

Fructose: Is It Bad For Our Health?

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Abstract

The current epidemic of obesity could be explained by the consumption of an extra 20-ounce soft drink each day. In addition to the calories and fructose they provide, soft drinks have little else to contribute to our diet. Since reducing calories from one source or another is an essential step, focusing on those sources that provide few, if any, other nutrients, is an attractive approach. High-fructose corn syrup (HFCS) is clearly a marker for highly refined foods -- the kind of food we want to avoid in our diet. The conclusions I have reached in this paper will not make the caloric sweetener industry happy. One needs to evaluate financial interests in terms of their public health implications. This will not be an easy task.

Introduction

Obesity is a major public health problem that is obviously multi-factorial. However, without food, we would fade away, and thus at some level, the foods we eat are clearly part of the problem. Food provides all of the energy that our bodies need. Quotes from two previous authors capture this issue and the need to identify what these food elements might be: “If then there is reason to be concerned about a dietary cause of a widespread disease, one should look for some constituent of man's diet that has been introduced recently or has increased considerably, recently (1).” “Some factor of diet and/or lifestyle must be driving weight upward, because human biology and our underlying genetic code cannot change in such a short time (2).”

This workshop is examining one component of the food supply--fructose--and what role, if any, it plays in this epidemic. There are at least two sides to this issue--some think we should be concerned about fructose, others think there is nothing to be worried about, and still others think that current evidence is not sufficient to support the claim that fructose is a significant contributor to the rise in overweight and obesity.

Reasoning that changes in food patterns might help identify a food-related component involved in this multi-factorial problem, we examined the changes in food consumption in the United States from the end of World War II through the end of the century using data from the USDA. The most striking change was the increase in use of high fructose corn syrup (HFCS), which replaced significant amounts of sugar in the diet. Just as HFCS was appearing in the US food supply, Professor Yudkin (1) wrote a book titled *Pure, White and Deadly*, in which he attributed the rising risks of obesity and heart disease to sugar. To quote his work again: "When you come to think of it, almost all of the tempting foods that are taken to satisfy appetite rather

than hunger contain carbohydrate that is either sugar or starch." "These carbohydrate-rich foods have another characteristic; they are all artificial foods that do not exist in nature."

Professor Yudkin's ideas were not taken very seriously, nor were those of Cleave (3), who blamed "... refining...in the carbohydrates [which] deceives the tongue and the appetite, and leads to over-consumption -- and this over-consumption is the sole primary cause of obesity." With the recognition of the special properties of fructose, whether in HFCS or as part of the sucrose molecule (table sugar), the concepts of Yudkin and of Cleave might need to be re-examined, and that is the purpose of this workshop.

Positive Energy Balance Produces Obesity

Obesity is the result of a prolonged small positive energy balance with fat storage as the result (4). This was unequivocally shown using doubly-labeled water (5). In **Table 1** the total daily energy expenditures of normal-weight and overweight people are compared. It is clear that both overweight men and women have higher energy expenditure than normal-weight ones at similar ages. To maintain this energy expenditure, they must eat an equivalent amount of food, and to gain weight they must, on average, eat even more. Just as a positive energy balance produces obesity (6,7), so an energy deficit produces weight loss and tips the balance in the opposite direction from overeating (8).

This fundamental concept, that a small positive energy balance over many months to years provides the basis for development of obesity, while true does not explain why this imbalance develops or fails to develop. The law of energy balance does not explain the biological control of food intake nor how fat is distributed over the body. The hedonic effects of food are not factored into the equation for energy balance, nor does energy balance help us to

understand genetic influences, which we know account for a significant amount of the susceptibility to obesity (9,10).

Table 1. Comparison of energy expenditure in normal-weight and overweight men and women using doubly-labeled water*

Age Group (years)	Normal Weight		Overweight	
	Body Mass Index	Mean Total Energy Expenditure (kcal/d)	Body Mass Index	Mean Total Energy Expenditure (kcal/d)
Males				
3-8	15.4	1,441	19.8	1,728
9-13	17.2	2,079	25.4	2,451
14-18	20.4	3,116	--	--
19-30	22.0	3,081	29.6	3,599
31-50	22.6	3,021	30.8	3,598
51-70	23.0	2,469	29.6	2,946
>70	22.8	2,238	27.8	2,510
Females				
3-8	15.6	1,487	20.3	1,669
9-13	17.4	1,907	24.7	2,346
14-18	20.4	2,302	27.6	2,798
19-30	21.4	2,436	29.8	2,677
31-50	21.6	2,404	31.9	2,895
51-70	22.2	2,066	30.4	2,176
>70	21.8	1,564	27.6	1,763

*Adapted from Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (5).

If a positive energy balance produces obesity, the question then becomes how much surplus of energy do we need on a daily basis to account for the current rate of weight gain of 1-2 kg per year over a range of 30 years in adult life? A gain of 1 kg in one year represents a net

storage of about 8,000 kcal. Since the efficiency of storage may be as low as 50% (11), this would translate into a gross intake of about 16,000 kcal more during the year than was expended. If we divide by 365 for the number of days in a year we conclude that an extra 50 kcal per day could account for a weight gain of 1 kg in 1 year.

Energy Available for Use in Foods

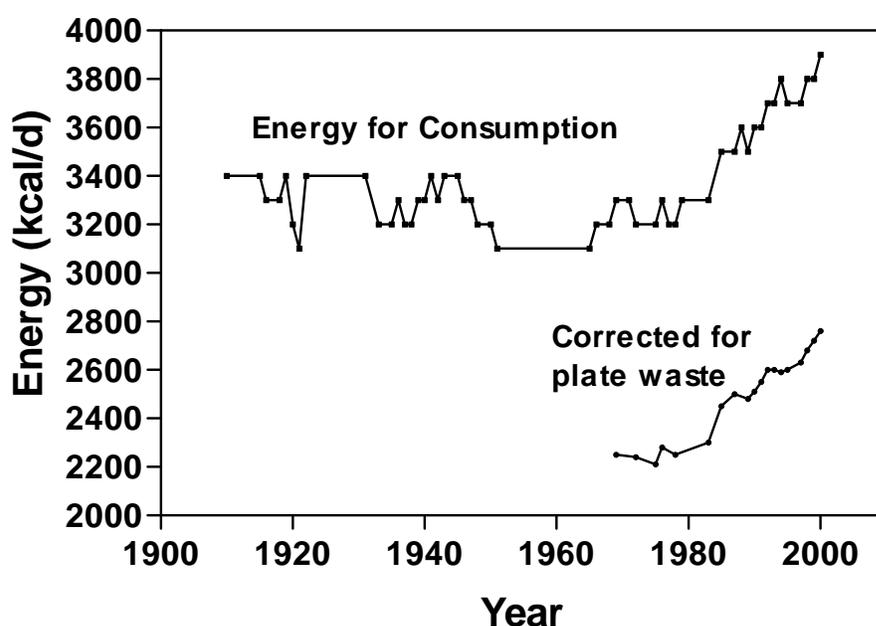


Figure 1. Changes in amount of energy from food available for consumption during the 20th century. This data is based on consumption data collected by the USDA. The corrected data represent an estimate of the difference between available and actual consumption of available calories. (Adapted from Reference 12).

Figure 1 shows the number of calories (energy) available from the food supply during the 20th century (12). This figure was fairly stable until about 1980. Thereafter there was an increase. When corrected for "plate waste," that is, food not eaten, these USDA data suggest that there was

a rise in energy intake between 1980 and 2000 of about 400 kcal per day. This is more than enough energy to account for the current rate of weight gain.

Types of Obesity

We have learned a lot about obesity during the 20th century (4). We know that it is not a single entity, and that there are many different ways to produce it (4,9). Some depend on diet composition and others do not. **Figure 2** depicts a number of environmental agents that can produce obesity by interacting with a susceptible host. For this discussion, I will focus on fructose/food as an environmental agent, while still recognizing that other agents play a role.

Obesity that is Independent of Diet Composition

At one extreme are the types of obesity that will develop independent of diet

composition. At the other

extreme are those where diet

composition plays a major role.

The most obvious examples of obesities that are not dependent on the diet composition are those due to single-gene defects and neuroendocrine disorders (4).

Children with leptin deficiency,

Epidemiological Model of Obesity

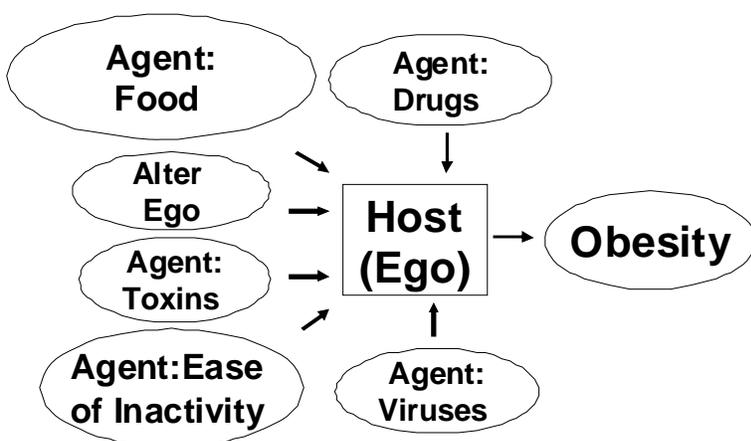


Figure 2. A diagram showing the relation between various environmental factors acting on a susceptible host to produce obesity. (Modified from Reference 4)

those who lack leptin receptors, individuals who fail to produce pro-opiomelanocortin, or those who have abnormalities in the melanocortin-4 receptor are clear-cut examples of people who have genetic disturbances where the drive to eat is so overwhelming that the composition of the

diet is irrelevant - they will eat just about anything. A second group of obesities, where diet is secondary, are those associated with neuroendocrine diseases including hypothalamic obesity, Cushing's syndrome, and polycystic ovary syndrome, all of which are also largely independent of diet (4).

Obesity that Is Dependent on Diet Composition

At the other end of the spectrum are the types of obesity that are influenced by diet. Cost of foods of different types, including cost of ingredients, availability, convenience, hedonic qualities, and fashion affect the response to foods and portion sizes that are available (13,14). Lower prices tend to increase food consumption--the costs of foods rich in fat and sugar are considerably less expensive per thousand calories than those of fresh fruits and vegetables--to take the extremes. High fructose corn syrup supplied a cheap alternative to sucrose, enabling widespread availability for larger portions of soft drinks at very low cost.

This symposium examined the effects of fructose as found in foods, mainly as HFCS, or as half of the sucrose molecule. The biology of fructose is interesting. It is more chemically reactive than glucose, and it circulates in blood at a much lower concentration than glucose. Fructose is an intermediate in the formation of trioses from glucose. The fructose 1-phosphate formed when fructose is absorbed into the liver can be readily converted to glycerol 3-phosphate, the precursor of triglyceride synthesis. Human milk has essentially no fructose. The primary source of fructose in traditional diets is from fruits, honey, and to some extent from nuts and vegetables. In Western diets, the primary sources are sucrose purified from sugar cane or sugar beets and HFCS.

It was the development of the worldwide sugar industry that provided human beings with their major source of dietary fructose. Sugar cane and sugar beets are grown in many countries

and processed to produce sucrose, which is 99% pure--all of the other vegetable components have been eliminated. This is as “refined” as you can get. In contrast, refined grain products still have considerable amounts of protein: refining only removes some 70% of the other components. As noted earlier, the fructose in sucrose has found competition from the fructose produced chemically in HFCS, for which corn starch is the starting product. In both cases the glucose-fructose combination provides the sweetness that so many people desire (3).

A few foods (apple juice, grape juice, and honey) have significant amounts of fructose. It takes 350-400 g of apples to produce an 8-ounce glass of apple juice http://www.foodstudents.net/pdf/apple_juice/background_apple_juice.pdf. Processed foods with a high concentration of fructose (5% by weight), either from HFCS or from sugar, along with fat are both cheap and taste good (13).

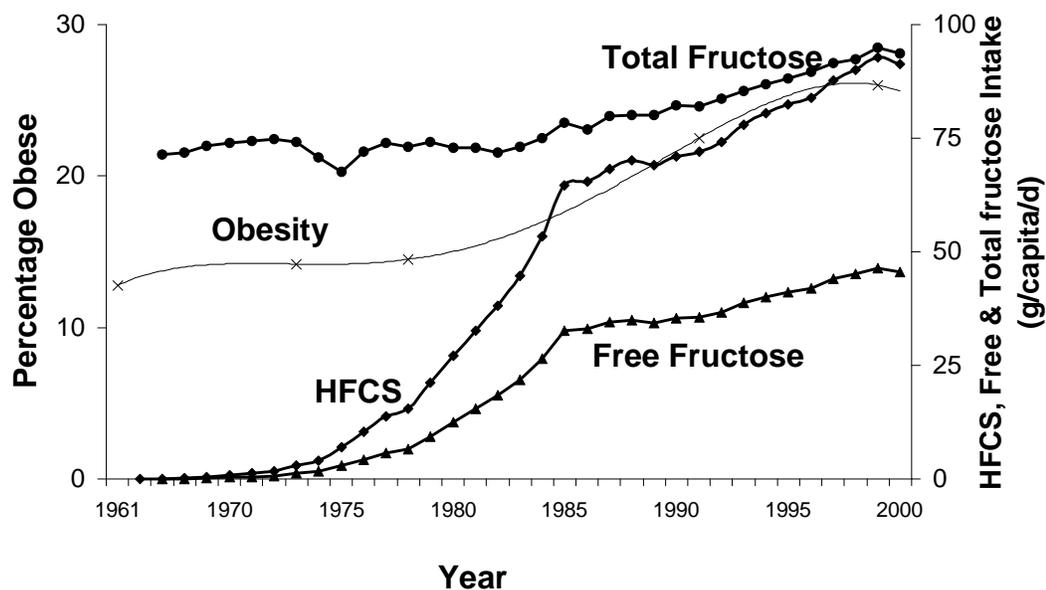
The remaining discussion will focus on fructose in beverages and in prepared foods--but it should be kept in mind that the sweetness of fructose, combined with the pleasantness of foods rich in fat that are often inexpensive, may interact to overpower the ability of the body and the pocketbook to maintain energy balance and thus body weight or energy homeostasis (15).

Calorically sweetened soft drinks

One of the consequences of the lower farm prices in the 1970s was a drop in the price of corn, which made it an inexpensive source of corn starch that can be converted to a high concentration of fructose used to make HFCS (16). With the development of isomerase technology in the late 1960s, starch could be converted into the highly sweet molecule, fructose, which as high-fructose corn syrup (HFCS is a blend of 42% or 55% fructose with glucose) was used to manufacture soft drinks and other highly processed foods. The rapid increase in HFCS in the food supply is shown graphically in **Figure 3** (17). From the early 1970s through the mid-

1990s, HFCS rapidly replaced sugar in many manufactured products, and almost entirely replaced sugar in soft drinks manufactured in the United States. In addition to being cheaper than sucrose, HFCS is very sweet. We have argued that this “sweetness” in liquid form is one factor driving the consumption of increased calories that are needed to fuel the current epidemic of obesity (17).

HFCS, Free and Total Fructose Consumption And Prevalence for Obesity and Overweight



Bray, Nielsen & Popkin, AJCN 2004;79: 537-544

Figure 3. Changing intake of fructose and high-fructose corn syrup intake plotted against the rising prevalence of obesity. (Reprinted from Reference 17)

Fructose differs in several ways from glucose, the other half of the sucrose (table sugar) molecule. Fructose is absorbed from the gastrointestinal tract by a different mechanism than glucose. When glucose is present with fructose it facilitates the absorption of fructose, which is rapidly taken up by the liver, its principal organ for metabolism. Glucose directly stimulates insulin release from the pancreatic beta-cell, but fructose does not. Fructose also enters muscle and other cells without depending on insulin, whereas most glucose enters cells in an insulin-

dependent manner. Finally once inside the cell, fructose can enter the pathways that provide the triglyceride backbone (glycerol) more efficiently than glucose. Thus, high consumption of fructose, as occurs with the rising consumption of soft drinks and the use of high-fructose corn sweeteners, may be a “fat equivalent” (18). In spite of these differences, it is the similarities of fructose-containing products (either sucrose or HFCS) that need to be emphasized.

Fructose-Containing Calorically Sweetened Beverages

A recent review looked at the relationship of fructose consumption to calorie intake and body weight and to the intake of other dietary components as examined in cross-sectional studies (N= 12 or 15) longitudinal studies (N = 5 or 6) or short term experimental studies (N = 7 or 9) in both children and adults (19). These are summarized in **Table 2** which compiles into a single table data from 3 tables in reference 19. Data are expressed as effect sizes (r) and 95% confidence intervals. Of the 12 cross-sectional studies examining the relation of caloric intake of

Table 2. Summary of average effect size of soft-drink consumption by type of research design* for both children and adults

Research Design	Cross-Sectional Studies		Longitudinal Studies		Short Experimental Studies		Overall Effect Size	
	r (95% CI)	n=	r (95% CI)	n=	r (95% CI)	n=	r (95% CI)	n=
Energy Intake	0.13 (0.12, 0.14)	12	0.24 (0.23, 0.26)	5	0.24 (0.16, 0.31)	9	0.16 (0.15, 0.16)	22
Body Weight	0.06 (0.03, 0.08)	12	0.03 (0.00, 0.06)	6	0.24 (0.18, 0.28)	7	0.06 (0.05, 0.08)	25
Milk Intake	-0.11 (-0.12, -0.10)	15	-0.21 (-0.27, -0.15)	5	----		-0.12 (-0.13, -0.11)	20

*Adapted from Tables 1, 2 and 3 of reference (19) with research design referring to whether they were cross-sectional, longitudinal or experimental; r = average effect size calculated using version 2 of the Comprehensive Meta-analysis software program. The authors of this paper considered an effect size of 0.1 as a small effect; 0.25 as medium; and 0.4 as large; n = number of studies in meta-analysis.

fructose-containing soft drink consumption, 10 found a moderately positive association. Among the five longitudinal studies the strength of the association was stronger. The authors concluded that when human beings consume soft drinks there is little caloric compensation. That is, the soft drinks are “added” calories and do not lower the intake of energy in other forms sufficiently to compensate for the beverage calories. In this review, the strengths of these relationships were greater in women and in adults. Vartanian and colleagues also pointed out that “...studies funded by the food industry reported significantly smaller effects than did non-industry-funded studies (19).”

Soft drinks are clearly a part of our culture and their consumption has risen steadily in the past 50 years. A 20-ounce soft drink made with HFCS has about 250 kcal. Thus an extra 20-ounce soft drink each day is more than enough to account for the increased body weight over the last quarter-century. Soft drinks are a prominent part of the fast-food culture. When individuals eat at a fast-food restaurant, compared to a day when they don't, the fast-food day has a larger intake of soft drinks and French-fried potatoes, and a smaller intake of cereal, vegetables, and milk (20).

The relation of soft-drink consumption and milk consumption is shown in Figure 4. As soft-drink consumption has increased (Figure 3), the consumption of milk, a major source of calcium, has decreased as shown in **Figure 4** and in the meta-analysis of cross-sectional studies where the effect size was small and in the longitudinal studies where it was moderate (19). Milk, particularly low-fat milk, is a valuable source of calcium for bone growth during the time of maximal bone accretion. Reducing consumption of beverages containing HFCS or glucose-

Milk and Regular Soft Drink Consumption

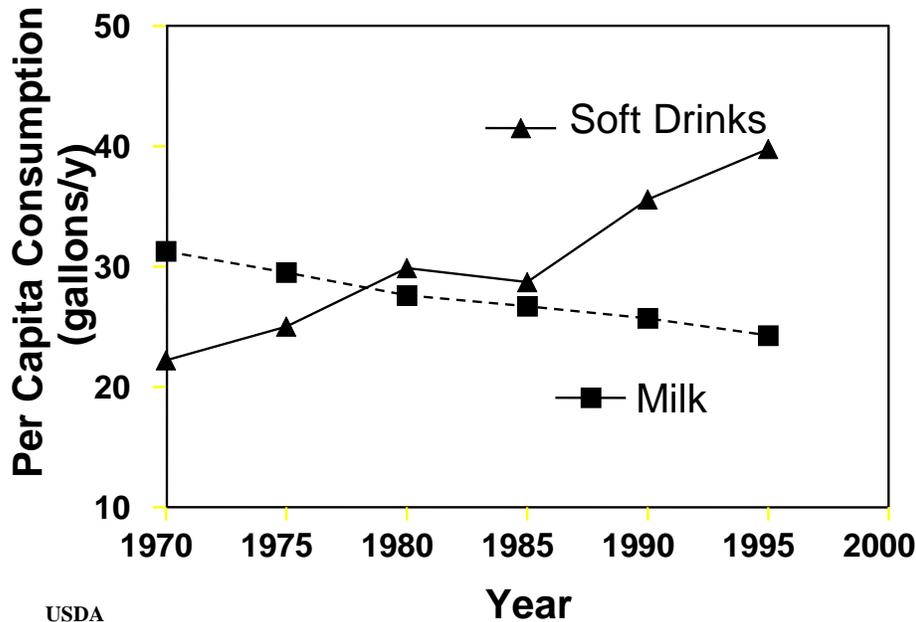


Figure 4. Changing intake of soft drinks and milk. As soft-drink consumption has increased, milk consumption has decreased. Drawn from data in the USDA/ERS Food Consumption, Prices, and Expenditures, 1970-97, statistical bulletin # 965.

fructose (sucrose) might reverse this pattern of decreased milk consumption.

Fructose-containing Soft-Drink Consumption and Body Weight Change

A critique of the relationship of fructose-containing soft drinks to the development of obesity in children has been published by Dietz (21). This is summarized in **Table 3**. These studies are also contained in Table 2, but were segregated in the paper by Dietz to focus on children. There are five studies in children that have shown a positive relationship of soft-drink consumption to weight gain (22-26). They make a case for some people that reducing the consumption of calorie-sweetened beverages by children and adolescents might be one strategy to reduce caloric intake and thus combat the obesity epidemic.

Several studies on the consumption of calorically sweetened beverages in relation to the epidemic of overweight have received significant attention (17,18). Ludwig and colleagues (22)

Table 3. Relation of soft-drink consumption in children to risk of increasing body weight from the paper in reference (21)

Author	Number of Subjects	Age range (years)	Duration	Association
Phillips et al. 2004 (26)	132	9-10	--	Positive
Welsh et al. 2005 (25)	10,904	2-3	1 yr	Positive
Berkey et al. 2004 (24)	12,192	9-14	Two 1 yr periods	Positive
Ludwig et al. 2001 (22)	548	11-12	Baseline and 2 yr	Positive
Striegel-Moore et al 2006 (23)	2,371	9-10	9-10 yr	Positive

Adapted from reference (21)

reported that the intake of soft drinks was a predictor of initial BMI in children in the Planet Health Study. They went on to show that higher soft-drink consumption also predicted the increase in BMI during nearly 2 years of follow-up. Those with the highest soft-drink consumption at baseline had the highest increase in BMI. In one of the few randomized, well controlled intervention studies, Danish investigators (27) showed that individuals consuming sugar-containing (half fructose) calorically sweetened beverages during 10 weeks gained weight, whereas subjects drinking the same amount of artificially sweetened beverages lost weight. Equally important, drinking sugar-sweetened beverages was associated with a small but significant increase in blood pressure. Women in the Nurses' Health Study (28) also showed that changes in the consumption of soft drinks predicted changes in body weight over several years of follow-up. In children, a study focusing on reducing intake of "fizzy" drinks and replacing them with water showed slower weight gain than in those not advised to reduce the intake of fizzy drinks (29).

In the Longitudinal Study of Child Development in Quebec (1998-2002) (30), 6.9% of children who were non-consumers of sugar-sweetened beverages between meals at the ages of 2.5 and 4.5 years were overweight at 2.5, 3.5, and 4.5 years, compared with 15.4% of children who consumed sugar-sweetened soft drinks 4-6 times or more per week between meals. The overall OR was more than doubled in multivariate analysis but was increased threefold in those with lower income.

Fructose and Cardiovascular Risk Factors

Fructose consumption, either in beverages or food, may have an additional detrimental effect. In a study of Swiss children, higher intake of fructose predicted a smaller LDL particle size--the higher risk for LDL-cholesterol (31). Fructose, unlike other sugars, increases serum uric acid levels. Nakagawa and colleagues (32) proposed that this happens when fructose is taken into the liver, its major organ for metabolism, where ATP is used by the enzyme phosphofructokinase to phosphorylate fructose to fructose-1-phosphate. The adenosine-5'-diphosphate can be further broken down to adenosine-5'-monophosphate, then to inosine 5'-phosphate and finally to uric acid. Thus, the metabolism of fructose in the liver leads to the production of uric acid. The authors proposed that the high levels of uric acid could set the stage for advancing cardiovascular disease by reducing the availability of nitric oxide (NO), which is crucial for maintaining normal blood pressure and for maintaining normal function of the vessel walls (endothelium) (32). If this hypothesis is borne out, it will provide another reason that nature preferred glucose over fructose as a substrate for metabolism during the evolutionary process. Soft-drink consumption has been linked to the development of cardiometabolic risk factors and the metabolic syndrome in participants in the Framingham Study (33). Individuals consuming one or more soft drinks per day had a higher prevalence of the metabolic syndrome

(OR = 1.48; 95% CI = 1.30-1.69) and an increased risk of developing the metabolic syndrome over 4 years of follow-up.

Conclusion

The current epidemic of obesity could be explained by the consumption of an extra 20-ounce soft drink each day. In addition to the calories and fructose they provide, soft drinks have little else to contribute to our diet. Since reducing calories from one source or another is an essential step, focusing on those sources that provide few, if any, other nutrients, is an attractive approach to me. The attribution "pure, white, and deadly" to sugar by Professor Yudkin in 1972 may yet be partly right. It is the fructose part of the sucrose (table sugar) molecule and the fructose from HFCS that best fits the title. HFCS is clearly a marker for highly refined foods -- the kind of food I want to avoid in my diet. The conclusions I have reached in this paper will not make the caloric sweetener industry happy. As Yudkin said 25 years ago (1), "I suppose it is natural for the vast and powerful sugar interests to seek to protect themselves, since in the wealthier countries sugar makes a greater contribution to our diets, measured in calories, than does meat or bread or any other single commodity." One needs to evaluate these financial interests in terms of their public health implications. This will not be an easy task

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