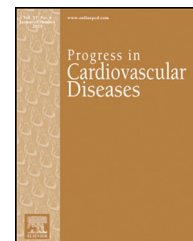


Available online at www.sciencedirect.com

ScienceDirect

www.onlinepcd.com

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

James J. DiNicolantonio^{a,*}, Sean C. Lucan^b, James H. O'Keefe^a

^aSaint Luke's Mid America Heart Institute, Kansas City, MO

^bDepartment of Family and Social Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY

ARTICLE INFO

Keywords:

Cardiovascular disease
Coronary heart disease
Fructose
Sucrose
Sugar
Saturated fat
Fatty acids
Lipids
Cholesterol
Lipoproteins

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.

© 2015 Elsevier Inc. All rights reserved.

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.

* Address reprint requests to James J. DiNicolantonio, PharmD, Saint Luke's Mid America Heart Institute, Kansas City, MO 64111.

E-mail address: jjdinicol@gmail.com (J.J. DiNicolantonio).

<http://dx.doi.org/10.1016/j.pcad.2015.11.006>

0033-0620/© 2015 Elsevier Inc. All rights reserved.

Please cite this article as: DiNicolantonio JJ, et al. The Evidence for Saturated Fat and for Sugar Related to Coronary Heart Disease. *Prog Cardiovasc Dis* (2015), <http://dx.doi.org/10.1016/j.pcad.2015.11.006>

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}

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 CHD⁴⁵—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 LDL⁵⁰ 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 calories⁵¹ (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

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 intake¹⁰⁰ 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*-fats¹⁰¹ 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 occurrence¹³¹ 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 beneficial 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 US¹⁴⁴ 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)

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.

Research by Dr. Lucan reported in this publication was supported by the Eunice Kennedy Shriver National Institute Of Child Health & Human Development of the National Institutes of Health under Award Number K23HD079606. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220.
2. Johnson T. Reducing the prevalence and costs of heart disease. *NCSL Legisbrief*. 2015;23:1–2.
3. Ahrens RA. Sucrose, hypertension, and heart disease an historical perspective. *Am J Clin Nutr*. 1974;27:403–422.
4. Stehbens WE. Anitschkow and the cholesterol over-fed rabbit. *Cardiovasc Pathol*. 1999;8:177–178.
5. Buja LM, Nikolai N. Anitschkow and the lipid hypothesis of atherosclerosis. *Cardiovasc Pathol*. 2014;23:183–184.
6. Bailey CH. Atheroma and other lesions produced in rabbits by cholesterol feeding. *J Exp Med*. 1916;23:69–84.

7. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Office of Disease Prevention and Health Promotion. <http://health.gov/dietaryguidelines/2015-scientific-report/>.
8. Dietary fat and its relation to heart attacks and strokes. Report by the Central Committee for Medical and Community Program of the American Heart Association. *JAMA*. 1961;175:389-391.
9. http://zerodisease.com/archive/Dietary_Goals_For_The_United_States.pdf.
10. Yudkin J. Dietary fat and dietary sugar in relation to ischaemic heart-disease and diabetes. *Lancet*. 1964;2:4-5.
11. Ravnskov U. Is saturated fat bad? In: De Meester F, Zibadi S, Watson RR, eds. Modern dietary fat intakes in disease promotion, part 2. *Nutr Health*; 2010. p. 109-119.
12. Robinson F, Hackett AF, Billington D, et al. Changing from a mixed to self-selected vegetarian diet—influence on blood lipids. *J Hum Nutr Diet*. 2002;15:323-329.
13. Mensink RP, Zock PL, Kester AD, et al. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146-1155.
14. Clarke R, Frost C, Collins R, et al. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ*. 1997;314:112-117.
15. Frantz Jr ID, Dawson EA, Ashman PL, et al. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. *Arteriosclerosis*. 1989;9:129-135.
16. Chait A, Brunzell JD, Denke MA, et al. Rationale of the diet-heart statement of the American Heart Association. Report of the Nutrition Committee. *Circulation*. 1993;88:3008-3029.
17. Ravnskov U. A hypothesis out-of-date. The diet-heart idea. *J Clin Epidemiol*. 2002;55:1057-1063.
18. Weinberg SL. The diet-heart hypothesis: a critique. *J Am Coll Cardiol*. 2004;43:731-733.
19. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA*. 1987;257:2176-2180.
20. Tribble DL, Holl LG, Wood PD, et al. Variations in oxidative susceptibility among six low density lipoprotein subfractions of differing density and particle size. *Atherosclerosis*. 1992;93:189-199.
21. Verhoye E, Langlois MR. Circulating oxidized low-density lipoprotein: a biomarker of atherosclerosis and cardiovascular risk? *Clin Chem Lab Med*. 2009;47:128-137.
22. Henriksen T, Mahoney EM, Steinberg D. Enhanced macrophage degradation of biologically modified low density lipoprotein. *Arteriosclerosis*. 1983;3:149-159.
23. Weidtmann A, Scheithe R, Hrboticky N, et al. Mildly oxidized LDL induces platelet aggregation through activation of phospholipase A2. *Arterioscler Thromb Vasc Biol*. 1995;15:1131-1138.
24. Korporeal SJ, Van Eck M, Adelmeijer J, et al. Platelet activation by oxidized low density lipoprotein is mediated by CD36 and scavenger receptor-A. *Arterioscler Thromb Vasc Biol*. 2007;27:2476-2483.
25. Wraith KS, Magwenzi S, Aburima A, et al. Oxidized low-density lipoproteins induce rapid platelet activation and shape change through tyrosine kinase and Rho kinase-signaling pathways. *Blood*. 2013;122:580-589.
26. Ferretti G, Rabini RA, Bacchetti T, et al. Glycated low density lipoproteins modify platelet properties: a compositional and functional study. *J Clin Endocrinol Metab*. 2002;87:2180-2184.
27. Daub K, Seizer P, Stellos K, et al. Oxidized LDL-activated platelets induce vascular inflammation. *Semin Thromb Hemost*. 2010;36:146-156.
28. Fernandez ML. Rethinking dietary cholesterol. *Curr Opin Clin Nutr Metab Care*. 2012;15:117-121.
29. Griffin BA, Freeman DJ, Tait GW, et al. Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: relative contribution of small, dense LDL to coronary heart disease risk. *Atherosclerosis*. 1994;106:241-253.
30. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Circulation*. 1997;95:69-75.
31. Dreon DM, Fernstrom HA, Campos H, et al. Change in dietary saturated fat intake is correlated with change in mass of large low-density-lipoprotein particles in men. *Am J Clin Nutr*. 1998;67:828-836.
32. Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. *JAMA*. 2001;286:1468-1474.
33. Mora S, Szklo M, Otvos JD, et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211-217.
34. Ramsden CE, Faurot KR, Carrera-Bastos P, et al. Dietary fat quality and coronary heart disease prevention: a unified theory based on evolutionary, historical, global, and modern perspectives. *Curr Treat Options Cardiovasc Med*. 2009;11:289-301.
35. Kitamura A, Iso H, Naito Y, et al. High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men. *Circulation*. 1994;89:2533-2539.
36. Stein O, Stein Y. Atheroprotective mechanisms of HDL. *Atherosclerosis*. 1999;144:285-301.
37. Plump AS, Scott CJ, Breslow JL. Human apolipoprotein A-I gene expression increases high density lipoprotein and suppresses atherosclerosis in the apolipoprotein E-deficient mouse. *Proc Natl Acad Sci U S A*. 1994;91:9607-9611.
38. Vega GL, Grundy SM. Hypoalphalipoproteinemia (low high density lipoprotein) as a risk factor for coronary heart disease. *Curr Opin Lipidol*. 1996;7:209-216.
39. Kinoshita B, Glick H, Preiss L, et al. Cholesterol and coronary heart disease: predicting risks in men by changes in levels and ratios. *J Invest Med*. 1995;43:443-450.
40. Stampfer MJ, Sacks FM, Salvini S, et al. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med*. 1991;325:373-381.
41. Akinyanju PA, Qureshi RU, Salter AJ, et al. Effect of an "atherogenic" diet containing starch or sucrose on the blood lipids of young men. *Nature*. 1968;218:975-977.
42. Naismith DJ, Stock AL, Yudkin J. Effect of changes in the proportions of the dietary carbohydrates and in energy intake on the plasma lipid concentrations in healthy young men. *Nutr Metab*. 1974;16:295-304.
43. Vorster HH, Kruger A, Wentzel-Viljoen E, et al. Added sugar intake in South Africa: findings from the Adult Prospective Urban and Rural Epidemiology cohort study. *Am J Clin Nutr*. 2014;99:1479-1486.
44. Yudkin J, Kang SS, Bruckdorfer KR. Effects of high dietary sugar. *Br Med J*. 1980;281:1396.
45. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3:213-219.
46. Taubes G. *Good calories, bad calories*. New York City, Knopf. 2007.
47. Albrink MJ, Meigs JW, Man EB. Serum lipids, hypertension and coronary artery disease. *Am J Med*. 1961;31:4-23.
48. Szanto S, Yudkin J. The effect of dietary sucrose on blood lipids, serum insulin, platelet adhesiveness and body weight in human volunteers. *Postgrad Med J*. 1969;45:602-607.
49. Szanto S, Yudkin J. Dietary sucrose and platelet behaviour. *Nature*. 1970;225:467-468.
50. Te Morenga LA, Howatson AJ, Jones RM, et al. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses

- of randomized controlled trials of the effects on blood pressure and lipids. *Am J Clin Nutr.* 2014;100(1):65–79.
51. Yudkin J. Dietary prevention of atherosclerosis. *Lancet.* 1970;1:418.
 52. Hite AH, Feinman RD, Guzman GE, et al. In the face of contradictory evidence: report of the Dietary Guidelines for Americans Committee. *Nutrition.* 2010;26:915–924.
 53. Yudkin J, Kakkar VV, Szanto S. Sugar intake, serum insulin and platelet adhesiveness in men with and without peripheral vascular disease. *Postgrad Med J.* 1969;45: 608–611.
 54. Bruckdorfer KR, Worcester NA, Yudkin J. Influence of diet on rat platelet aggregation. *Nutr Metab.* 1977;21(Suppl 1):196–198.
 55. Szanto S, Yudkin J. Plasma lipids, glucose tolerance, insulin levels and body-weight in men after diets rich in sucrose. *Proc Nutr Soc.* 1969;28:11a–12a.
 56. Reiser S, Handler HB, Gardner LB, et al. Isocaloric exchange of dietary starch and sucrose in humans. II. Effect on fasting blood insulin, glucose, and glucagon and on insulin and glucose response to a sucrose load. *Am J Clin Nutr.* 1979;32: 2206–2216.
 57. Stout RW, Bierman EL, Ross R. Effect of insulin on the proliferation of cultured primate arterial smooth muscle cells. *Circ Res.* 1975;36:319–327.
 58. Pfeifle B, Ditschuneit HH, Ditschuneit H. Insulin as a cellular growth regulator of rat arterial smooth muscle cells in vitro. *Horm Metab Res.* 1980;12:381–385.
 59. Pfeifle B, Ditschuneit H. Effect of insulin on growth of cultured human arterial smooth muscle cells. *Diabetologia.* 1981;20:155–158.
 60. Kersten S. Mechanisms of nutritional and hormonal regulation of lipogenesis. *EMBO Rep.* 2001;2:282–286.
 61. Waddell WR, Geyer RP, Hurley N, et al. Abnormal carbohydrate metabolism in patients with hypercholesterolemia and hyperlipemia. *Metabolism.* 1958;7:707–716.
 62. Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. *J Am Diet Assoc.* 2010;110:1307–1321.
 63. Barua RS, Ambrose JA. Mechanisms of coronary thrombosis in cigarette smoke exposure. *Arterioscler Thromb Vasc Biol.* 2013;33:1460–1467.
 64. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. *Transl Res.* 2013;162:237–251.
 65. Reiser S, Michaelis OE, Cataland S, et al. Effect of isocaloric exchange of dietary starch and sucrose in humans on the gastric inhibitory polypeptide response to a sucrose load. *Am J Clin Nutr.* 1980;33:1907–1911.
 66. DiNicolantonio JJ, O’Keefe JH, Lucan SC. Added fructose: a principal driver of type 2 diabetes mellitus and its consequences. *Mayo Clin Proc.* 2015;90:372–381.
 67. Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. *Am J Clin Nutr.* 1980;33:273–278.
 68. Gutman RA, Basilico MZ, Bernal CA, et al. Long-term hypertriglyceridemia and glucose intolerance in rats fed chronically an isocaloric sucrose-rich diet. *Metabolism.* 1987;36:1013–1020.
 69. Pagliassotti MJ, Shahrokhi KA, Moscarello M. Involvement of liver and skeletal muscle in sucrose-induced insulin resistance: dose–response studies. *Am J Physiol.* 1994;266: R1637–R1644.
 70. Vrana ASZ, Kazdova L, Fabry P. Insulin sensitivity of adipose tissue on serum insulin concentrations in rats fed sucrose and starch diets. *Nutr Rep.* 1971:31–37.
 71. Bruckdorfer KR, Kang SS, Yudkin J. Insulin sensitivity of adipose tissue of rats fed with various carbohydrates. *Proc Nutr Soc.* 1974;33:4a–5a.
 72. Dunnigan MG, Fyfe T, McKiddie MT, et al. The effects of isocaloric exchange of dietary starch and sucrose on glucose tolerance, plasma insulin and serum lipids in man. *Clin Sci.* 1970;38:1–9.
 73. Cohen AM, Teitelbaum A. Effect of dietary sucrose and starch on oral glucose tolerance and insulin-like activity. *Am J Physiol.* 1964;206:105–108.
 74. Hutter N, Baena M, Sanguesa G, et al. Liquid fructose supplementation in LDL-R–/– mice fed a western-type diet enhances lipid burden and atherosclerosis despite identical calorie consumption. *IJC Metab Endocr.* 2015;9:12–21.
 75. Stanhope KL, Schwarz JM, Keim NL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest.* 2009;119:1322–1334.
 76. Jenkins AJ, Best JD, Klein RL, et al. Lipoproteins, glycoxidation and diabetic angiopathy. *Diabetes Metab Res Rev.* 2004;20: 349–368.
 77. Ahmed N, Furth AJ. Failure of common glycation assays to detect glycation by fructose. *Clin Chem.* 1992;38:1301–1303.
 78. Bunn HF, Higgins PJ. Reaction of monosaccharides with proteins: possible evolutionary significance. *Science.* 1981;213:222–224.
 79. Seneff S, Wainwright G, Mascitelli L. Is the metabolic syndrome caused by a high fructose, and relatively low fat, low cholesterol diet? *Arch Med Sci.* 2011;7:8–20.
 80. Lopes A, Vilela TC, Taschetto L, et al. Evaluation of the effects of fructose on oxidative stress and inflammatory parameters in rat brain. *Mol Neurobiol.* 2014;50:1124–1130.
 81. Delbosc S, Paizanis E, Magous R, et al. Involvement of oxidative stress and NADPH oxidase activation in the development of cardiovascular complications in a model of insulin resistance, the fructose-fed rat. *Atherosclerosis.* 2005;179:43–49.
 82. Lanter BB, Sauer K, Davies DG. Bacteria present in carotid arterial plaques are found as biofilm deposits which may contribute to enhanced risk of plaque rupture. *mBio.* 2014;5: e01206–e01214.
 83. Vasselli JR, Scarpace PJ, Harris RB, et al. Dietary components in the development of leptin resistance. *Adv Nutr.* 2013;4:164–175.
 84. Lucan SC, DiNicolantonio JJ. How calorie-focused thinking about obesity and related diseases may mislead and harm public health. An alternative. *Public Health Nutr.* 2014;18(4): 571–581.
 85. Stubbs A, Kotfila C, Xu H, et al. Identifying risk factors for heart disease over time: overview of 2014 i2b2/UTHealth shared task Track 2. *J Biomed Inform.* 2015. [pii: S1532-0464(15)00140-9].
 86. Chhabra R, O’Keefe JH, Patil H, et al. Association of coronary artery calcification with hepatic steatosis in asymptomatic individuals. *Mayo Clin Proc.* 2013;88:1259–1265.
 87. Lim JS, Mietus-Snyder M, Valente A, et al. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat Rev Gastroenterol Hepatol.* 2010;7:251–264.
 88. Schwarz JM, Noworolski SM, Wen MJ, et al. Effect of a high-fructose weight-maintaining diet on lipogenesis and liver fat. *J Clin Endocrinol Metab.* 2015;100:2434–2442.
 89. Schwarz J-M, Noworolski SM, Wen MJ, et al. Isocaloric fructose restriction for 10 days reduces hepatic de novo lipogenesis and liver fat in obese Latino and African American children. Poster presented at: ENDO 2015; March 5, 2015; San Diego, California; 2015. [Endocrine Society website. <https://endo.confex.com/endo/2015endo/webprogram/Paper19571.html>. Accessed May 12, 2015].

90. Brown CM, Dulloo AG, Yepuri G, et al. Fructose ingestion acutely elevates blood pressure in healthy young humans. *Am J Physiol Regul Integr Comp Physiol*. 2008;294:R730-R737.
91. Young JB, Landsberg L. Stimulation of the sympathetic nervous system during sucrose feeding. *Nature*. 1977;269:615-617.
92. Bruckdorfer KR, Khan IH, Yudkin J. The lipid content of the aortas of rats given sucrose. *Proc Nutr Soc*. 1972;31:9a-10a.
93. Yudkin J, Szanto S. Hyperinsulinism and atherogenesis. *Br Med J*. 1971;1:349.
94. Leosdottir M, Nilsson PM, Nilsson JA, et al. Dietary fat intake and early mortality patterns—data from The Malmo Diet and Cancer Study. *J Intern Med*. 2005;258:153-165.
95. Ravnkov U. The questionable role of saturated and polyunsaturated fatty acids in cardiovascular disease. *J Clin Epidemiol*. 1998;51:443-460.
96. Siri-Tarino PW, Sun Q, Hu FB, et al. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr*. 2010;91:535-546.
97. Hooper L, Summerbell CD, Higgins JP, et al. Dietary fat intake and prevention of cardiovascular disease: systematic review. *BMJ*. 2001;322:757-763.
98. Harcombe Z, Baker JS, Cooper SM, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. *Open Heart*. 2015;2:e000196.
99. Harcombe Z, Davies B, Baker JS, Sculthorpe N, DiNicolantonio JJ, Grace F. Evidence from randomized controlled trials does not support current dietary fat guidelines: A systematic review and meta-analysis. 2016. (unpublished).
100. Hooper L, Martin N, Abdelhamid A, et al. Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev*. 2015;6:Cd011737.
101. de Souza RJ, Mente A, Maroleanu A, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ*. 2015;351:h3978.
102. Ptaschitz NG, Strand E, Norekval TM, et al. Dietary intake of saturated fat is not associated with risk of coronary events or mortality in patients with established coronary artery disease. *J Nutr*. 2015;145:299-305.
103. de Oliveira Otto MC, Mozaffarian D, Kromhout D, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. *Am J Clin Nutr*. 2012;96:397-404.
104. O'Sullivan TA, Hafekost K, Mitrou F, et al. Food sources of saturated fat and the association with mortality: a meta-analysis. *Am J Public Health*. 2013;103:e31-e42.
105. Ramsden CE, Hibbeln JR, Majchrzak SF, et al. n-6 fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHD risk: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2010;104:1586-1600.
106. Woodhill JM, Palmer AJ, Leelarthaepin B, et al. Low fat, low cholesterol diet in secondary prevention of coronary heart disease. *Adv Exp Med Biol*. 1978;109:317-330.
107. Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ*. 2013;346:e8707.
108. Li Y, Hruby A, Bernstein AM, et al. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. *J Am Coll Cardiol*. 2015;66:1538-1548.
109. Jakobsen MU, O'Reilly EJ, Heitmann BL, et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr*. 2009;89:1425-1432.
110. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr*. 2000;71:1455-1461.
111. Hu FB. Are refined carbohydrates worse than saturated fat? *Am J Clin Nutr*. 2010;91:1541-1542.
112. Maegawa H, Kobayashi M, Ishibashi O, et al. Effect of diet change on insulin action: difference between muscles and adipocytes. *Am J Physiol*. 1986;251:E616-E623.
113. Hallfrisch J, Ellwood KC, Michaelis OE, et al. Effects of dietary fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. *J Nutr*. 1983;113:1819-1826.
114. Reiser S, Bohn E, Hallfrisch J, et al. Serum insulin and glucose in hyperinsulinemic subjects fed three different levels of sucrose. *Am J Clin Nutr*. 1981;34:2348-2358.
115. Basu S, Yoffe P, Hills N, et al. The relationship of sugar to population-level diabetes prevalence: an econometric analysis of repeated cross-sectional data. *PLoS One*. 2013;8:e57873.
116. Goran MI, Uliaszczek SJ, Ventura EE. High fructose corn syrup and diabetes prevalence: a global perspective. *Glob Public Health*. 2013;8:55-64.
117. Gross LS, Li L, Ford ES, et al. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr*. 2004;79:774-779.
118. Robertson WB, Strong JP. Atherosclerosis in persons with hypertension and diabetes mellitus. *Lab Invest*. 1968;18:538-551.
119. Vigorita VJ, Moore GW, Hutchins GM. Absence of correlation between coronary arterial atherosclerosis and severity or duration of diabetes mellitus of adult onset. *Am J Cardiol*. 1980;46:535-542.
120. Elkeles RS. Insulin and atheroma. *Lancet*. 1969;1:1211.
121. Waller BF, Palumbo PJ, Lie JT, et al. Status of the coronary arteries at necropsy in diabetes mellitus with onset after age 30 years. Analysis of 229 diabetic patients with and without clinical evidence of coronary heart disease and comparison to 183 control subjects. *Am J Med*. 1980;69:498-506.
122. Soler NG, Pentecost BL, Bennett MA, et al. Coronary care for myocardial infarction in diabetics. *Lancet*. 1974;1:475-477.
123. Lapidus L, Bengtsson C, Blohme G, et al. Blood glucose, glucose tolerance and manifest diabetes in relation to cardiovascular disease and death in women. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Acta Med Scand*. 1985;218:455-462.
124. Garcia MJ, McNamara PM, Gordon T, et al. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes*. 1974;23:105-111.
125. Stout RW. Blood glucose and atherosclerosis. *Arteriosclerosis*. 1981;1:227-234.
126. Venkataraman K, Khoo CM, Leow MK, et al. New measure of insulin sensitivity predicts cardiovascular disease better than HOMA estimated insulin resistance. *PLoS One*. 2013;8:e74410.
127. Gast KB, Tjeerdema N, Stijnen T, et al. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One*. 2012;7:e52036.
128. Opie LH, Stubbs WA. Carbohydrate metabolism in cardiovascular disease. *Clin Endocrinol Metab*. 1976;5:703-729.
129. Stout RW. The relationship of abnormal circulating insulin levels to atherosclerosis. *Atherosclerosis*. 1977;27:1-13.
130. Stout RW. Diabetes and atherosclerosis—the role of insulin. *Diabetologia*. 1979;16:141-150.

131. Welborn TA, Wearne K. Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. *Diabetes Care*. 1979;2:154-160.
132. Pyorala K. Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care*. 1979;2:131-141.
133. Ducimetiere P, Eschwege E, Papoz L, et al. Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. *Diabetologia*. 1980;19:205-210.
134. Alajbegovic S, Metelko Z, Alajbegovic A, et al. Hyperglycemia and acute myocardial infarction in a nondiabetic population. *Diabetol Croat*. 2003;32:169-174.
135. Fuller JH, Shipley MJ, Rose G, et al. Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. *Lancet*. 1980;1:1373-1376.
136. Yang Q, Zhang Z, Gregg EW, et al. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Intern Med*. 2014;174:516-524.
137. Pure JY. *White and deadly*. Penguin Books. 2012.
138. Yudkin J. Dietary carbohydrate and ischemic heart disease. *Am Heart J*. 1963;66:835-836.
139. Yudkin J. Dietetic aspects of atherosclerosis. *Angiology*. 1966;17:127-133.
140. Bray GA, Popkin BM. Dietary sugar and body weight: have we reached a crisis in the epidemic of obesity and diabetes?: health be damned! Pour on the sugar. *Diabetes Care*. 2014;37:950-956.
141. <http://webarchives.cdlib.org/sw1tx36512/> <http://www.ers.usda.gov/AmberWaves/April03/Indicators/behinddata.htm>.
142. Hansen L, Dragsted LO, Olsen A, et al. Fruit and vegetable intake and risk of acute coronary syndrome. *Br J Nutr*. 2010;104:248-255.
143. Wang X, Ouyang Y, Liu J, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ*. 2014;349:g4490.
144. Ng SW, Slining MM, Popkin BM. Use of caloric and noncaloric sweeteners in US consumer packaged foods, 2005-2009. *J Acad Nutr Diet*. 2012;112:1828-1834.e1-6.
145. Zampelas A. Still questioning the association between egg consumption and the risk of cardiovascular diseases. *Atherosclerosis*. 2012;224:318-319.