Is it time to reconsider the role of saturated fats in the human diet?

Rebecca Guenard

- **Dietary guidelines from multiple sources recommend people limit the amount of saturated fats in their diets.**
- **Some researchers say there is not a clear enough picture of how fats function in the body to assume saturated fats play a nefarious role.**
- **Recent findings on *in vivo* fat behavior indicate we need more science on saturated fats.**

Do scientists have a clear or murky picture of the health risks associated with saturated fat consumption? That depends on who you ask.

According to the World Health Organization (WHO), "existing evidence suggests that the intake of fatty acids is a major determinant of the serum lipid and lipoprotein profile." When measured through blood tests their values can determine a person's risk for cardiovascular disease (CVD). Numerous epidemiological studies associate high amounts of total cholesterol and triglycerides with the disease. Moreover, studies have shown the effect is cumulative and large amounts of lipids in a young individual predict later incidence of CVD.

The extensive findings on the relationship between fatty acid intake and CVD supported the idea, particularly in the United States, that decreasing fat in the diet would result in a lean, healthy population. Public policy enforced this ideology for 40 years. In that time, rates of obesity and diabetes grew, prompting some scientists to question the basis for a low-fat diet.

Scrutiny of dietary fat research over the last two decades has revealed the importance of discerning between types of fat. As a result, the majority of health agencies around the world have banned trans-fatty acids as an artificial food ingredient. (Calculations in the US indicate that trans-fat bans reduced CVD mortality by 4.5% (https://doi.org/10.1016/j.jhealeco.2015.09.005).) Further analyses of research findings has also confirmed the health benefits of unsaturated fatty acids. The fate of saturated fats, however, still awaits consensus. Most guidelines recommend their consumption be limited, but some scientists question whether we have a clear enough understanding of the function of saturated fats in the body.

"I always circle back to the fact that the current dietary recommendations have been vetted," says Penny Kris-Etherton, professor of nutritional sciences at The Pennsylvania State University in University Park, Pennsylvania, USA. "The Dietary Guidelines for Americans say there is strong evidence that saturated fats increase LDL cholesterol and that is a risk factor for CVD."

CURRENT GUIDELINES

For the unfamiliar reader, dietary fats consist mainly of triglycerides—a molecule with three fatty acids attached to a glycerol backbone. The properties of the molecule depend on its fatty acid composition. The number and location of

their double bonds, as well as the length of their carbon chains distinguish fatty acids from each other.

Saturated fatty acids (SFA) have no double bonds, while monounsaturated fatty acids (MUFA) have one double bond and polyunsaturated fatty acids (PUFA) have two or more double bonds. The WHO says the most abundant SFA in the diet have 16 (C16:0; palmitic acid) or 18 (C18:0; stearic acid) carbon atoms. Oleic acid (C18:1) is the most abundant MUFA and the most abundant PUFA are linoleic acid (C18:2n-6) and α-linolenic acid (C18:3n-3).

In 2016 Ronald Mensink, professor of molecular nutrition at Maastricht University, the Netherlands, conducted a systematic review of 84 dietary studies for the WHO to evaluate what happens to serum lipid and lipoprotein levels when

TABLE. 1. Major naturally occurring SFA. These fats are differentiated on the basis of their carbon chain length. The categories are not standardized, but tend towards short-chain (4 to 6 carbon atoms), medium-chain (8 to 12 carbon atoms), long-chain (14 to 20 carbon atoms), and very long-chain (22 or more carbon atoms). Source: Astrup, A. *et al. J Am Coll Cardiol.* 2020; 76(7):844-57.

Abbreviation	Common name	Chain length	Major Dietary Source
4:0	Butyric	Short	Dairy foods
6:0	Caproic	Short	Dairy foods
8:0	Caprylic	Medium	Dairy foods, coconut and palm kernel oils
10:0	Capric	Medium	Dairy foods
12:0	Lauric	Medium	Coconut milk and oil
14:0	Myristic	Long	Dairy foods
15:0	Pentadecanoic	Long	Red meat, dairy, oils
16:0	Palmitic	Long	Red meat, dairy, palm oil
17:0	Heptadecanoic	Long	Red meat, dairy
18:0	Stearic	Long	Dairy, meat, chocolate

MUFA, PUFA or carbohydrates replace SFA in the diet (https://apps.who.int/iris/handle/10665/338049). The researchers assessed total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, LDL cholesterol to HDL cholesterol ratio, total cholesterol to HDL cholesterol ratio, triglyceride to HDL cholesterol ratio, apolipoprotein A-I (ApoA-I) and apolipoprotein B (ApoB).

Mensink performed a multiple regression analysis and found that subjects had a more favorable serum lipoprotein profile when they increased PUFA and MUFA in a diet that still contained SFA instead of replacing it with a mixture of carbohydrates. He specified that partially replacing SFA with PUFA had a greater effect on lowering LDL cholesterol and triglycerides. When SFA intake remained below 10% of a subject's total energy intake, the individual maintained a desirable serum profile.

Based on Mensink's study which corroborates with many others, the WHO now indicates that maintaining cardiovascular health means reducing SFA intake to less than 10% of calories. Current US guidelines also advise this threshold, while the American Heart Association recommends that people limit saturated fat consumption to 5-6% of their energy intake. That percentage is equivalent to about 13 grams a day for a 2,000 calorie diet. In the United Kingdom, the recommendation is no more than 20 grams per day for women, 30 grams for men.

SFA DISTINCTIONS

However, there are aspects of reviews on dietary fat research that leave some scientists wondering if saturated fats really contribute to chronic disease. When researchers dig into the data to determine the effect of individual SFA on serum profiles they find that there are differences. Cholesterol and triglyceride levels can go up or down for fatty acids like, lauric (C12:0), myristic (C14:0) or palmitic acid, while studies show stearic acid has no effect. This SFA specific variation of serum lipid profiles has prompted some to question if we have a complete understanding of how SFA behave in the body.

Kris-Etherton says that concentrating on types of SFA diverts attention from the more relevant point. "What some people would say is that there are some SFA that are better than others, but it is important to point out that individual saturated fatty acids are not as good as unsaturated fats," she says. "Stearic acid may be neutral, but it is not as good as oleic acid and linoleic acid." Nevertheless, Kris-Etherton acknowledges there are interesting data to suggest we need to start paying attention to the food matrix.

"There is wider evidence that foods have different properties because of the rich mix of nutrients, vitamins, minerals, and phytochemicals which together make up what is called the food matrix," said Nita Forouhi, population health and nutrition professor at the University of Cambridge, School of Clinical Medicine, in Cambridge, England, UK, when interviewed by the online magazine verywellhealth (https://tinyurl.com/yckvkr2u).

THE COMPANY SFA KEEP

Last November, Forouhi and a team of researchers evaluated data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. They compared the dietary habits of 10,529 people in 10 European countries who developed heart disease against 16,730 people who did not (https://doi.org/10.1161/JAHA.120.019814).

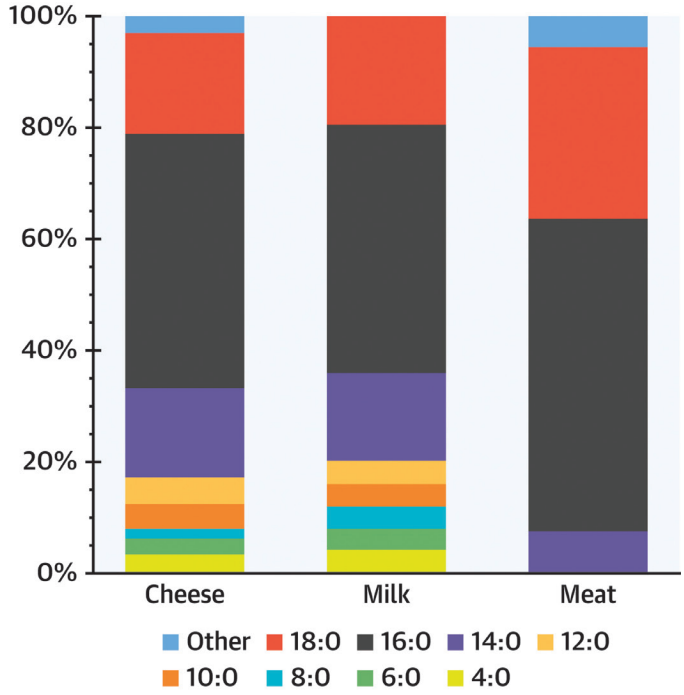


FIG. 1. Saturated Fatty Acid Profiles of Major Food Sources. These data indicate that food sources contain saturated fatty acids in different proportions which leads to diverse physical and chemical characteristics and differing effects on various blood lipids and lipoproteins. Source: Astrup, A. *et al. J Am Coll Cardiol.* 2020; 76(7):844-57

After accounting for other factors that might influence heart disease like, age, sex, and lifestyle choices, such as smoking, Forouhi and her team found that total dietary fat intake did not determine a person's chance of developing heart disease. However, when they stratified the SFA by their food sources the team came to a different conclusion.

Nearly 80% of participants in the study consumed an excess of SFA, more than dietary guidelines recommend. Again, the high level of SFA alone did not represent a risk factor. Instead, they determined SFA from red meat and butter raised serum lipid levels in participants more than when they ate cheese, yoghurt, or fish. In their paper, Forouhi's team points out that fermented dairy generates Vitamin K and bioactive peptides, in addition to the probiotics that exist, which could counter the negative effects of SFA.

Forouhi acknowledges that her studies are observational and prohibit the assignment of a cause and effect. Based on the results of previous studies; however, a growing body of research does support some of her findings. The isomer composition of an SFA seems to influence its *in-vivo* behavior, with odd-chain SFA affecting serum lipids differently than even-chain SFA. Eating palmitic acid, for example, has been shown to increase blood cholesterol levels while pentadecanoic acid (C15:0) consumption may lower the risk of heart disease (https://tinyurl.com/4r95by8x). The former is more often found in red meat, the later in dairy. (For more on odd-chain fatty acids see *INFORM*, Oct 2021, https://tinyurl.com/42weebmz)

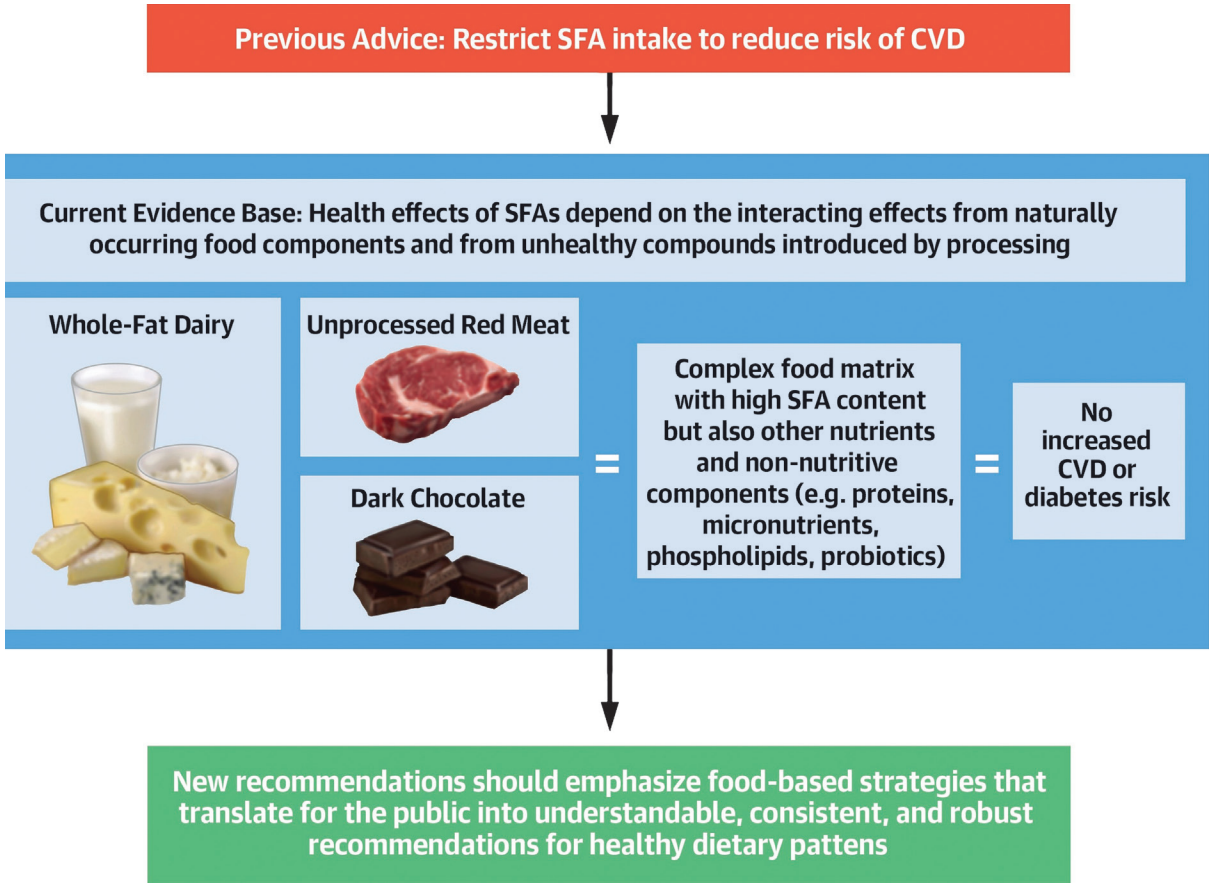


FIG. 2. Some researchers are arguing that the latest data dietary guidelines should be updated from a focus on limiting saturated fats to guidelines that educate the public on how to choose healthy foods. Source: Astrup, A. *et al. J Am Coll Cardiol.* 2020; 76(7):844-57

One research team argues that conjuncture based on observed associations does not sufficiently explain the role of SFA. Marit Kolby (formerly Marit Kolby Zinöcker), assistant professor of nutrition at Oslo New University College, in Oslo, Norway has proposed that studying short-term changes in serum lipid profiles does not provide an adequate understanding of dietary fats in the body throughout a lifetime.

A NEW HYPOTHESIS

Like many researchers, Kolby is eager for direct evidence of a molecular mechanism that explains cholesterol's role in developing CVD. In a paper published in *The American Journal of Clinical Nutrition* last year, she argues that no current models explain the response of serum lipoprotein levels when altering dietary fatty acids (https://doi.org/10.1093/ajcn/nqaa322). Instead of being a pathogenic process, Kolby's team proposes serum changes could be part of cellular regulation of cholesterol in order to maintain homeostasis.

Kolby wanted an explanation for the association between SFA consumption and observed increases of LDL cholesterol in blood. "To me it was logical to start by looking at cells and membranes, because most of the body's cholesterol is contained in membranes not in the blood," she says. "I started looking for evidence that changes in intake of dietary fatty acids would affect regulatory mechanisms for cholesterol content in cell membranes."

According to Kolby's hypothesis, eating PUFA results in cell membranes that are fluid and require cholesterol from the blood to introduce stiffness into the membrane. Whereas, eating saturated fats leads to membranes that require less stabilization by cholesterol which instead flows into the blood stream. She presumes cholesterol in the bloodstream could be acting as a reserve to fortify cell membranes as needed (https://tinyurl.com/47sbjdxe).

"It is possible that inflammation—in concert with other metabolic abnormalities, like insulin resistance—causes an increase in blood cholesterol due to dysfunctional lipid uptake and/or metabolism," says Kolby. This would provide an alternative explanation for why high cholesterol leads to heart disease. Eating whole foods instead of ultra-processed foods, moving enough, sleeping enough, stressing less, and keeping good social relations to avoid chronic inflammation is more important than avoiding saturated fat, she says.

Time, and more research, will tell if Kolby's hypothesis has clout, but findings in other areas of lipids research indicate we may be misunderstanding how the body uses fat stores.

EMERGING IDEAS

There is other evidence that stockpiles of lipids do not necessarily mean a sign of disease. In the September 2021 issue of *INFORM* magazine, we reported on a research group led by Alex Gould at The Francis Crick Institute in London, UK, using

Tracking cholesterol's movement

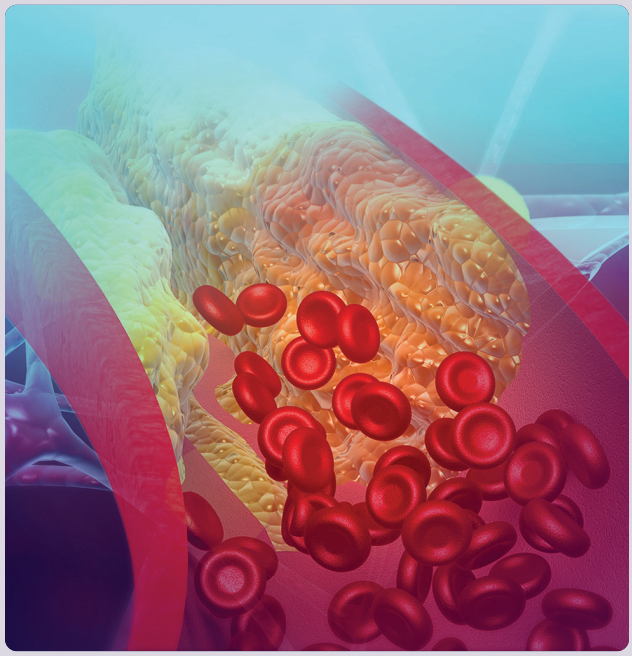
A research collaboration between Stanford University School of Medicine in Stanford, California, USA and the University of Barcelona in Barcelona, Spain has resulted in identifying the mechanism responsible for transporting cholesterol from organelles within cells. The researchers say their results could contribute to developing future treatments against pathologies caused by dysfunctions in the intracellular cholesterol transport. The findings also shed light on the function of cholesterol within the human body.

For the most part, the cholesterol that cells use comes from the blood, reaching the lysosomes where it is distributed to different intracellular compartments. However, there are still unsolved questions related to the precise molecular events that regulate the exit of cholesterol from this organelle and its transport towards the membrane and the cell endoplasmic reticulum.

For cells to maintain homeostasis it is important that an adequate supply of cholesterol flows in and out of lysosomes regularly. Carles Enrich, a biomedicine researcher at the University of Barcelona, and his collaborators determined which transporters were responsible for assisting cholesterol with its exist from lysosomes. "This process requires the coordinated action of NPC1 and NPC2 transporters together with the bis(monoaclyglycero)phosphate (BMP) lysosomal lipid to mobilize and export free cholesterol," says Enrich in a press release for the publication of the findings in the *Journal of Cell Biology* (https://doi.org/10.1083/jcb.202105060).

Disorders such as Niemann-Pick type C disease are due to mutations in the lysosomal cholesterol transporters NPC1 and NPC2. The disease (currently without a cure) prevents cholesterol and other fats from being metabolized normally, eventually causing liver, spleen and brain damage.

In order to identify the genes that alter intracellular cholesterol or BMP levels, the researchers conducted two genome-wide CRISPR screenings—one under normal conditions, the other with the NPC1 proteins blocked. "Our genetic screenings identified a high number of genes involved in the cholesterol and BMP metabolic regulation, whose role was unknown to date. In addition, we confirmed a tight correlation and regulation between the levels of these lipids," said Albert Lu, another University of Barcelona researcher on the team.



One of the molecules involved in this process is SNX13, a protein in the endoplasmic reticulum that negatively regulates the exit of cholesterol from lysosomes to the plasmatic membrane, thus reducing the amount of the lipid. "Given the lack of the function of NPC1, the reduction of SNX13 caused a redistribution of lysosomal cholesterol towards the plasmatic membrane, which indicates that SNX13 could be an important regulator in this cholesterol transport pathway," Lu says.

the *Drosophila* fruit fly to study lipid droplets (https://tinyurl.com/ybndrbc8). Once considered pathogenic themselves, the tarnished reputation of lipid droplets may soon shine.

"The fact that they correlate with a disease does not mean they are causing that disease. Our work suggest that lipid droplets are actually one of the body's ways of fighting back against the disease," Gould told *INFORM* last year.

Lipid droplets were initially determined to serve as mere energy reserves, inertly waiting to provide a cell with fuel. But Gould discovered that they also perform an important role of protecting PUFAs during oxidative stress (https://doi.org/10.1016/j.cell.2015.09.020). He found that the droplets encapsulated dietary linoleic acid, for example, to prevent free radical formation and preserve vital PUFAs during cell development.

More recently, the researchers focused on surface proteins on lipid droplets within renal cells to understand their involvement in kidney disease. When they turned the genes that generate the enzymes that synthesize or digest triglycerides on and off, the team observed an effect on the fly's cell health. The group ultimately concluded that when fruit flies feed on a high-fat diet, the renal cells protect the kidneys

from damage by sequestering lipids into droplets (https://doi.org/10.1371/journal.pbio.30012302021).

In January, a different research group observed another unique service role that lipid droplets provide. Animal science professor Shihuan Kuang and his postdoc Feng Yue at Purdue University in Lafayette, IN, USA discovered that fat inside adult muscle stem cells determine how the stem cells behave (https://tinyurl.com/5tzrefkr).

When adult muscle cells are injured, latent stem cells become active to repair the injury. Lipid droplets accompany the stem cells when they arrive at the injury site. The researchers determined the cells could differentiate into two types of cells: muscle cells that repaired damage and self-renewal cells to resupply the used stock. Kuang says the lipid droplets somehow maintain a healthy balance of cells. When there are more droplets around, the stem cells continue to divide. To keep the stem cells from dividing uncontrollably, as happens with cancer, the cells seem to deplete themselves of the droplets and return to a dormant state (https://tinyurl.com/bdzcehx3).

As new research on the good deeds conducted by lipid droplets continue to unfold, we have to remind ourselves not to draw any connections to human dietary choices. The experiments have only been conducted on cells and animals, thus far. However, these studies reveal that fat plays a more complex role in cellular function than we realize.

"For the scientists who say: 'There are problems with the evidence.' We should get more science and resolve some of the controversies," says Kris-Etherton. "I tell people, pay attention to authoritative recommendations right now. That is the best thing we can do."

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Attend the 2022 AOCS Annual Meeting & Expo session on Health & Nutrition chaired by Matthew Picklo to learn more on the topic of saturated fats.