

Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity^{1,2}

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ABSTRACT

Obesity is a major epidemic, but its causes are still unclear. In this article, we investigate the relation between the intake of high-fructose corn syrup (HFCS) and the development of obesity. We analyzed food consumption patterns by using US Department of Agriculture food consumption tables from 1967 to 2000. The consumption of HFCS increased > 1000% between 1970 and 1990, far exceeding the changes in intake of any other food or food group. HFCS now represents > 40% of caloric sweeteners added to foods and beverages and is the sole caloric sweetener in soft drinks in the United States. Our most conservative estimate of the consumption of HFCS indicates a daily average of 132 kcal for all Americans aged ≥ 2 y, and the top 20% of consumers of caloric sweeteners ingest 316 kcal from HFCS/d. The increased use of HFCS in the United States mirrors the rapid increase in obesity. The digestion, absorption, and metabolism of fructose differ from those of glucose. Hepatic metabolism of fructose favors de novo lipogenesis. In addition, unlike glucose, fructose does not stimulate insulin secretion or enhance leptin production. Because insulin and leptin act as key afferent signals in the regulation of food intake and body weight, this suggests that dietary fructose may contribute to increased energy intake and weight gain. Furthermore, calorically sweetened beverages may enhance caloric overconsumption. Thus, the increase in consumption of HFCS has a temporal relation to the epidemic of obesity, and the overconsumption of HFCS in calorically sweetened beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 2004;79:537–43.

KEY WORDS Epidemiology, food intake, obesity, artificial sweeteners, fructose

INTRODUCTION

As obesity has escalated to epidemic proportions around the world, many causes, including dietary components, have been suggested. Excessive caloric intake has been related to high-fat foods, increased portion sizes, and diets high both in simple sugars such as sucrose and in high-fructose corn syrup (HFCS) as a source of fructose (1–3). In this article, we discuss the evidence that a marked increase in the use of HFCS, and therefore in total fructose consumption, preceded the obesity epidemic and may be an important contributor to this epidemic in the United States.

To provide a common frame of reference for the terms used in this paper, the following definitions should be understood. *Sugar* is any free monosaccharide or disaccharide present in a food. *Sugars* includes at least one sugar; *composite sugars* refers to the aggregate of all forms of sugars in a food and is thus distinguishable from specific types of sugar, such as fructose, glucose, or

sucrose. *Added sugar* is sugar added to a food and includes sweeteners such as sucrose, HFCS, honey, molasses, and other syrups. *Naturally occurring sugar* is sugar occurring in food and not added in processing, preparation, or at the table. *Total sugars* represents the total amount of sugars present in a food and includes both naturally occurring and added sugars. *Free fructose* is fructose that exists in food as the monosaccharide. *Fructose* refers to both the free and bound forms of fructose (4).

Added sweeteners are important components of our diet, representing 318 kcal of dietary intake for the average American aged ≥ 2 y, or 16% of all caloric intake as measured by a nationally representative survey in 1994–1996 (5). Sweet corn-based syrups were developed during the past 3 decades and now represent close to one-half of the caloric sweeteners consumed by Americans (6, 7). HFCS made by enzymatic isomerization of glucose to fructose was introduced as HFCS-42 (42% fructose) and HFCS-55 (55% fructose) in 1967 and 1977, respectively, and opened a new frontier for the sweetener and soft drink industries. Using a glucose isomerase, the starch in corn can be efficiently converted to glucose and then to various amounts of fructose. The hydrolysis of sucrose produces a 50:50 molar mixture of fructose and glucose. The development of these inexpensive, sweet corn-based syrups made it profitable to replace sucrose (sugar) and simple sugars with HFCS in our diet, and they now represent 40% of all added caloric sweeteners (8). Fructose is sweeter than sucrose. In comparative studies of sweetness, in which the sweetness of sucrose was set at 100, fructose had a sweetness of 173 and glucose had a sweetness of 74 (9). If the values noted above are applied, HFCS-42 would be 1.16 times as sweet as sucrose, and HFCS-55 would be 1.28 times as sweet as sucrose. This contrasts with the estimates reported by Hanover and White (10). In their study, the sweetness of sucrose was set at 100 as in reference 8. Fructose, however, had a sweetness of only 117, whereas a 50:50 mixture of fructose and sucrose had a sweetness of 128. It is difficult to see why fructose and sucrose combined would be sweeter than either one alone and as sweet as HFCS-55. On the basis of data in Agriculture Handbook no. 8 from the US Department of Agriculture (USDA) (11), a cola beverage in 1963

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had 39 kcal/100 g, whereas a cola beverage in 2003 had 41 kcal/100 g. Because the number of calories per 100 g has not changed substantially over the past 40 y, current beverages are probably sweeter, depending on the temperature at which they are served.

HFCS has become a favorite substitute for sucrose in carbonated beverages, baked goods, canned fruits, jams and jellies, and dairy products (10). The major user of HFCS in the world is the United States; however, HFCS is now manufactured and used in many countries throughout the world (7). In the United States, HFCS is the major source of caloric sweeteners in soft drinks and many other sweetened beverages and is also included in numerous other foods; therefore, HFCS constitutes a major source of dietary fructose. Few data are available on foods containing HFCS in countries other than the United States (7).

THE BIOLOGY

Absorption of fructose

The digestive and absorptive processes for glucose and fructose are different. When disaccharides such as sucrose or maltose enter the intestine, they are cleaved by disaccharidases. A sodium-glucose cotransporter absorbs the glucose that is formed from cleavage of sucrose. Fructose, in contrast, is absorbed further down in the duodenum and jejunum by a non-sodium-dependent process. After absorption, glucose and fructose enter the portal circulation and either are transported to the liver, where the fructose can be taken up and converted to glucose, or pass into the general circulation. The addition of small, catalytic amounts of fructose to orally ingested glucose increases hepatic glycogen synthesis in human subjects and reduces glycemic responses in subjects with type 2 diabetes mellitus (12), which suggests the importance of fructose in modulating metabolism in the liver. However, when large amounts of fructose are ingested, they provide a relatively unregulated source of carbon precursors for hepatic lipogenesis.

Fructose and insulin release

Along with 2 peptides, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 released from the gastrointestinal tract, circulating glucose increases insulin release from the pancreas (13, 14). Fructose does not stimulate insulin secretion *in vitro*, probably because the β cells of the pancreas lack the fructose transporter Glut-5 (15, 16). Thus, when fructose is given *in vivo* as part of a mixed meal, the increase in glucose and insulin is much smaller than when a similar amount of glucose is given. However, fructose produces a much larger increase in lactate and a small (1.7%) increase in diet-induced thermogenesis (17), which again suggests that glucose and fructose have different metabolic effects.

Insulin and leptin

Insulin release can modulate food intake by at least 2 mechanisms. First, Schwartz et al (18) have argued that insulin concentrations in the central nervous system have a direct inhibitory effect on food intake. In addition, insulin may modify food intake by its effect on leptin secretion, which is mainly regulated by insulin-induced changes in glucose metabolism in fat cells (19, 20). Insulin increases leptin release (21) with a time delay of several hours. Thus, a low insulin concentration after ingestion of fructose would be associated with lower average leptin concentrations than would be seen after ingestion of glucose. Because

leptin inhibits food intake, the lower leptin concentrations induced by fructose would tend to enhance food intake. This is most dramatically illustrated in humans who lack leptin (22, 23). Persons lacking leptin (homozygotes) are massively obese (22), and heterozygotes with low but detectable serum leptin concentrations have increased adiposity (23), which indicates that low leptin concentrations are associated with increased hunger and gains in body fat. Administration of leptin to persons who lack it produces a dramatic decrease in food intake, as expected. Leptin also increases energy expenditure, and during reduced calorie intake, leptin attenuates the decreases in thyroid hormones and 24-h energy expenditure (24). To the extent that fructose increases in the diet, one might expect less insulin secretion and thus less leptin release and a reduction in the inhibitory effect of leptin on food intake, ie, an increase in food intake. This was found in the preliminary studies reported by Teff et al (25). Consumption of high-fructose meals reduced 24-h plasma insulin and leptin concentrations and increased postprandial fasting triacylglycerol concentrations in women but did not suppress circulating ghrelin concentrations.

Fructose and metabolism

The metabolism of fructose differs from that of glucose in several other ways as well (3). Glucose enters cells by a transport mechanism (Glut-4) that is insulin dependent in most tissues. Insulin activates the insulin receptor, which in turn increases the density of glucose transporters on the cell surface and thus facilitates the entry of glucose. Once inside the cell, glucose is phosphorylated by glucokinase to become glucose-6-phosphate, from which the intracellular metabolism of glucose begins. Intracellular enzymes can tightly control conversion of glucose-6-phosphate to the glycerol backbone of triacylglycerols through modulation by phosphofructokinase. In contrast with glucose, fructose enters cells via a Glut-5 transporter that does not depend on insulin. This transporter is absent from pancreatic β cells and the brain, which indicates limited entry of fructose into these tissues. Glucose provides "satiety" signals to the brain that fructose cannot provide because it is not transported into the brain. Once inside the cell, fructose is phosphorylated to form fructose-1-phosphate (26). In this configuration, fructose is readily cleaved by aldolase to form trioses that are the backbone for phospholipid and triacylglycerol synthesis. Fructose also provides carbon atoms for synthesis of long-chain fatty acids, although in humans, the quantity of these carbon atoms is small. Thus, fructose facilitates the biochemical formation of triacylglycerols more efficiently than does glucose (3). For example, when a diet containing 17% fructose was provided to healthy men and women, the men, but not the women, showed a highly significant increase of 32% in plasma triacylglycerol concentrations (27).

Overconsumption of sweetened beverages

One model for producing obesity in rodents is to provide sweetened (sucrose, maltose, etc) beverages for them to drink (28). In this setting, the desire for the calorically sweetened solution reduces the intake of solid food, but not by enough to prevent a positive caloric balance and the slow development of obesity. Adding the same amount of sucrose or maltose as of a solid in the diet does not produce the same response. Thus, in experimental animals, sweetened beverages appear to enhance caloric consumption.

Fructose and soft drinks

A similar argument about the role of overconsumption of calorically sweetened beverages may apply to humans (29–32).



TABLE 1Availability of high-fructose corn syrup (HFCS) in the US caloric sweetener supply¹

Year	HFCS	Total caloric sweeteners	HFCS as percentage of total caloric sweeteners	Percentage of HFCS from HFCS-42	Percentage of HFCS from HFCS-55
	$g \cdot person^{-1} \cdot d^{-1}$	$g \cdot person^{-1} \cdot d^{-1}$	%	%	%
1966	0.0	165.9	0.0	—	—
1970	0.8	175.1	0.4	100.0	0.0
1975	7.1	168.8	4.2	100.0	0.0
1980	27.3	176.0	15.5	71.2	28.8
1985	64.7	184.4	35.1	34.3	65.7
1990	71.0	195.7	36.3	41.0	59.0
1995	82.3	211.7	38.9	39.9	60.1
2000	91.6	218.0	42.0	38.8	61.2

¹ Data from reference 8. HFCS-42 and HFCS-55, HFCS containing 42% and 55% fructose, respectively.

Mattes (29) reported that when humans ingest energy-containing beverages, energy compensation is less precise than when solid foods are ingested. In another study in humans, DiMeglio and Mattes (30) found that when 15 healthy men and women were given a carbohydrate load of 1880 kJ/d (450 kcal/d) as a calorically sweetened soda for 4 wk, they gained significantly more weight than when the same carbohydrate load was given in a solid form as jelly beans. Additional support for our hypothesis that calorically sweetened beverages may contribute to the epidemic of obesity comes from a longitudinal study in adolescents. Ludwig et al (31) showed that in adolescents participating in the Planet Health project, the quantity of sugar-sweetened beverages ingested predicted initial body mass index (BMI; in kg/m^2) and gain in BMI during the follow-up period. Raben et al (32) designed a randomized, double-blind study to compare the effect of calorically sweetened beverages with that of diet drinks on weight gain in moderately overweight men and women. This European study found that drinking calorically sweetened beverages resulted in greater weight gain over the 10-wk study than did drinking diet drinks. Compared with the subjects who consumed diet drinks, those who consumed calorically sweetened

beverages did not compensate for this consumption by reducing the intake of other beverages and foods and thus gained weight. The beverages in this study were sweetened with sucrose, whereas in the United States almost all calorically sweetened beverages are sweetened with HFCS. Thus, we need a second randomized controlled study that compares sucrose- and HFCS-sweetened beverages. This could establish whether the form of the caloric sweetener played a role in the weight gain observed in the study by Raben et al (32).

The results of the studies by Raben et al (32) and Ludwig et al (31) suggest that the rapid increase in the intake of calorically sweetened soft drinks could be a contributing factor to the epidemic of weight gain. Between 1970, when HFCS was introduced into the marketplace, and 2000, the per capita consumption of HFCS in the United States increased from $0.292 kg \cdot person^{-1} \cdot y^{-1}$ ($0.6 lb \cdot person^{-1} \cdot y^{-1}$) to $33.4 kg \cdot person^{-1} \cdot y^{-1}$ ($73.5 lb \cdot person^{-1} \cdot y^{-1}$), an increase of > 100-fold (8) (Table 1). The total consumption of fructose increased nearly 30%. The consumption of free fructose showed a greater increase, which reflected the increasing use of HFCS (Figure 1). During the same interval, the consumption of sucrose decreased nearly 50%, and

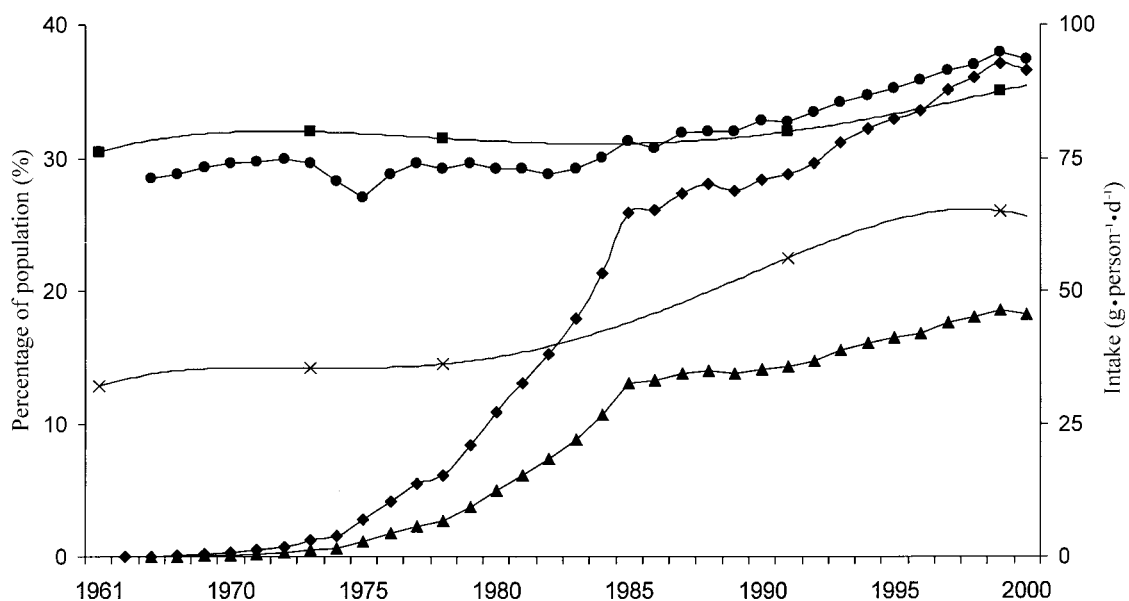


FIGURE 1. Estimated intakes of total fructose (●), free fructose (▲), and high-fructose corn syrup (HFCS, ◆) in relation to trends in the prevalence of overweight (■) and obesity (x) in the United States. Data from references 7 and 35.

the intakes of sucrose and HFCS are now nearly identical. Although this shift has clearly led to a major increase in free-fructose consumption, it is unclear how much of the increase in consumption of calorically sweetened soft drinks is a result of the shift to beverages in which one-half of the fructose is free rather than bound with glucose as in sucrose. A recent review described many facets of this issue (3).

HFCS USE AND INTAKE

Availability of HFCS in the food supply

In 1970 HFCS represented < 1% of all caloric sweeteners available for consumption in the United States, but the HFCS portion of the caloric sweetener market jumped rapidly in the 1980s and by 2000 represented 42.0% of all caloric sweeteners (Table 1) (8). HFCS-42 was initially the only HFCS component, but by the early 1980s, HFCS-55 had become the major source and constituted 61.2% of all HFCS in 2000. These data are based on per capita food disappearance data. In the absence of direct measures of HFCS intake, these data provide the best indirect measure of the HFCS available for consumption in the United States. The data are useful for studying trends but probably overestimate intake patterns. Although it is useful to understand that HFCS intake represents more than two-fifths of the total intake of caloric sweeteners in the United States, it is also important to recognize that the proportion of HFCS in some foods is much higher than that in other foods.

Foods containing HFCS

In the United States, HFCS is found in almost all foods containing caloric sweeteners. These include most soft drinks and fruit drinks, candied fruits and canned fruits, dairy desserts and flavored yogurts, most baked goods, many cereals, and jellies. Over 60% of the calories in apple juice, which is used as the base for many of the fruit drinks, come from fructose, and thus apple juice is another source of fructose in the diet. Lists of HFCS-containing foods can be obtained from organizations concerned with HFCS-related allergies (33). It is clear that almost all caloric sweeteners used by manufacturers of soft drinks and fruit drinks are HFCS (4, 34). In fact, about two-thirds of all HFCS consumed in the United States are in beverages. Aside from beverages, there is no definitive literature on the proportion of caloric sweeteners that is HFCS in other processed foods. HFCS is found in most processed foods; however, the exact compositions are not available from either the manufacturer or any publicly available food-composition table.

Trends in obesity and HFCS availability

There are important similarities between the trend in HFCS availability and the trends in the prevalence of obesity in the United States (Figure 1). Using age-standardized, nationally representative measures of obesity at 5 time points from 1960 to 1999 (35) and data on the availability of HFCS collected annually over this same period, we graphed both patterns. The data on obesity are from the National Center for Health Statistics for the following periods: 1960–1962 (National Health Examination Survey I), 1971–1975 [National Health and Nutrition Examination Survey (NHANES)], 1976–1980 (NHANES II), 1988–1994 (NHANES III), and 1999 (NHANES 1999–2000) (35). The HFCS data are those from Table 1. The prevalence of overweight (BMI of 25–29.9)

and the prevalence of obesity (BMI > 30) were fit with fourth-order polynomial curves so that the limited number of data points could be fitted into a curve to capture the US trends. We also included estimates of free-fructose intake and total fructose intake. Total fructose is the sum of free fructose and fructose that is part of the disaccharide sucrose. Free fructose is the monosaccharide in HFCS and is also obtained in small amounts from other sources. Free-fructose intake closely follows the intake of HFCS. Total fructose intake increased nearly 30% between 1970 and 2000.

Estimated HFCS consumption

The intake of caloric sweeteners in the United States has increased rapidly, and nationally representative data from 1994 to 1998 from the USDA allow us to estimate an intake of 318 kcal/d for the average US resident aged ≥ 2 y. This value is one-sixth of the intake of all calories and close to one-third of the intake of all carbohydrates and represents a significant increase over the past 2 decades (Table 2). As the intake of caloric sweeteners increased, so did the fructose load, which increased from 158.5 to 228 kcal \cdot person⁻¹ \cdot d⁻¹ between 1977–1978 (36) and 1994–1998 (38, 39).

Furthermore, as shown in Table 2, the major increase in the intake of caloric sweeteners from 1977 to 1998 came from the intake of soft drinks and fruit drinks, and these intake values were 105 and 31 kcal \cdot person⁻¹ \cdot d⁻¹, respectively, of the total added sugar intake of 318 kcal \cdot person⁻¹ \cdot d⁻¹ in 1994–1998. Moreover, more than one-half of the increased caloric sweetener intake during this time period came from the intake of these beverages. The intakes of these 2 types of beverages and of desserts total about two-thirds of all caloric sweetener intake in the United States today (Table 2).

We have no way to directly measure total HFCS use. However, one Food and Drug Administration study used very conservative methods to estimate HFCS use for the nationally representative dietary intake sample from 1977 to 1978 from the USDA (35). Using measures of the proportion of HFCS in each food, Glinsmann et al (40) created food category-wide estimates of the proportion of caloric sweeteners that is HFCS. We applied those same proportions to a set of food groups to estimate the use of caloric sweeteners not only during 1977–1978 but also during later periods. Using our conversion technique applied to the initial 1977–1978 Nationwide Food Consumption Survey data, we obtained results that were only 4 kcal higher than the estimates of Glinsmann et al (39). This approach is based on HFCS composition in the early 1980s. With the use of the USDA value of 4.2 g HFCS/tsp (0.84 g/mL), the availability of HFCS in the food supply in the early 1980s was only one-half of the current availability on a gram per capita basis (as shown in Table 1). Thus, we feel confident that we can use this approach to provide a conservative lower limit of HFCS intake.

In Table 2, the 2 columns at the right contain our estimates of HFCS intake and total fructose intake. On the basis of the trend in intakes, our estimate of HFCS intake for the most recent period of measurement from 1994–1998 is 132 kcal \cdot person⁻¹ \cdot d⁻¹ (37). This represents a shift between 1977–1978 and 1994–1998 from 4.5% of total calories to 6.7% of total calories, or from 10.1% of carbohydrates to 13.1% of carbohydrates (41). The estimate of total fructose intake, which was obtained from the intakes of sucrose and HFCS, would be somewhat higher if we knew the fructose content of the fruit drinks.



TABLE 2Trends in intakes of added sugar (sucrose) and high-fructose corn syrup (HFCS) by Americans aged ≥ 2 y¹

	Soft drinks	Fruit drinks	Desserts	Total added sugar	Estimated HFCS intake ²	Estimated total fructose intake ³
Intake (kcal · person ⁻¹ · d ⁻¹)						
1977–1978	52	18	54	235	80	158.5
1989–1991	74 ⁴	19	47 ⁴	242	95	170
1994–1998	105 ^{4,5}	31 ^{4,5}	60 ^{4,5}	318 ^{4,5}	132	228
Percentage of total energy (%)						
1977–1978	2.9	1.0	3.0	13.1	4.5	8.8
1989–1991	4.1 ⁴	1.1	2.6 ⁴	13.5	5.3	9.4
1994–1998	5.3 ^{4,5}	1.6 ^{4,5}	3.0 ^{4,5}	16.0 ^{4,5}	6.7	11.5
Percentage of total carbohydrates (%)						
1977–1978	6.5	2.3	6.8	29.5	10.1	19.8
1989–1991	8.5 ⁴	2.2	5.4 ⁴	27.8	10.9	19.5
1994–1998	10.4 ^{4,5}	3.1 ^{4,5}	5.9 ^{4,5}	31.5 ^{4,5}	13.1	22.8

¹ Data from references 36–39.² Coefficients derived from Glinsmann et al (40) were used to estimate HFCS intake.³ Estimated as 50% of sucrose + fructose in HFCS.⁴ Significantly different from 1977–1978, $P \leq 0.01$ (t test).⁵ Significantly different from 1989–1991, $P \leq 0.01$ (t test).**Distribution of HFCS intake matters!**

We also explored the distribution of HFCS consumption by examining quintiles of caloric sweetener intake among Americans aged ≥ 2 y (Table 3). Most of the increase in caloric sweetener intake from the middle quintile to the upper quintile came from increases in the intake of calorically sweetened beverages, particularly soft drinks. Consumers in the top quintile, which represents 20% of all Americans, consume $> 11\%$ of their calories from HFCS. Again, remember that this is a very conser-

vative estimate. This same group obtains almost one-half of its carbohydrates from caloric sweeteners and one-fifth of its carbohydrates from HFCS.

DISCUSSION

Genetic factors play an important role in the development of obesity (42). However, the rapidity with which the current epidemic of obesity has descended on the United States (35) and

TABLE 3Distribution of consumption of added caloric sweeteners and high-fructose corn syrup (HFCS) by quintile (Q) of added sugar intake in persons aged ≥ 2 y (1994–1996, 1998)¹

	Q1 (n = 3907)	Q2 (n = 4259)	Q3 (n = 4228)	Q4 (n = 3645)	Q5 (n = 2988)	Total (n = 19 027)	P for trend
Added caloric sweeteners							
Intake (kcal · person ⁻¹ · d ⁻¹)							
Soft drinks	6	31	69	129	290	105	0.022
Fruit drinks	4	14	26	43	69	31	0.003
Total	69	169	263	388	703	318	0.001
Percentage of total energy in kcal (%)							
Soft drinks	0.4	1.9	3.7	6.0	10.2	5.3	0.004
Fruit drinks	0.3	0.8	1.4	2.0	2.4	1.6	0.0001
Total	4.9	10.2	14.0	18.1	24.7	16.0	0.0004
Percentage of carbohydrates (%)							
Soft drinks	0.9	3.8	7.3	11.6	18.8	10.4	0.003
Fruit drinks	0.6	1.7	2.8	3.9	4.5	3.1	0.0004
Total	10.5	20.8	27.9	35.0	45.6	31.4	0.0002
HFCS							
Intake (kcal · person ⁻¹ · d ⁻¹)							
Soft drinks	4	22	49	91	205	74	0.022
Fruit drinks	3	10	18	30	49	22	0.004
Total	21	58	103	166	316	132	0.012
Percentage of total energy in kcal (%)							
Soft drinks	0.3	1.3	2.6	4.2	7.2	3.7	0.005
Fruit drinks	0.2	0.6	1.0	1.4	1.7	1.1	<0.0001
Total	1.5	3.5	5.5	7.7	11.1	6.7	0.0007
Percentage of carbohydrates (%)							
Soft drinks	0.6	2.7	5.2	8.2	13.3	7.3	0.003
Fruit drinks	0.4	1.2	1.9	2.7	3.2	2.2	0.0002
Total	3.2	7.2	10.9	14.9	20.5	13.1	0.0002

¹ Data from references 38 and 39 (weighted to be nationally representative).

many other countries (43) makes environmental factors the more likely explanation. From a public health perspective, the key question is whether there are modifiable environmental agents that could have triggered this epidemic and that might be altered. Several environmental agents, including reduced levels of physical activity (44), a decrease in smoking, increased portion size (2), eating outside the home and at fast-food restaurants, and changes in the types of food that are ingested (45), have been suggested. In this article, we propose that the introduction of HFCS and the increased intakes of soft drinks and other sweetened beverages have led to increases in total caloric and fructose consumption that are important contributors to the current epidemic of obesity.

In this article, we address an important potential hypothesis by which HFCS may have an environmental link with the epidemic of obesity. When total calorie intake is fixed, ie, if a person eats the same amount of fructose, glucose, or sucrose in a metabolically controlled setting, the response should be the same, and this was shown by McDevitt et al (46). This situation is not one in which differences in taste and portion size are allowed to operate. However, many biological factors that we noted in this article suggest that calorically sweetened beverages are associated with overconsumption when the sweetener is in a liquid form (29–32). The collective data suggest that overconsumption of beverages sweetened with HFCS and containing > 50% free fructose and the increased intake of total fructose may play a role in the epidemic of obesity. Whether HFCS used in solid food produces the same overconsumption as it does in beverages is unknown, but we suspect that if the HFCS was entirely in the solid form, it would not pose the same problem (30). Total fructose, both free fructose and fructose combined in sucrose, in both beverages and solid food may be viewed as a precursor to fat because of the ease with which the carbon skeleton of fructose can form the backbone for triacylglycerols and be used for the synthesis of long-chain fatty acids (25). Additional clinical trials are clearly needed to buttress the conclusions of Raben et al (32) that beverages containing sugar caused more weight gain over 10 wk than did diet beverages.


There is a distinct likelihood that the increased consumption of HFCS in beverages may be linked to the increase in obesity. One US study showed that beverages sweetened with HFCS are linked with increased energy intake and weight gain (31). Furthermore, we showed that the increase in the use of HFCS was concurrent with the increase in obesity rates in the United States. HFCS was introduced into the food supply just before 1970 and increased rapidly to constitute > 40% of the sweeteners used by 2000 (8). The increase in HFCS consumption just preceded the rapid increase in the prevalence of obesity that occurred between the National Center for Health Statistics survey in 1976–1980 and the next survey in 1988–1994 (35) (Figure 1).

HFCS is used in soft drinks, and HFCS and apple juice, which has 65% fructose, are used as the principal sweeteners for fruit drinks. The increasing consumption of calorically sweetened soft drinks has been associated with a decrease in the intake of milk (5, 8, 47, 48). This relation adds another mechanism by which HFCS consumption in beverages may be related to the epidemic of obesity. Per capita calcium intake decreased from 890 to 860 mg/d between 1970 and 1981 but has increased slowly since then (8). This was a mean 3% decrease that probably reflected a much larger decrease in calcium intake at the upper ends of the skewed distribution for intake. In US teenagers, total calcium

intake decreased by > 50 mg/d (> 10%) between 1977 and 1996 (49). A convincing set of epidemiologic and clinical studies suggests that dairy products may have a favorable effect on body weight and insulin resistance in both children and adults (50–52). During the interval from 1970 to 1990, the intake of whole milk decreased 58%. However, the intake of cheese, which is high in fat, increased and partially offset the decrease in calcium intake from milk (8). Because milk is a major source of dietary calcium for most humans, this decrease in milk intake may play an important role in the decrease in calcium in the diet.

One possible public health option is to address the sweet taste preference of humans by reducing HFCS and, if sweetness is needed, relying on artificial sweeteners to make up any difference in sweetness. It is becoming increasingly clear that soft drink consumption may be an important contributor to the epidemic of obesity, in part through the larger portion sizes of these beverages and through the increased intake of fructose from HFCS and sucrose (53). If HFCS acts as an agent in the disease, then reducing exposure to this agent may help to reduce the epidemic (54).

Some will question our measures of HFCS intake and availability. Our very conservative estimate of HFCS use and the Food and Drug Administration data showed high HFCS intakes for a large segment of the US population (39).

In conclusion, we believe that an argument can now be made that the use of HFCS in beverages should be reduced and that HFCS should be replaced with alternative noncaloric sweeteners. Sweetness is a preferred taste as well as an acquired one that may be enhanced by exposure to sweet foods. The hypothesis that providing sodas and juice drinks in which caloric sweeteners are partially or completely replaced with noncaloric sweeteners will help reduce the prevalence of obesity is worth testing. If the intake of calorically sweetened beverages is contributing to the current epidemic, then reducing the availability of these beverages by removing soda machines from schools would be a strategy worth considering, as would reducing the portion sizes of sodas that are commercially available (55). 

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REFERENCES

1. Bray GA, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr* 1998;68:1157–73.
2. Young LR, Nestle M. The contribution of expanding portion sizes to the US obesity epidemic. *Am J Public Health* 2002;92:246–9.
3. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr* 2002;76:911–22.
4. Smith SM. High fructose corn syrup replaces sugar in processed food. *Environ Nutr* 1998;11:7–8.
5. Nielsen SJ, Siega-Riz AM, Popkin BM. Trends in energy intake in U.S. between 1977 and 1996: similar shifts seen across age groups. *Obes Res* 2002;10:370–8.
6. Higley NA, White JS. Trends in fructose availability and consumption in the United States. *Food Technol* 1991;45:118–22.
7. Vuilleumier S. Worldwide production of high-fructose syrup and crystalline fructose. *Am J Clin Nutr* 1993;58(suppl):733S–6S.
8. Putnam JJ, Allshouse JE. Food consumption, prices and expenditures, 1970–97. US Department of Agriculture Economic Research Service statistical bulletin no. 965, April 1999. Washington, DC: US Government Printing Office, 1999.
9. Krause MV, Mahan LK. Food, nutrition and diet therapy. 7th ed. Philadelphia: WB Saunders Company, 1984.



10. Hanover LM, White JS. Manufacturing, composition, and applications of fructose. *Am J Clin Nutr* 1993;58(suppl):724S–32S.
11. Watt BK, Merrill AL. Composition of foods: raw, processed, prepared. Agriculture handbook no. 8. Washington, DC: US Government Printing Office, 1963.
12. Petersen KF, Laurent D, Yu C, Cline GW, Shulman GI. Stimulating effects of low-dose fructose on insulin-stimulated hepatic glycogen synthesis in humans. *Diabetes* 2001;50:1263–8.
13. Edwards DM, Todd JF, Mahmoudi M, et al. Glucagon-like peptide 1 has a physiological role in the control of postprandial glucose in humans: studies with the antagonist exendin 9–39. *Diabetes* 1999;48:86–93.
14. Vilsboll T, Krarup T, Madsbad S, Holst JJ. Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. *Regul Pept* 2003;114:115–21.
15. Curry DL. Effects of mannose and fructose on the synthesis and secretion of insulin. *Pancreas* 1989;4:2–9.
16. Sato Y, Ito T, Udaka U, et al. Immunohistochemical localization of facilitated-diffusion glucose transporters in rat pancreatic islets. *Tissue Cell* 1996;28:637–43.
17. Schwarz J-M, Schutz Y, Froidevaux F, et al. Thermogenesis in men and women induced by fructose vs glucose added to a meal. *Am J Clin Nutr* 1989;49:667–74.
18. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000;404:661–71.
19. Muller WM, Gregoire FM, Stanhope KL, et al. Evidence that glucose metabolism regulated leptin secretion from cultured rat adipocytes. *Endocrinology* 1998;39:551–8.
20. Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. *Curr Opin Lipidol* 2002;13:51–9.
21. Saad MF, Khan A, Sharma A, et al. Physiological insulinemia acutely modulated plasma leptin. *Diabetes* 1998;47:544–9.
22. Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* 2002;110:1093–1103.
23. Farooqi IS, Keogh JM, Kamath S, et al. Partial leptin deficiency and human adiposity. *Nature* 2001;414:34–5.
24. Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. *J Clin Endocrinol Metab* 2002;87:2391–4.
25. Teff K, Elliot S, Tschoep MR, et al. Consuming high fructose meals reduces 24 hour plasma insulin and leptin concentrations, does not suppress circulating ghrelin, and increases postprandial and fasting triglycerides in women. *Diabetes* 2002;52(suppl):A408(abstr).
26. Mayes PA. Intermediary metabolism of fructose. *Am J Clin Nutr* 1993;58(suppl):754S–65S.
27. Bantle JP, Raatz SK, Thomas W, Georgopoulos A. Effects of dietary fructose on plasma lipids in healthy subjects. *Am J Clin Nutr* 2000;72:1128–34.
28. Scalfani A. Starch and sugar tastes in rodents: an update. *Brain Res Bull* 1991;27:383–6.
29. Mattes RD. Dietary compensation by humans for supplemental energy provided as ethanol or carbohydrate in fluids. *Physiol Behav* 1996;59:179–87.
30. DiMeglio DP, Mattes RD. Liquid versus solid carbohydrate: effects on food intake and body weight. *Int J Obes Relat Metab Disord* 2000;24:794–800.
31. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet* 2001;357:505–8.
32. Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr* 2002;76:721–9.
33. Hurt-Jones M. The allergy self-help cookbook: over 350 natural food recipes, free of all common food allergens. Emmaus, PA: Rodale Press, 2002.
34. Park YK, Yetley E. Intakes and food sources of fructose in the United States. *Am J Clin Nutr* 1993;58(suppl):737S–47S.
35. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002;288:1723–7.
36. Rizek RL. The 1977–78 Nationwide Food Consumption Survey. *Fam Econ Rev* 1978;2001;4:3–7.
37. Tippet KS, Mickle SJ, Goldman JD, Sykes KE, Cook DA, Sebastian RS. Food and nutrient intakes by individuals in the United States, 1 day, 1989–91. Continuing Survey of Food Intakes by Individuals 1989–91, Nationwide Food Surveys report no. 91-2. Beltsville, MD: US Department of Agriculture, Agriculture Research Service, 1995.
38. Tippet KS, Cypel YS. Design and operation: the Continuing Survey of Food Intakes by Individuals and the Diet and Health Knowledge Survey 1994–96. Continuing Survey of Food Intakes by Individuals 1994–96, Nationwide Food Surveys report no. 96-1. Beltsville, MD: US Department of Agriculture, Agriculture Research Service, 1998.
39. United States Department of Agriculture, Agricultural Research Service. Design and operation: the Continuing Survey of Food Intakes by Individuals and the Diet and Health Knowledge Survey, 1994–96 and 1998. Beltsville, MD: US Department of Agriculture, Agricultural Research Service, 2000.
40. Glinesman WH, Irausquin H, Park YK. Evaluation of health aspects of sugars contained in carbohydrate sweeteners. Report of Sugars Task Force, 1986. *J Nutr* 1986;116:S1–216.
41. Popkin BM, Nielsen SJ. The sweetening of the world's diet. *Obes Res* 2003;11:1325–32.
42. Rankinen T, Perusse L, Weisnagel SJ, Snyder EE, Chagnon YC, Bouchard C. The human obesity gene map: the 2001 update. *Obes Res* 2002;10:196–243.
43. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i–xii, 1–253.
44. Prentice AM, Jebb SA. Obesity in Britain: gluttony or sloth? *Br Med J* 1995;311:437–9.
45. Troiano RP, Flegal KM. Overweight children and adolescents: description, epidemiology, and demographics. *Pediatrics* 1998;101:497–504.
46. McDevitt RM, Poppitt SD, Murgatroyd PR, Prentice AM. Macronutrient disposal during controlled overfeeding with glucose, fructose, sucrose, or fat in lean and obese women. *Am J Clin Nutr* 2000;72:369–77.
47. Cavadini C, Siega-Riz AM, Popkin BM. US adolescent food intake trends from 1965 to 1996. *Arch Dis Child* 2000;83:18–24.
48. Harnack L, Stang J, Story M. Soft drink consumption among US children and adolescents: nutritional consequences. *J Am Diet Assoc* 1999;99:436–41.
49. Carruth BR, Skinner JD. The role of dietary calcium and other nutrients in moderating body fat in preschool children. *Int J Obes Relat Metab Disord* 2001;25:559–66.
50. Davies KM, Heaney RP, Recker RR, et al. Calcium intake and body weight. *J Clin Endocrinol Metab* 2000;85:4635–8.
51. Pereira MA, Jacobs DR Jr, Van Horn L, et al. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA study. *JAMA* 2002;287:2081–9.
52. Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC. Regulation of adiposity by dietary calcium. *FASEB J* 2000;14:1132–8.
53. Barr SI, McCarron DA, Heaney RP, et al. Effects of increased consumption of fluid milk on energy and nutrient intake, body weight, and cardiovascular risk factors in healthy older adults. *J Am Diet Assoc* 2000;100:810–7.
54. Nielsen SJ, Popkin BM. Patterns and trends in portion sizes, 1977–1998. *JAMA* 2003;289:450–3.
55. Bray GA. The fluoride hypothesis and diobesity. How to prevent diabetes by preventing obesity. In: Medeiros-Neto G, Halpern A, Bouchard C, eds. Progress in obesity research: 9. Proceedings of the 9th International Congress on Obesity. Surrey, United Kingdom: John Libbey Eurotext, 2003:26–8.