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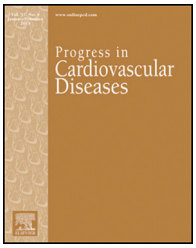

The Evidence for Saturated Fat and for Sugar Related to Coronary Heart Disease

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ABSTRACT

Dietary guidelines continue to recommend restricting intake of saturated fats. This recommendation follows largely from the observation that saturated fats can raise levels of total serum cholesterol (TC), thereby putatively increasing the risk of atherosclerotic coronary heart disease (CHD). However, TC is only modestly associated with CHD, and more important than the total level of cholesterol in the blood may be the number and size of low-density lipoprotein (LDL) particles that contain it. As for saturated fats, these fats are a diverse class of compounds; different fats may have different effects on LDL and on broader CHD risk based on the specific saturated fatty acids (SFAs) they contain. Importantly, though, people eat foods, not isolated fatty acids. Some food sources of SFAs may pose no risk for CHD or possibly even be *protective*. Advice to reduce saturated fat in the diet without regard to nuances about LDL, SFAs, or dietary sources could actually *increase* people's risk of CHD. When saturated fats are replaced with refined carbohydrates, and specifically with added sugars (like sucrose or high fructose corn syrup), the end result is not favorable for heart health. Such replacement leads to changes in LDL, high-density lipoprotein (HDL), and triglycerides that may increase the risk of CHD. Additionally, diets high in sugar may induce many other abnormalities associated with elevated CHD risk, including elevated levels of glucose, insulin, and uric acid, impaired glucose tolerance, insulin and leptin resistance, non-alcoholic fatty liver disease, and altered platelet function. A diet high in added sugars has been found to cause a 3-fold increased risk of death due to cardiovascular disease, but sugars, like saturated fats, are a diverse class of compounds. The monosaccharide, fructose, and fructose-containing sweeteners (e.g., sucrose) produce greater degrees of metabolic abnormalities than does glucose (either isolated as a monomer, or in chains as starch) and may present greater risk of CHD. This paper reviews the evidence linking saturated fats and sugars to CHD, and concludes that the latter is more of a problem than the former. Dietary guidelines should shift focus away from reducing saturated fat, and from replacing saturated fat with carbohydrates, specifically when these carbohydrates are refined. To reduce the burden of CHD, guidelines should focus particularly on reducing intake of concentrated sugars, specifically the fructose-containing sugars like sucrose and high-fructose corn syrup in the form of ultra-processed foods and beverages.

Statement of Conflict of Interest: see page 5.

Authors' contributions: JJD conducted the primary literature review, conceived the paper, and drafted the initial text. SCL and JOK contributed citations, revised arguments, and substantively revised the text. All authors contributed to the writing of the final manuscript.

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Abbreviations and Acronyms

CAD = coronary artery disease

CHD = coronary heart disease

CV = cardiovascular

HDL = high-density lipoprotein

HFCS = high fructose corn syrup

LDL = low-density lipoprotein

MI = myocardial infarction

NAFLD = non-alcoholic fatty liver disease

oxLDL = oxidized low-density lipoprotein

SFA = saturated fatty acids

TC = total serum cholesterol

TG = triglyceride

US = United States

CVD = cardiovascular disease

Background and history

Atherosclerotic coronary heart disease (CHD) is responsible for one in every six deaths in the United States (US).[1] Almost 1 million myocardial infarctions (MIs) occur each year,[1] and approximately 15% of patients die as a result of their event.[1] CHD is also a leading cause of morbidity throughout the developed world, and a substantial driver of health-care related costs.[2]

In trying to limit the global burden of CHD, prevention is a key strategy. Historically, dietary approaches to CHD prevention focused on cholesterol.

The presence of cholesterol in atherosclerotic plaque was first reported in 1843.[3] Subsequent studies in the early part of the 20th century showed that feeding rabbits cholesterol produced atherosclerosis.[4–6] The fact that rabbits are naturally herbivores (never eating cholesterol in their usual diet) made the significance of these experiments uncertain, and while dietary cholesterol intake may exert some effects on serum cholesterol and ultimately atherosclerotic plaques in humans, dietary cholesterol has increasingly become less of a concern for CHD.[7] Other dietary culprits may be of greater concern.

During the 1950s, American scientist Ancel Keys developed a theory of dietary saturated fat as the principal promoter of elevated serum cholesterol and heart disease. Keys' theory was embraced by the American Heart Association (AHA), who in 1961 officially recommended that Americans lower their intake of saturated fat.[8] The theory was also embraced by the US federal government as outlined in its 1977 Dietary Goals.[9]

A competing theory gained less traction than Keys' but nonetheless had its proponents. Around the same time Key's made his case against saturated fat, a British physiologist, John Yudkin, argued that sugar was actually more closely related to CHD incidence and mortality.[10]

In truth, both Yudkin and Keys could find support for their theories in observational studies, partly because people eat foods, not isolated food constituents. Dietary sources of saturated fat are also often dietary sources of sugar and people who eat large amounts of sugar often also eat large amounts of saturated fat.

Today, with more than a half-century of science since Yudkin and Keys developed their theories, there are now ample data to better assess the potential contributions of saturated fat and sugar to CHD. This paper will review the evidence to date, considering basic science, epidemiology, and clinical-trial data pertaining to CHD risk, CHD events, and CHD mortality.

Saturated fat and CHD risk factors

Although the magnitude of the effect likely varies by specific dietary intake and individual susceptibility,[11,12] it is well-accepted that saturated fats can raise blood levels of total cholesterol (TC).[13–15] Since the majority of blood cholesterol is packaged in low-density lipoproteins (LDL), elevations in TC reflect elevations in LDL.[16] LDL is thought to raise the risk of CHD, and LDL is often referred to as "bad cholesterol."

However, LDL is actually a heterogeneous group of particles, and the sum total of all LDL particles considered together is only modestly associated with cardiovascular (CV) risk.[17,18] For instance, the Framingham Heart Study showed that in men over 50 and in women there was no association between elevated TC (which would mostly be packaged in LDL) and CHD.[19]

A consideration with LDL and CHD risk may be particle size and density. Small, dense LDL particles may behave differently than large buoyant ones. Small-dense LDL is more susceptible to oxidation and is pro-atherogenic,[20–22] pro-thrombotic,[23–26] and pro-inflammatory.[27] Conversely large buoyant LDL may be resistant to oxidation and may even be anti-atherogenic.[28] Although the role in particle size in predicting CV events remains controversial, it may not be the total serum level of LDL that matters as much as the relative proportion of small to large particles.

A high concentration of small-dense LDL and a low concentration of large buoyant LDL has been associated with greater CHD risk.[29] In the Quebec Cardiovascular Study, there was a 3-fold increase in CHD risk in individuals with small-dense LDL after adjustment for total LDL concentration, and other lipid fractions.[30]

Randomized trial data suggest that eating saturated fats can decrease small-dense LDL and increase large buoyant LDL.[31] In other words, consumption of saturated fat may favorably shift LDL proportions to be *protective* against CHD—although, admittedly, not all literature supports the benign or protective nature of large buoyant LDL.[32,33]

Regardless, just as LDL is not a single type of particle, saturated fat is not single kind of fat. Saturated fats are a heterogeneous group of compounds; their effects differ based on the specific fatty acids they contain. For example, while the saturated fatty acid (SFA), palmitate, seems to raise levels of LDL, the SFA, stearate, does not.[34]

The metabolic aspects of SFAs are complex and non-uniform but existing evidence suggests that certain SFAs may confer measurable benefits for lipid profiles and CHD risk. For instance, several SFAs enhance the metabolism of high-density lipoprotein (HDL).[34] HDL is often referred to as "good cholesterol" as this cholesterol-containing lipoprotein is associated with lower risk of CHD. In general, the higher the HDL level, and lower the level of non-HDL cholesterol or the TC/HDL ratio, the better.[35–38] In fact, the TC/HDL ratio is a better predictor of CHD risk than TC, LDL alone, or various other lipid makers (e.g., apolipoproteins A-I, A-II and B).[39,40]

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Notably, the SFAs stearate and laurate reduce the TC/HDL ratio.[13,34] Thus, saturated fats that contain these SFAs specifically may act to *reduce* CHD risk.

Sugar and CHD risk factors

Reducing saturated fat or any other component from one's diet almost inevitably means replacement with something else. When carbohydrates (particularly refined carbohydrates like sugar) replace saturated fats, the result can be unfavorable effects on lipid profiles: TC tends to increase,[41,42] HDL tends to fall,[13,43,44] and triglycerides (TGs)—also associated with CHD[45]—tend to rise.[13,46,47]

Consuming moderate amounts of sugar has been shown to increase TC and TGs.[48,49] A diet high in sugar has been shown to increase TC, TGs, and LDL[50] as well as the TC/HDL ratio.[39,40,47] It has been estimated that to match the cholesterol increases seen within a typical range of sugar consumption, an individual would need to consume saturated fats at a level of about 40% of daily calories[51] (well outside the typical range of intake, which the best available estimates might place at about 9–10%).[52]

In addition to lipid derangements, consuming a diet high in sugar for just a few weeks has been found to cause numerous changes seen in CHD and other vascular disease.[48,53] Both human and animal studies show various metabolic risk for CHD with high sugar diets (e.g., impaired glucose tolerance, insulin resistance, elevated uric acid level, and altered platelet function).[48,53–55] All of these abnormalities can be reversed when reverting to a diet low in sugar.[55,56]

Among sugar-related adverse effects, hyperglycemia itself can lead to glycated LDL, which has been shown to activate platelets,[23–26] and induce vascular inflammation.[27] And hyperinsulinemia may increase CHD risk through a variety of mechanisms: stimulating smooth muscle cell proliferation,[57–59] increasing lipogenesis,[60] or inducing dyslipidemia,[61] inflammation, oxidative stress, and platelet adhesiveness.[62–64]

To be clear though, sugar, like saturated fat, is a heterogeneous class of compounds. Among the sugars, the monosaccharide, fructose, and the disaccharide, sucrose (fructose + glucose), seem to be of greater concern than glucose alone (as a monosaccharide, or as a polysaccharide in starch). The fructose-containing sugars seem to cause greater derangement when it comes to elevated insulin levels,[56,65,66] reduced insulin sensitivity,[67–71] increased fasting glucose concentrations,[72,73] and increased glucose and insulin responses to a sucrose load.[56,65] Providing liquid fructose supplementation to a western-type diet in mice increases lipid burden and atherosclerosis despite identical calorie consumption.[74]

Fructose, as compared to glucose, increases oxidized low-density lipoprotein (oxLDL)[75]; and the effects of oxLDL on vascular cells cause pathology commonly found in atherosclerosis and CAD, such as endothelial cell dysfunction/apoptosis, foam cell formation, abnormal vascular tone and blood flow, inflammation, increased cell adhesion molecule expression, pro-clotting, and increased intracellular oxidative stress.[76] The level of oxLDL is significantly higher in patients with CAD, and the sensitivity of oxLDL for predicting CAD is substantially better than the Global Risk Assessment Score (GRAS) that derives from multiple risk factors including age, TC, HDL, blood pressure, diabetes, and smoking (sensitivity 76% for oxLDL vs. just 20% for GRAS). The specificity of oxLDL is 90%, thus, fructose's noteworthy ability to increase oxLDL in humans undoubtedly increases the risk of CAD.

Additionally, fructose increases the levels of advanced glycation end products[77,78]—which, in turn, may lead to dysfunctional macrophages entering the arterial wall and contribute to atherosclerosis.[79] Oxidative stress, reactive oxygen species forming in the heart and aorta, and lipid peroxidation may also play a role in fructose-induced adverse cardiac effects.[80,81] So might an increase in sympathetic nerve activity.[82]

Added fructose—generally in the forms of sucrose and high-fructose corn syrup (HFCS) in processed foods and beverages—also appears to be especially potent for producing diet-induced leptin resistance.[83] Leptin, "the satiety hormone", suppresses hunger and regulates energy balance, and thus is a key hormone in the maintenance of normal body weight. Leptin resistance may be a fundamental cause of obesity,[83,84] itself a risk factor for CHD.[85]

Excess intake of fructose or fructose-containing sweeteners also markedly increases risk for non-alcoholic fatty liver disease (NAFLD)—the most common liver disease in the US,[86,87] and a strong independent risk factor for CHD (probably in part due to associated systemic inflammation).[86] The association between CHD and NAFLD is stronger than the link between CHD and smoking, hypertension, male gender, diabetes, high cholesterol, or metabolic syndrome.[86] Markedly reducing intake of added sugars, especially sucrose and HFCS, can lead to NAFLD regression and, presumably, reduction of associated CHD risk.[88,89]

Consuming fructose or sucrose has been found to increase myocardial oxygen demand, cardiac sympathetic nerve activity, and platelet adhesiveness.[48,90,91] Feeding sucrose to rats causes the development of atheroma, the degree to which depends on the amount of sucrose (but, notably, not fat) in the diet.[92] Moreover, feeding sucrose to rats, as compared to starch, significantly increases the lipid content (total cholesterol, and the free and esterified fractions of cholesterol, and TG) of the aorta.[92] Finally, sucrose leads to increases in 11-hydroxycorticosteroids (for example corticosterone) in a proportion of human subjects, possibly also increasing CHD risk.[93]

Saturated fat and CHD events and mortality

Although some saturated fats may affect some lipid fractions in ways that could theoretically increase the risk of CHD, a large Swedish-population study found no association between fat intake (of any type) and CHD.[94] A review of cohort and case–control studies likewise did not demonstrate a clear role of saturated fats in CHD.[95] Moreover, meta-analyses show that there is limited and inconclusive evidence for modification of total or saturated fat on CHD,[96] or CV morbidity or mortality.[97]

In 1961, there were no randomized trial data to support the AHA dietary fat guidelines, which advised restricting saturated fat. There were also no trial data to support the 1977 US Dietary

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Goals, or even the subsequent 1983 Dietary Fat Guidelines from the UK.[98] In fact, an updated meta-analysis demonstrates that still, to this day, no randomized trial data exist to support any of these guidelines (over a quarter century later).[99]

Conversely, meta-analyses of randomized controlled trials show no reduction in all-cause mortality or CV mortality with reduced saturated fat intake[100] and no reduction in total CVD or risk factors like diabetes.[101] Even in patients with established CHD, there does not seem to be any association between dietary intake of saturated fats and CHD events or mortality.[102]

Importantly though—as mentioned earlier—people do not eat isolated fatty acids; they eat foods that are mixes of various fatty acids and other food constituents. So for instance, while higher intakes of saturated fats from meat sources (particularly processed meats) may increase the risk for CHD, higher intakes of saturated fats from dairy sources may pose no increase in risk and may actually *decrease* risk.[103,104]

As for the effects of reducing consumption of saturated fats, reducing consumption generally means increasing intake of some other dietary component. Replacing saturated fats with other fats like *trans*-fats[101] or omega-6 polyunsaturated oils has been found to increase all-cause mortality.[105–107] Replacing saturated fats with whole grains may be beneficial for CHD,[108] while replacing saturated fats with refined carbohydrates does not decrease risk,[108] and may increase risk of non-fatal MI,[109,110] particularly when the carbohydrates are concentrated sugars.[111]

Sugar and CHD events and mortality

A diet high in added sugars promotes insulin resistance[56,65,75,112,113] and diabetes,[114–117] and patients with diabetes have more coronary atherosclerosis than patients without diabetes,[118–120] particularly severe narrowing of the left main coronary artery.[121] Diabetes increases the risk of death from MI[122,123] and from CV disease more generally,[124] even after controlling for lipids, blood pressure, and other covariates.[125]

Regardless of diabetes status, degree of insulin resistance is associated with future CV events[126,127] and severity of MI.[128] An elevated insulin response to sugar (an oral glucose load) has been found in patients with atherosclerosis of the peripheral, cerebral, and coronary arteries,[129,130] and insulin levels following a glucose challenge have been independently associated with MI occurrence[131] and CHD mortality.[131–133]

Dietary sugar may induce asymptomatic hyperglycemia, which has been linked to CHD death.[134,135] Moreover, a diet high in added sugars has been found to cause a 3-fold increased risk of death due to CV disease.[136]

Historical perspective and discussion

It is worth noting that saturated fat and sugar share many common dietary sources today, in an era of ultra-processed foods, but their co-occurrence in the diet is a relatively recent phenomenon over the course of human history.

For most of the roughly 200,000 years that our species has roamed the planet, humans had been hunters and gatherers. Animal-derived foods would have likely contributed at least some calories to the diets of most people through the ages, and some of the fats in those foods would have been saturated. Most diets would have also consisted of considerable carbohydrates and some people may have even had access to sugars (e.g., in the form of ripened fruit), but there would have been no refined carbohydrates or added sugars at all (except perhaps for rare and serendipitous finds of wild honey).

The situation would have slowly begun to change though around 10,000 years ago, first with the advent of agriculture and subsequently with the refining of grain and the isolation of sugar. While sugar would have been essentially absent from the diet of most humans 2000 years ago, by 1750 AD, the average consumption of sugar per person in Britain may have been about 4 pounds per year.[137] Sugar intake since then may have increased exponentially, with average consumption in 1850 being closer to 25 lb per year, and average consumption in 1950 being about 120 lb per year.[138–140] Today, the average intake of added sugars (including sucrose and high fructose corn syrup) remains very near to this level (demonstrating a greater than 25-fold increase in just over 250 years, or a period of time representing only about 0.1% of the total time our species has been eating).[141]

Sugars occurring naturally in whole foods like fruits and vegetables pose no problem for CHD. Indeed fruits and vegetables (which are likely similar to the plant foods our species has been eating for tens of thousands of years) are associated with lower risk for CHD,[142] and cardiovascular and all-cause mortality.[143] The sugars in these foods occur in reasonable doses and in the context of fiber, water, and other likely benficial constituents.

The problem is refined sugars. For instance, even minimally refined products like fruit juice might increase CHD risk,[142] and ultra-processed products are of even greater concern. Products with added sugars now represent approximately 75% of all packaged foods and beverages in the US[144] Most commonly, these sugars are fructose-containing varieties (e.g., sucrose, HFCS, or straight fructose crystals), which may raise CHD risk even more than other sugars.

Ultra-processed foods also often tend to be sources of saturated fat (including those containing perhaps the most worrisome SFA, palmitate). But whereas advice to avoid processed foods makes for sound dietary guidance, recommendation to avoid SFAs does not. Avoiding saturated fats, or rather the whole foods that contain them, might misdirect dietary behavior away from foods that may be harmless or even protective (e.g. the dairy foods humans have been consuming for millennia) and toward foods that may be harmful (e.g., novel, low-fat, ultra-processed, modern products, with added sugars replacing saturated fats).

Conclusion

Many lines of evidence implicate added sugars more than saturated fat as etiologic in CHD. We urge dietary guidelines to shift focus away from recommendations to reduce saturated fat and toward recommendations to avoid added sugars. Specifically, recommendations should support the eating of whole foods (e.g. foods from living botanical plants)

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and the avoidance of ultra-processed foods (i.e., foods from industrial processing plants).

Salient Points

• Dietary guidelines continue to recommend restricting intake of saturated fats. This recommendation is based largely on the observation that saturated fats can raise levels of TC, thereby putatively increasing the risk of CHD.

• TC matters less for CHD than how cholesterol is packaged into transport particles. LDL is one class of transport particles, with different implications for CHD depending on particle size and density. Small-dense LDL is more susceptible to oxidation and is pro-atherogenic,[20–22] pro-thrombotic,[23–26] and pro-inflammatory.[27] Conversely large buoyant LDL is resistant to oxidation and may even be anti-atherogenic.[145]

• Eating saturated fat can decrease small-dense LDL and increase large buoyant LDL.[31]

• But saturated fat is a diverse class of compounds, with different implications for lipid profiles and CHD risk depending on the type of fatty acids the fats contains. The SFA, palmitate, raises levels of LDL; the SFA, stearate, does not. Stearate and laurate reduce the TC/HDL ratio.[34]

• Importantly, people eat foods, not isolated fatty acids, and the mix of fatty acids and other food components matters. Some food sources of SFAs may increase the risk of CHD (e.g., processed meats) but other may have no effect or even decrease the risk (e.g. dairy foods).

• Meta-analyses of randomized trials do not demonstrate a clear role for saturated fat in increasing all-cause mortality or CHD mortality.[98,100]

• Saturated fats have played some role in the human diet for the last 2.6 million years. Conversely, added sugars have only played a significant role in the last few hundred years. In the modern era of ultra-processed foods, dietary sources of saturated fats are also often dietary sources of sugar.

• When sugar replace saturated fats, the result can be unfavorable effects on lipid profiles: TC tends to increase,[41,42] HDL tends to drop,[13,43,44] and triglycerides tend to rise[13,46,47]

• High sugar diets are associated with impaired glucose tolerance, insulin resistance, elevated uric acid level, and altered platelet function[48,53–55]—abnormalities that can be reversed when reverting to a diet low in sugar.[55,56]

• Sugar-related hyperglycemia is associated with pro-inflammatory and prothrombotic glycated LDL, and sugar-related hyperinsulinemia is associated with smooth muscle cell proliferation,[57–59] lipogenesis,[60] dyslipidemia,[61] inflammation, oxidative stress, and increased platelet adhesiveness.[62–64]

• Some sugars may be more problematic than others with regard to CHD risk: fructose, and fructose-containing sweeteners (e.g. sucrose or high-fructose corn syrup) may present greater risk of CHD than glucose (alone or as starch).[56,65,75] Fructose, as compared to glucose, increases oxidized low-density lipoprotein (oxLDL)[75]; which likely leads to endothelial cell dysfunction/apoptosis, foam cell formation, abnormal vascular tone and blood flow, inflammation, increased cell adhesion molecule expression, pro-clotting, and increased intracellular oxidative stress.[76] Additionally, fructose increases the levels of advanced glycation end products[77,78]—which, may lead to dysfunctional macrophages entering the arterial wall and contribute to atherosclerosis.[79] Oxidative stress, reactive oxygen species forming in the heart and aorta, and lipid peroxidation may also play a role in fructose-induced adverse cardiac effects.[80,81]

• Feeding sucrose to rats causes the development of atheroma, the degree to which depends on the amount of sucrose (not fat) in the diet.[92] Humans that develop ischemic heart disease have been found to eat more sugar, not more fat.[139]

• Sugar seems to act as both a predisposing factor for heart disease (e.g. through inflammatory, thrombotic, oxidative, and hormonal pathways), and a precipitating factor (e.g. through an increase in myocardial oxygen demand, cardiac sympathetic nerve activity, and platelet adhesiveness).[48,90,91]

• Replacing saturated fats with sugars increases the risk of non-fatal MI[109,110] A diet high in added sugars has been found to cause a 3-fold increased risk of death due to cardiovascular disease.[136]

• Dietary guidelines should shift focus away from reducing saturated fat, and from replacing saturated fat with carbohydrates, especially when these carbohydrates are refined. To reduce the burden of CHD, guidelines should focus particularly on reducing intake of concentrated sugars, specifically the fructose-containing sugars added by industry like sucrose and high-fructose corn syrup.

Statement of Conflict of Interest

None of the authors have any conflicts of interests with regard to this publication.

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