration for follow-up than feeding trials. Rigorous studies on the relationship between seafood consumption and health outcomes in children—including the birth to age 24 months population—and that account for key cofounders that are generalizable to the United States need to be conducted to address the gaps and limitations in the existing body of evidence.

Third, assessment of exposure to seafood intake was not uniform across studies. The observational studies reviewed used FFQs, a diet diary, or single questions in a questionnaire to assess intake, with different definitions of what “seafood” entailed and often with multiple types of seafood with varying mercury content aggregated into one question. FFQs and questionnaires also varied in their response options for types of seafood (e.g., fatty or oily fish vs shellfish) sources (i.e., farmed or wild caught) or processing method (e.g., canned), or preparation method. The metric used to quantify fish intake also varied (e.g., servings per week, grams, high consumer vs low consumer). Measurement reference periods often differed as well, and most studies assessed the diet only at one time point. Likewise, it was unclear how database values were applied for the presumably beneficial effects of seafood, including omega-3 fatty acids, iron, iodine, vitamin D, and protein. Variability also surrounded whether the FFQs were validated; some studies used a “semi validated” tool and other studies did not indicate. Few studies reported biomarker data to compare omega-3 fatty acid levels with self-reported intake.

Fourth, the measurement error inherent in all self-reported dietary data was an unavoidable limitation of the existing data used to address this topic. FFQs have considerable systematic measurement error that is known to attenuate relationships with health outcomes in general. More specifically, little is known regarding measurement error in reporting of fish and seafood.

Fifth, measuring neurocognitive development is very challenging. Various assessment methods were used. Some were general cognitive development tests and some were specific to certain conditions, such as ADD or ADHD. A variety of tests were used for screening and assessment, and many were specific to particular age groups. Among the studies the Committee examined, few included a clinical or comprehensive psychological evaluation. Most often social-emotional and behavioral assessments were based on parental or self-report, which may have introduced bias. The tests varied in their level of evaluation of psychometric properties, like reliability and validity, and some tests were commonly used while others were not. Some tests measured specific cognitive domains directly, while others measured secondary characteristics, like emotion and sociability, intelligence/IQ, or adaptive functioning skills. Statistical analysis and modeling of data also varied across the body of literature, with some studies controlling for methylmercury in the models while other studies did not measure methylmercury or did not adjust for its potential confounding role.

Additional research is needed to address these limitations and further contribute standardized data regarding specific intermediate and long-term outcomes resulting from seafood consumption during childhood.

SUMMARY

Fats are an important component of the American diet, contributing about one-third of the total calories consumed after infancy. The types and food sources of fats consumed have distinct metabolic and health effects. This chapter reviewed and summarized the current scientific evidence on the types of dietary fat consumed over the life course and risk of CVD. Most Americans consume more than 10 percent of their total calories as saturated fat, exceeding the recommendations of current dietary guidelines.[2] Because of the high incidence of CVD in the United States, the health effects of reducing saturated fat in the diet is of particular public health importance.

The Committee concluded that reducing saturated fat intake and replacing it with unsaturated fats, particularly polyunsaturated fat, lowers the incidence of CVD in adults. Also,

the replacement of saturated with unsaturated fats in the diet reduces serum total and LDL-C in adults and children, particularly boys. However, the benefits of replacing saturated fat with carbohydrates are less clear. This replacement reduces total and LDL-C, less so than with polyunsaturated fat but also lowers HDL-C, and it raises triglycerides. Evidence to differentiate among sources of carbohydrate (e.g., sugars, refined vs complex) and their impact on blood lipids remains inadequate to draw clear conclusions.

In agreement with the 2015 Committee, the differing effects of the type and food source of macronutrient substitution for saturated fat in the diet may be a reason for the limited evidence regarding whether replacing saturated fat with carbohydrates or with monounsaturated fat confers CVD benefits. Most studies did not report, or analyses did not distinguish between substitutions of saturated fat by different types of carbohydrates (e.g., refined grains vs whole grains). Similarly, it is challenging to identify an independent association of replacing saturated fat with monounsaturated fat and CVD because the main sources of monounsaturated fat in a typical American diet are animal fats, which contain both saturated fat and monounsaturated fat. Evidence reviewed from RCTs and PCSs showed benefits of plant sources of monounsaturated fats, such as olive oil and nuts, on CVD risk. Thus, it is pertinent that future studies assess, quantify and distinguish the type and food sources of the macronutrients compared.

Different types of fatty acids also may elicit distinct cardiometabolic effects. This is especially relevant among polyunsaturated fats. Intake of omega-3 polyunsaturated fatty acids, particularly EPA and DHA from food sources such as seafood and algae, lowers blood triglycerides, and in adults, is associated with lower risk of CVD. Intake of food sources of omega-6 polyunsaturated fatty acids such as some vegetable oils, lowers blood total and LDL-C, and LA but not AA, intake may be associated with lower risk of CVD in adults.

Because dietary cholesterol is found only in animal-source foods that are typically also sources of saturated fat, the independent effects on CVD are difficult to assess. Nevertheless, dietary patterns that include lower intake of dietary cholesterol are associated with reduced risk of CVD.[270] This further illustrates the importance of considering the effect of any nutrient or food component on CVD within the context of the overall dietary pattern, rather than a reductionist approach of one food component in isolation.

Considering the totality of the scientific evidence, including the present systematic review, the Committee concluded that lowering intake of saturated fat and replacing it with primarily plant-sourced unsaturated fats, lowers serum total and LDL-C and the incidence of CVD. This recommended shift from saturated to unsaturated fats most naturally occurs in the context of healthy dietary patterns such as those with high Healthy Eating Index (HEI) scores, including

the Healthy Mediterranean-Style or Healthy Vegetarian Eating Patterns diets (see ***Part D. Chapter 14: USDA Food Patterns for Individuals Ages Two and Older***). These healthy dietary patterns are characterized by higher consumption of vegetables, fruits, whole grains, low-fat dairy, and seafood, and lower consumption of red and processed meat, and lower intakes of refined grains, and sugar-sweetened foods and beverages (See ***Part D. Chapter 8: Dietary Patterns***).

Humans have no dietary requirements for saturated fat or cholesterol because they synthesize them from other dietary substrates. Additionally, the intake of both nutrients are associated with the risk of CVD. Thus, the Committee recommends that dietary cholesterol and saturated fat intake be as low as possible within a healthy dietary pattern, and that saturated fat intake be limited to less than of 10 percent of total energy intake, as recommended by the *2015-2020 Dietary Guidelines for Americans*. This recommendation applies to adults and children ages 2 years and older. It is important to recognize that the health effects of dietary saturated fat—or any other nutrient—depend not only on the total amount consumed, but also the specific type of saturated fatty acids inherent within the food matrix, sources and degree of processing, and the overall dietary pattern. The recommended dietary pattern should replace food sources of saturated fat with food sources of polyunsaturated fats by substituting some animal-source foods, especially processed meats and certain dairy products, with sources of polyunsaturated fats, such as seafood, seeds, nuts, legumes, and appropriate vegetable oils. In addition, if meat and dairy foods are included in the dietary pattern, choosing lean cuts and lower fat dairy options is preferred.

This chapter also reviewed and discussed the scientific evidence on the consumption of seafood during childhood and adolescence and two outcomes: 1) risk of CVD, and 2) neurocognitive development and health. The Committee found insufficient evidence to draw a conclusion about the relationship of seafood intake during childhood and these outcomes. However, no adverse associations were reported.

For each of the neurocognitive outcomes examined, the Committee concluded that the evidence available was insufficient to determine an association with seafood intake. This was mostly due to the relatively small number of studies, the methodological heterogeneity among them and the mainly null or mild positive associations. Although the present review did not specifically focus on the safety of seafood intake, the Committee relied on safety evaluations conducted by the U.S. Food and Drug Administration and the Environmental Protection Agency, and noted that among the studies reviewed, all but one did not find negative associations of seafood intake and cognitive outcomes. Thus, within the parameters of the studies reviewed,

intake of seafood during childhood is not related to unfavorable neurocognitive development. The Committee also reviewed the evidence of seafood intake during pregnancy and cognitive development in the infant (see ***Part D. Chapter 2: Food, Beverage, and Nutrient Consumption during Pregnancy***) and found favorable associations with some but not all neurocognitive development domains.

The Committee recommends that the seafood-related guidance of the 2010 and 2015 Committees remain in place, with slight modifications: Two or more servings of cooked seafood per week are recommended for ages 2 years and older to ensure intake of key nutrients and as part of an overall healthy dietary pattern; serving sizes vary based on age (see FDA guidance).[271] Choices of fish and seafood with emphasis on species higher in omega-3 polyunsaturated fatty acids and with low methylmercury and are advised, following Federal and local fish and seafood advisories. For those following dietary patterns that do not include seafood, regular intake of other foods high in omega-3 fatty acids, such as flaxseeds, walnuts, soy oil, algae and eggs that contain omega-3 fatty acids, is appropriate. The *2020-2025 Dietary Guidelines for Americans* should contain information on amounts and types of seafood to consume as well as those to avoid based on the methylmercury content. Special emphasis should be made with regard to the birth to age 24 months age group and women who are pregnant or lactating. The Committee recognizes that recommendations to increase seafood consumption by the American public can have environmental consequences and such impacts should be evaluated in the development of the *Dietary Guidelines for Americans*.

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