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A Critical Examination of the Evidence Relating High Fructose Corn Syrup and Weight Gain

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The use of high fructose corn syrup (HFCS) has increased over the past several decades in the United States while overweight and obesity rates have risen dramatically. Some scientists hypothesize that HFCS consumption has uniquely contributed to the increasing mean body mass index (BMI) of the U.S. population. The Center for Food, Nutrition, and Agriculture Policy convened an expert panel to discuss the published scientific literature examining the relationship between consumption of HFCS or "soft drinks" (proxy for HFCS) and weight gain. The authors conducted original analysis to address certain gaps in the literature. Evidence from ecological studies linking HFCS consumption with rising BMI rates is unreliable. Evidence from epidemiologic studies and randomized controlled trials is inconclusive. Studies analyzing the differences between HFCS and sucrose consumption and their contributions to weight gain do not exist. HFCS and sucrose have similar monosaccharide compositions and sweetness values. The fructose:glucose (F:G) ratio in the U.S. food supply has not appreciably changed since the introduction of HFCS in the 1960s. It is unclear why HFCS would affect satiety or absorption and metabolism of fructose any differently than would sucrose. Based on the currently available evidence, the expert panel concluded that HFCS does not appear to contribute to overweight and obesity any differently than do other energy sources. Research recommendations were made to improve our understanding of the association of HFCS and weight gain.

Keywords body mass index, overweight, obesity, sucrose, fructose, glucose

INTRODUCTION

Overweight and obesity have become increasingly problematic in the United States from an individual and a population perspective. According to the body mass index (BMI) categories defined by the Centers for Disease Control and Prevention (CDC), about 65% of the U.S. adult population aged 20–74 years is currently overweight. In addition, 31% of all overweight adults are classified as obese. In 1976–80, only 47% and 15% of adults in the United States were considered overweight and obese, respectively (CDC, 2004). About 16% of American children and adolescents aged 6–19 years are also currently overweight. Two decades ago, about 6% of individuals in this age group were classified as overweight (CDC, 2004). Prior to 1976–80, such dramatic overweight and obesity rates were not observed in the United States.

Overweight and obese individuals are subject to societal stigmatization and are at increased risk for deleterious health conditions, including type 2 diabetes, cardiovascular diseases, hypertension, osteoarthritis, and some cancers (CDC, 2004). Overweight and obesity increase health care costs (USDA, 2004) and mortality rates (Mokdad et al., 2004, 2005; Flegal et al., 2005).

Overweight and obesity are influenced by many genetic and environmental contributors, including race/ethnicity, age, physical activity, sedentary behaviors, food consumption patterns, smoking, technological advancements, and psychological factors (CDC, 2004; Columbia Univ., 2000; Rashad and Grossman 2004). Researchers, government officials, politicians, and activist organizations are contributing significant resources in an

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attempt to understand and reduce the overweight and obesity "epidemic" in the United States.

All sources of energy consumed in excess of energy needs can contribute to increased BMI and risk of overweight and obesity. However, several arguments suggest that, in addition to providing energy, high fructose corn syrup (HFCS) may contribute to the development of overweight and obesity via other mechanisms. In the United States, HFCS has increasingly replaced refined sugar (sucrose) in many foods and most sweetened beverages. Outside the United States, HFCS is not used extensively, and sucrose continues to be the primary caloric sweetener.

Several types of HFCS—HFCS-42, HFCS-55, and HFCS-90—are produced by the food industry. Using enzymes to isomerize dextrose-based corn syrups, HFCS-42 was developed in the 1960s and contains 42% fructose, 53% glucose, and 5% higher saccharides. In the 1970s, the production of "super-sweet" HFCS-90—containing 90% fructose, 9% glucose, and 1% higher saccharides—was made possible by passing HFCS-42 through an ion-exchange column. HFCS-55, which contains 55% fructose, 42% glucose, and 3% higher saccharides, was produced by blending HFCS-42 with HFCS-90 (Chaplin and Bucke, 1990; USDA, 2005; Hanover and White, 1993).

Sucrose, a disaccharide, is composed of two monosaccharides, fructose and glucose, in a ratio of 50:50. In sucrose, the monosaccharides are bound together in a covalent bond that is readily cleaved in the gastrointestinal tract by the enzyme sucrase. Although their monosaccharide compositions are very similar to sucrose, the monosaccharides in HFCS-42 and HFCS-55 are not covalently bonded; that is, their monosaccharides are free in solution. The major difference between sucrose and HFCS-42 and HFCS-55 is their percent moisture content (5% versus 29% and 23%, respectively) (Hanover and White, 1993).

The various formulations of HFCS have distinct applications within the food production industry. HFCS-42 is mainly used in baked goods, canned fruits, and condiments, while HFCS-55 is almost exclusively found in regular carbonated soft drinks (RCSD), other sweetened beverages (fruit drinks/ades), ice cream, and frozen desserts. In addition to its role in HFCS-55 production, HFCS-90 "is valued in natural and 'light' foods, where very little is needed to provide sweetness" (CRA, 2002).

Studies showing that the consumption of the monosaccharide fructose increases overall food intake, resulting in weight gain, are limited and occasionally contradictory. Some animal studies have found an association between fructose consumption and a reduction in food intake (Friedman, 1990). In humans, fructose absorption is facilitated by glucose and other monosaccharides, such as galactose. Excess fructose consumption by itself is known to cause gastric distress and osmotic diarrhea. The impact of fructose consumption on hormone levels, satiety, and subsequent short- and long-term food consumption is a complex relationship that deserves further study, a detailed discussion of which is beyond the scope of this review.

More importantly, the evidence from metabolism studies on fructose alone is irrelevant to the HFCS and weight gain debate. HFCS is not fructose. HFCS is compositionally similar to sucrose. The fructose concentrations used in most fructose metabolism studies greatly exceed the daily fructose consumption of the average American. Even if it were established that consuming fructose leads to over-consumption and weight gain, this would not imply that consuming HFCS also leads to over-consumption and weight gain.

Recently, several hypotheses concerning the causes of overweight and obesity have centered on HFCS. These hypotheses imply that HFCS is unique in its contribution to overweight and obesity beyond being a source of energy. In addition, because soft drinks are consumed by diverse age, socioeconomic, and race/ethnic groups in the United States, soft drink consumption is often utilized as a "proxy" of overall HFCS consumption in studies examining overweight and obesity in the United States.

The Center for Food, Nutrition, and Agriculture Policy convened an expert panel to critically and thoroughly examine the existing evidence linking HFCS consumption to changes in BMI and body weight. The objective of the expert panel was to assess the strength of the evidence for the role of HFCS as a unique contributor to an increased risk of overweight and obesity.

METHODOLOGY

A thorough literature search was conducted using PubMed. Medical subject heading (MeSH) key words used to search the database included: high fructose corn syrup, obesity, sucrose, and beverages. Several types of studies were identified from the search including literature reviews, commentaries, ecological and epidemiologic studies, randomized controlled trials (RCTs), and animal studies. We utilized the ISI *Web of Science*® to identify widely-cited scientific publications to discuss in detail in this manuscript. Recently published studies were included based on the professional judgment of the panel.

ARGUMENTS CONSIDERED

Several arguments have been proposed suggesting that HFCS warrants special attention for the prevention of overweight and obesity because this sweetener has specific properties that uniquely contribute to weight gain. We have organized and summarized these arguments using diagrams (Figs. 1–2). Figure 1 contains a conceptual overview of the arguments. The figure attempts to summarize the major lines of argument and indicate the evidence that would be necessary to support it. Rounded boxes show the beginning and end points of an argument, rectangular boxes indicate an action or process, rectangular boxes with two extra vertical lines designate a sub-process, and non-rectangular parallelograms indicate a proxy. Recurring proxies for HFCS throughout the scientific literature are the various classifications of "soft drinks." The question mark symbol indicates that data is currently not sufficient to support the proposed claim. Figure 2 details the theoretical mechanisms referred to in Fig. 1. Arrows specify the argument flow and the stages at which evidence is required in order to support the argument. If contradictory evidence is available at any point along the path to weight gain, the argument for that particular path is rendered invalid. Any

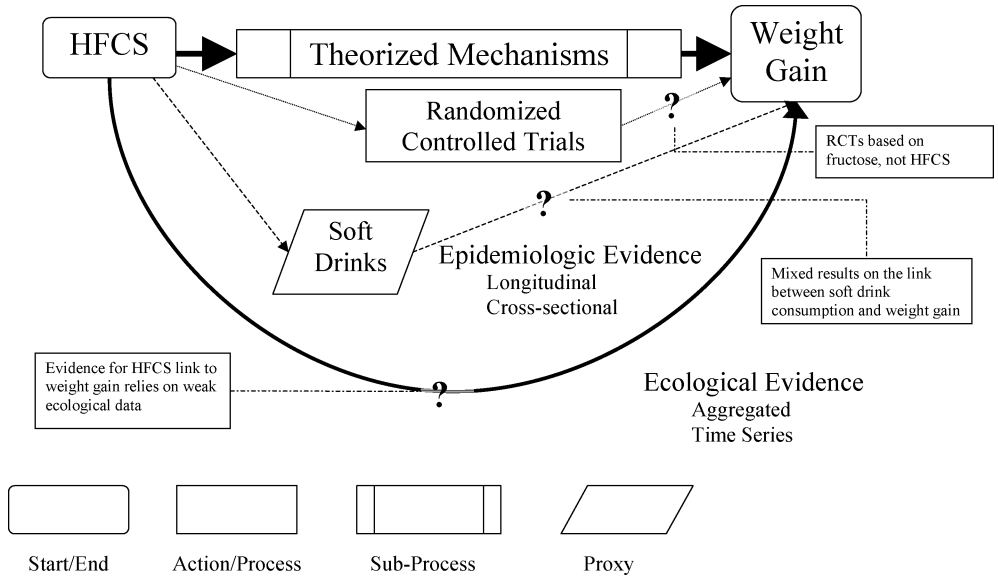

Figure 1 Conceptual overview of the proposed arguments supporting the relationship between high fructose corn syrup (HFCS) consumption and weight gain. Rounded boxes show the beginning and end points of an argument; rectangular boxes indicate an action or process; rectangular boxes with two extra vertical lines designate a sub-process; non-rectangular parallelograms indicate a proxy. Recurring proxies for HFCS throughout the scientific literature are the various classifications of "soft drinks." Arrows specify the argument flow and the stages at which evidence is required in order to support the argument. The question marks indicate that data is currently not sufficient to support the proposed claim. Figure produced by authors.

of the ensuing sub-processes are irrelevant if a line of argument has been shown to be invalid, regardless of whether or not the ensuing sub-processes have been technically validated by other evidence. Once the chain of logic has been broken, the argument is no longer valid. Although lack of evidence does not invalidate an argument, it does make the truth of an argument indeterminate.

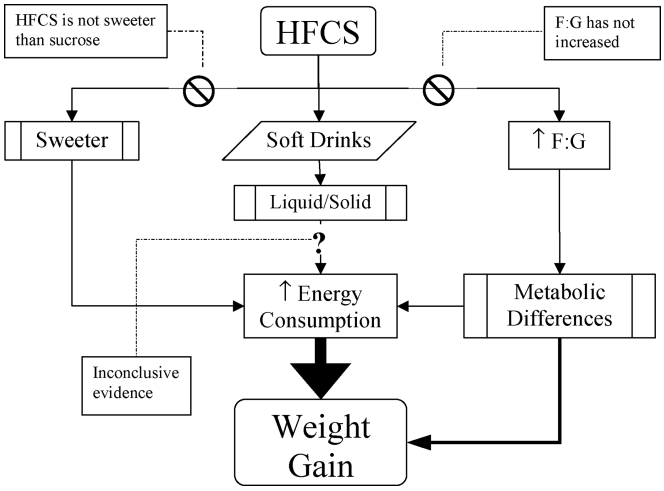

Figure 2 Conceptual overview of the theorized mechanisms supporting the relationship between high fructose corn syrup (HFCS) consumption and weight gain. Rounded boxes show the beginning and end points of an argument; rectangular boxes indicate an action or process; rectangular boxes with two extra vertical lines designate a sub-process; non-rectangular parallelograms indicate a proxy. Recurring proxies for HFCS throughout the scientific literature are the various classifications of "soft drinks." Arrows specify the argument flow and the stages at which evidence is required in order to support the argument. The not symbol (⃠) indicates that evidence that contradicts the claim is available. The question mark indicates that data is currently not sufficient to support the proposed claim. Figure produced by authors.

Figure 1 illustrates the hypothesis that HFCS consumption is positively associated with weight gain via one or more theorized mechanisms. Two types of studies—ecological and epidemiologic—have been extensively cited in support of this relationship. Epidemiologic studies typically utilize various classifications of "soft drinks" as a proxy for HFCS in an attempt to evaluate a putative link between HFCS consumption and weight gain. A small number of randomized controlled trials have also examined the association between "soft drink" consumption and weight gain.

Figure 2 provides further detail of the theorized mechanisms linking HFCS consumption and weight gain. According to discussions in the scientific literature, there are three possible mechanisms: 1) HFCS is "sweeter" than sucrose, leading to greater energy consumption and weight gain, 2) humans do not compensate for excess energy provided by soft drinks (HFCS proxy), leading to greater energy consumption and weight gain, and 3) increased levels of HFCS in the food supply has increased the fructose:glucose (F:G) ratio of the American diet, causing adverse metabolic effects that either directly or indirectly (via greater energy consumption) lead to weight gain. It has been argued that increasing the F:G ratio may: 1) increase hepatic lipogenesis, leading to increased fat production and weight gain, and/or 2) decrease the release of the satiety hormones insulin and leptin and increase the release of the hunger hormone ghrelin, leading to greater energy consumption and weight gain. The not symbol (⃠) indicates that evidence that contradicts the claim is available.

In the following sections, we will review the ecological and epidemiologic studies and the RCTs that directly or indirectly address the relationship between HFCS consumption and risk of overweight and obesity. The details of the studies are presented in Tables 1–4, identifying the type of study and data used, a summary of the results, and any remarks from the authors of this review. In addition, we will also address the feasibility of each of the theorized mechanisms outlined above.

Table 1 Review of ecological studies on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
Gross et al., 2004.	Ecological Per capita nutrient consumption data from the U.S. Department of Agriculture (USDA) and type 2 diabetes prevalence data from the CDC	From 1909 to 1997, the incidence of type 2 diabetes was significantly and positively associated with per capita intakes of fat ($r = 0.84$; $P < 0.001$), total carbohydrate ($r = 0.55$; $P < 0.001$), protein ($r = 0.71$; $P < 0.001$), fiber ($r = 0.16$; $P = 0.027$), corn syrup ($r = 0.83$; $P < 0.001$), and total energy ($r = 0.75$; $P < 0.001$). Multivariate nutrient-density model found that the percent of total energy contributed by corn syrup was positively associated ($b = 0.0132$; $P = 0.038$), and the percent of total energy contributed by fiber was negatively associated ($b = -13.86$; $P < 0.01$), with the incidence of type 2 diabetes.	"Corn syrup" is used inappropriately by Gross et al. "Corn syrup" (ACH Food Co., 2003) is a corn-based sweetener containing various amounts of glucose (dextrose), maltose, isomaltose, maltotriose, and higher molecular weight saccharides. (Chaplin and Bucke, 1990) Unlike corn syrups, HFCS contains fructose in addition to other saccharides. (Hanover and White, 1993)
Harnack et al., 2000.	Ecological Per capita nutrient and energy availability in the United States between 1976–80 and 1988–94 Food and nutrient data from various agriculture, business, and medical databases	The authors observed a decline in per capita availability for seven food categories and an increase in per capita availability for 17 food categories, one of which was corn sweeteners (283.4%). They also noted that the increase in per capita availability of total energy during this time period coincided with the increase in the percentage of overweight children, adolescents, and adults. The per capita availability of many other foods, such as 1% milk (423.8%), poultry (84.5%), and frozen vegetables (72.9%), also increased substantially during this time period.	The ecological data are insufficient to determine which trends, if any, are independently associated with rising overweight and obesity rates. Harnack *et al*. did not directly evaluate the association between BMI values and intake of either total energy or specific macronutrients.
Nielsen and Popkin, 2004.	Ecological Analyzed data from the Nationwide Food Consumption Survey (NFCS) 1977–78 ($n = 29{,}695$), the Continuing Survey of Food Intake for Individuals (CSFII) 1989–91 ($n = 14{,}658$), CSFII 1994–96, 98 ($n = 19{,}027$), and the National Health and Nutrition Examination Survey (NHANES) 1999–2001 ($n = 9965$) to determine consumption trends of specific beverages among all individuals aged ≥ 2 years.	Survey participants were divided into four age categories: 2–18 years, 19–39 years, 40–59 years, and ≥ 60 years. Nielsen and Popkin reported that sweetened beverage (soft drinks plus fruit drinks) consumption increased for all age groups between 1977–78 and 1999–2001 with an overall 135% increase in energy intake from sweetened beverages.	The authors presented no data supporting any relationship between overweight and obesity and the consumption of soft drinks or fruit drinks.
Popkin and Nielsen, 2003.	Ecological Analyzed associations between caloric sweetener consumption trends, percent urbanization, and per capita gross national product (GNP) in multiple countries. Analyzed food-disappearance data to estimate caloric sweetener consumption from 103 countries in 1962 and from 127 countries in 2000.	These authors found a 74 kcal/person increase in per capita caloric sweetener availability between 1962 and 2000. Using pooled regressions from 1962 and 2000, Popkin and Nielsen attributed about 82% of the increase in caloric sweetener consumption to GNP and urbanization shifts. They credited the remaining 18% increase in caloric sweetener consumption to unmeasured factors, such as changes in food production and/or consumer behavior.	These authors only addressed trends in worldwide caloric sweetener consumption. No assessment of the relationship between caloric sweetener consumption and overweight and obesity was undertaken.

Table 2 Review of cross-sectional epidemiologic studies on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
Forshee and Storey, 2003.	Cross-Sectional Utilized CSFII 1994–96, 98 to examine consumption patterns of non-water beverages [milk, fruit juices, regular fruit drinks/ades, diet fruit drinks/ades, regular carbonated soft drinks (RCSD), and diet carbonated soft drinks (DCSD)] among 1749 children (6–11 years) and adolescents (12–19 years).	After controlling for age, race/ethnicity, and family income, these authors found that BMI had a statistically significant and positive relationship with DCSD consumption for both boys ($p < 0.05$) and girls ($p < 0.05$). Since DCSD contains little, if any, energy, these beverages were most likely a marker, not a cause, of higher BMI values among study participants. Overweight children are more likely to consume DCSD in an attempt to control or decrease their weight. BMI did not show an association with RCSD or fruit drink/ade consumption.	Study limitations include no controls for sedentary behaviors, physical activity, and intake of energy from sources other than beverages in the model. In addition, BMI and beverage consumption were self-reported and subject to measurement error. Causal inferences cannot be made from cross-sectional study designs.
Forshee et al. (2004).	Cross-sectional Utilized data from NHANES 1988–94 in order to examine the relative association of demographic variables, beverage consumption, physical activity, and sedentary behaviors with BMI for 2216 adolescents aged 12–16 years. Separate analyses of the dietary assessment tools—one 24-hour dietary recall (24HR) and one food frequency questionnaire (FFQ)—included in NHANES 1988–94. In order to control for total energy, energy from sources other than beverages was calculated ($E_{Other} = E_{Total} - E_{Bev}$) and included in the 24 HR and the FFQ models.	In the 24 HR multivariate regression model, consumption of DCSD ($b = 0.0041$; 95% CI = 0.0007 to 0.0074) was positively associated with BMI for females ($p < 0.05$). Neither RCSD nor fruit drinks/ades were associated with BMI for females or males. In the FFQ multivariate regression model, consumption of DCSD ($b = 0.0408$; 95% CI = 0.0169 to 0.0647) was positively associated with BMI for females ($p < 0.05$). No relationship was observed between any other beverage consumption category and BMI for either females or males.	Since food and beverage consumption, physical activity, and television viewing were self-reported, these variables are subject to measurement error. In addition, by truncating television viewing at a maximum of 5 hours/day, an artificial ceiling was imposed on this variable. Causal inferences cannot be made from cross-sectional study designs.
French et al. 2003.	Cross-sectional Analyzed soft drink consumption trends among children aged 6–17 years. Soft drinks were defined as "carbonated beverages (all United States Department of Agriculture database codes starting with 924) and included flavored waters and juice drinks." (French et al., 2001). Data were obtained from NFCS 1977–78 (n = 8908) and CSFII 1994–96, 98 (n = 3177).	The overall prevalence of soft drink consumption among children aged 6–17 years was 48% higher in 1994–96, 98 than in 1977–78. Mean soft drink intake increased from 5 to 12 oz/day (155 to 370 g/day).	The relationship between soft drink consumption and BMI was not examined. Causal inferences cannot be made from cross-sectional study designs.
Giammattei et al. (2003).	Cross-sectional Investigated the relationship between BMI, television viewing, and regular and diet soft drink consumption among non-diabetic sixth and seventh grade non-Hispanic white (n = 188), Latino (n = 167), and Asian (n = 30) students from 3 different schools in Santa Barbara County, California. Of these 385 children, 305 children completed a questionnaire of 18 lifestyle questions.	Found that 17.9% of the students were at-risk of overweight (BMI ≥85th and <95th percentile), while 17.4% of the students were overweight (BMI ≥95th percentile). Only the number of hours of television viewing on a school night and the total number of soft drinks consumed per day were significantly associated with BMI. When regular and diet soft drinks were analyzed separately, BMI z-scores ($P = 0.001$) and percent body fat ($P = 0.0002$) remained positively and significantly associated with diet soft drink consumption only. BMI z-scores ($P = 0.08$) and percent body fat ($P = 0.06$) were not significantly associated with regular soft drink consumption.	Since the study was limited to sixth and seventh grade students from 3 schools in Santa Barbara County, California, the generalizability of this study to other students is limited. Casual inferences cannot be made from cross-sectional study designs.
Grant et al. (2004).	Cross-sectional Studied the relationship between anthropometric status and macronutrient intake among Pacific Island children aged 2–5 years living in New Zealand.	Of the 56 children who provided height, weight, and 2-day food records, 32 were classified as obese (BMI ≥95th percentile) and 24 were classified as non-obese (BMI <95th percentile).	Consumption of foods and beverages sweetened with HFCS is very limited in New Zealand since HFCS is almost exclusively produced and consumed within the United States. However,

(Continued on next page)

Table 2 Review of cross-sectional epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
	Classified children with a BMI ≥95th percentile of the CDC's BMI-for-age tables as obese.	After adjusting for age and gender, the obese children consumed significantly more total energy than did the non-obese children ($P < 0.05$). The obese children consumed more of all types of foods, not just more of specific foods, than did the non-obese children. Percent of total energy obtained from fat, carbohydrate, sugars, and sucrose was not significantly different between the obese and non-obese children.	Grant et al. did evaluate the relationship between sucrose, which has a monosaccharide composition similar to that of HFCS-42 and HFCS-55, and obesity. The study did not control for physical activity. Causal inferences cannot be made from cross-sectional study designs.
Nicklas et al. (2003).	Cross-sectional Analyzed the relationship between BMI and food consumption patterns among 1562 African-American (AA) and Euro-American (EA) 10-year-olds in Bogalusa, Louisiana between 1973 and 1994 (The Bogalusa Heart Study). Combined the children at-risk for overweight (BMI ≥ 85th and <95th percentile) with the overweight children (BMI ≥ 95th percentile) into one overweight group.	After controlling for total energy intake, age, study year, ethnicity, gender, and ethnicity-gender interaction, the authors found positive associations between overweight and consumption (in grams) of total foods and beverages (OR = 1.77; $p < 0.05$), snacks (OR = 1.24; $p < 0.05$), and low-quality foods (OR = 1.35; $p < 0.01$). Food consumption patterns that included consumption of sweets (OR = 1.38; $p < 0.05$) and sweetened beverages (OR = 1.33; $p < 0.001$) were also associated with overweight. After analyzing the association between food consumption patterns and overweight status by ethnicity-gender groups, only EA males and EA females showed positive associations between overweight and consumption of sweets ($p < 0.05$ for both) and sweetened beverages ($p < 0.01$ for males; $p < 0.05$ for females). For EA males and EA females, positive associations were also found between overweight and consumption of total foods and beverages ($p < 0.05$ for both), particularly from low-quality foods ($p < 0.05$ for both). A positive association between overweight and consumption of the dinner meal ($p < 0.05$) was observed for EA males only. AA females showed negative associations between overweight and consumption of fruits/fruit juices ($p < 0.01$) and fruit/fruit juices/vegetables ($p < 0.01$), total number of meals consumed ($p < 0.05$), and consumption of the breakfast meal ($p < 0.05$). The model explained about 4–8% of the variance in BMI for the various ethnic-gender groups, and soft drink consumption alone explained approximately 1% of the variance in the model.	The results from the Nicklas *et al.* study must be interpreted with caution because none of the models examining associations among eating-pattern variables and overweight status controlled for physical activity. Causal inferences cannot be made from cross-sectional study designs.
Rajeshwari et al. (2005).	Cross-sectional Bogalusa Heart Study Analysis of the relationships between sweetened-beverage consumption and BMI, total energy intake, and milk consumption All sweetened-beverages were assigned to one of the following categories: soft drinks, fruit drinks, iced tea with sugar, and coffee with sugar. Study participants were categorized as either non-consumers, low-consumers, medium-consumers, or high-consumers of sweetened-beverages.	Between 1973 and 1994, mean BMI significantly increased for each of the four sweetened-beverage consumption categories, but there were no differences in mean BMI among any of the four consumption categories. Only the medium-consumers ($p < 0.001$) and high-consumers ($p < 0.001$) of sweetened-beverages significantly increased their mean gram consumption during this time period.	The results from this study must be interpreted with caution due to regional variations in sweetened-beverage consumption patterns among children. The models did not control for physical activity. Causal inferences cannot be made from cross-sectional study designs.

Table 2 Review of cross-sectional epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
Zizza et al. (2001).	Cross-sectional Data from NFCS 1977–78 (n = 4472), CSFII 1989–91 (n = 2373), and CSFII 1994–96 (n = 1648). Analyzed snacking trends among individuals aged 19–29 years	Sweetened beverages (regular soft drinks, diet soft drinks, and fruit drinks) were one of the major contributors of energy from snacking occasions. Overall snacking prevalence increased from 77% in 1977–78 to 84% in 1994–96. Energy consumed per snacking occasion increased by 26%, while the number of snacks consumed per day increased by 14%.	The relationship between snacking and BMI was not examined. The models did not control for physical activity. Causal inferences cannot be made from cross-sectional study designs.

ECOLOGICAL EVIDENCE

Overview

Ecological (population) studies use aggregate data to describe relationships between substance exposure and some other variable (e.g. disease) either among several populations over different geographical areas or within one population over several time periods (Coggon et al., 1997; CDC, 2005). Ecological studies produce the weakest evidence linking substance exposure and health outcomes because ecological studies are highly susceptible to bias, confounding, and chance (CDC, 2005; Robinson, 1950; Greenland and Morgenstern, 1989, 1991). Relative to other study designs, ecological studies are less expensive and time-consuming, yet they can not establish cause-effect relationships or even individual-level associations. Ecological studies can be useful tools to generate hypotheses for later testing by rigorous analysis (CDC, 2005). Spurious relationships, often called "ecological fallacies," can result from using aggregate data to imply cause-effect relationships (Morgenstern, 1995; King, 1997).

Because the data points are averages and not individuals, it is impossible to determine whether a higher consumption of particular foods or food ingredients by individuals is associated with higher BMI values for those individuals. It has even been shown that the correlation between two variables using averages may be the opposite sign of the correlation between the same two variables measured among individuals. For example, Robinson reported in 1950 that the individual correlation of being foreign born and illiteracy was 0.118, but when aggregated to percentages by state, the correlation was −0.526 (Robinson, 1950). Relying on the correlation produced by aggregated data would have given the wrong answer by a large margin. The same type of error may occur when using average food consumption data to explain average BMI data.

Additionally, ecological data are usually small samples. Statistical models need to control for all potential confounding factors or the results will be biased. For a complex problem like obesity, this typically means that you need hundreds or thousands of data points to have sufficient statistical power while controlling for all of the reasonable potential confounding variables. In this case, U.S. per capita HFCS consumption data are available only from 1967 to 2003 for a total of 37 data points (USDA, 2004). These are far too few data points to properly control for the dozens of societal changes that may have been associated with changes in obesity prevalence over the past four decades.

Literature Review of the Ecological Studies

Four widely cited ecological studies that hypothesize a relationship between HFCS consumption and weight gain were found in the scientific literature.

Gross et al. (2004), using per capita nutrient consumption data from the U.S. Department of Agriculture (USDA) and type 2 diabetes prevalence data from the CDC, examined the relationship between the consumption of refined carbohydrates and the incidence of type 2 diabetes—a disease strongly linked to overweight and obesity (CDC, 2004). According to their initial analyses of the available data from 1909 to 1997, the incidence of type 2 diabetes was significantly and positively associated with per capita intakes of fat, total carbohydrate, protein, fiber, corn syrup, and total energy. When the study authors utilized a multivariate nutrient-density model, the percent of total energy contributed by corn syrup was positively associated and the percent of total energy contributed by fiber was negatively associated with the incidence of type 2 diabetes.

Harnack et al. (2000) observed a decline in per capita availability for seven food categories and an increase in per capita availability for 17 food categories, one of which was corn sweeteners. They also noted that the increase in per capita availability of total energy during this time period coincided with the increase in the percentage of overweight children, adolescents, and adults. The per capita availability of many other foods, such as 1% milk, poultry, and frozen vegetables also increased substantially during this time period. Harnack et al. did not directly evaluate the association between BMI values and intake of either total energy or specific macronutrients.

Nielsen and Popkin (2004) reported that sweetened beverage (soft drinks plus fruit drinks) consumption increased for all age groups between 1977–78 and 1999–2001 with an overall 135% increase in energy intake from sweetened beverages. The relationship between beverage consumption and BMI was not examined.

Popkin and Nielsen (2003) found a large increase in per capita caloric sweetener availability between 1962 and 2000,

Table 3 Review of longitudinal epidemiologic studies on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
Berkey et al., 2004.	Longitudinal U.S. Growing Up Today Study (GUTS) Analyzed the relationship between BMI and intakes of sugar-added beverages, milk, fruit juices, and diet soda in a cohort of more than 10,000 males and females aged 9-14 years in 1996.	Positive association between BMI and sugar-added beverage consumption for boys ($p = 0.038$), but the association was not statistically significant for girls ($p = 0.096$). For each serving of sugar-added beverages consumed per day, BMI increased by 0.028 kg/m^2 for boys and by 0.021 kg/m^{2}for girls from the previous year. When total energy was included in the model, the associations were not significant for either boys ($p = 0.317$) or girls ($p = 0.167$).	This study found no statistically significant association between sugar-added beverage consumption and BMI after controlling for total energy. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Field et al., 2004.	Longitudinal GUTS Investigated the association between BMI and the intake of various snack foods, including sugar-sweetened beverages.	After controlling for a variety of potential confounders, including total energy intake, no relationship was found between snack food intake and annual change in BMI for either girls ($b = -0.006$) or boys ($b = -0.004$). According to these authors, "[w]hen servings per day of sugar-sweetened beverages were included as snack foods the association between snack food intake and change in BMI z-score was similar to the main findings" (Field et al., 2004) for girls (b = -0.004) and boys (b = -0.003).	This study found no association between snack food consumption (including sugar-sweetened beverages) and BMI. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Ludwig et al., 2001.	Longitudinal A cohort of 548 ethnically diverse schoolchildren aged 11–12 years enrolled in Massachusetts public schools Examined the relationship between BMI and consumption of sugar-sweetened drinks Changes in BMI and sugar-sweetened drink consumption were measured for 19 months.	Average sugar-sweetened drink consumption increased from 1.22 to 1.44 servings/day—a difference of 0.22 servings/day. After controlling for baseline anthropometrics and demographics, dietary variables, physical activity, television viewing, and total energy intake, the estimated association of sugar-sweetened drinks with BMI was a 0.24 kg/m^2 increase in BMI for each additional serving/day increase in sugar-sweetened drink consumption ($p = 0.03$).	For the average increase in sugar-sweetened drink consumption (0.22 servings/day), this model predicted an annual BMI increase of 0.05 kg/m^2 assuming all other variables in the model remained constant. Nielsen and Popkin (2004), reported that between 1977 and 1996, mean consumption of sweetened beverages increased from 2.02 to 2.55 servings/day for a mean increase of 0.53 servings/day. Using the Ludwig et al. estimate, the predicted increase in BMI would be 0.13 kg/m^2 for an increase of 0.53 servings/day of sugar-sweetened drink consumption [(0.53 servings/day)(0.24 kg/m^2/servings/day)]. The data are not nationally representative.
Newby et al., 2004.	Longitudinal North Dakota Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). Cohort of 1345 children aged 2-5 years visited WIC clinics at least twice between January 1995 and June 1998. Explored the relationship between beverage consumption and changes in BMI	Found no significant relationships between any of the beverages analyzed and BMI. When soda was analyzed separately, an increase in soda consumption of 1 oz/day (31 g/day) predicted a non-significant decrease of 0.01±0.02 BMI units (kg/m^2)/year ($P = 0.50$). When all beverages were included in the model, an increase in soda consumption of 1 oz/day (31 g/day) predicted an identical BMI unit/year decrease ($P = 0.58$).	This study found no relationship between soda consumption and the BMI values of young children. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Schulze et al., 2004.	Longitudinal Nurses' Health Study II Cohort of 51,603 females Examined the relationship between sugar-sweetened beverage consumption, weight change, and risk of type 2 diabetes.	After controlling for a wide range of potential confounders including physical activity, smoking, other components of the diet, and other variables, between 1991 and 1995, those individuals whose sugar-sweetened beverage consumption remained consistent at either ≤1 drink/week (n = 38,737) or ≥1 drink/day (n = 2366) increased in weight by	More than half of the respondents in the Nurses' Health Study II were excluded from the Schulze *et al*. analysis because of various exclusion criteria. The mean change in sugar-sweetened beverage consumption for the low-high (≤1 drink/week to ≥1 drink/day) consumption category was significantly different from the mean change for the

Table 3 Review of longitudinal epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
		3.21 kg/4 years (1.8 lb/year) and 3.12 kg/4 years (1.7 lb/year), respectively. Those individuals with the greatest decrease ($\geq$1 drink/day to $\leq$1 drink/week; n=1020) or increase ($\leq$1 drink/week to $\geq$1 drink/day; n = 1007) in their sugar-sweetened beverage consumption experienced a weight increase of 1.34 kg/4 years (0.7 lb/year) and 4.69 kg/4 years (2.6 lb/year), respectively. The remaining individuals whose sugar-sweetened beverage consumption patterns did not fit these four consumption categories were classified by the study as "Other." This would include, for example, individuals who consistently consumed 2-6 drinks/week or who switched from $\geq$1 drink/day to 2-6 drinks/week. The "Other" category included 16% of the cohort population, and the average weight increase for this category was 3.04 kg/4 years (1.7 lb/year). The cohort was also studied from 1995 to 1999. During this time, individuals who consistently consumed $\leq$1 drink/week (n = 39,279) or $\geq$1 drink/day (n = 2340) gained an average of 2.04 kg/4 years (1.1 lb/year) and 2.21 kg/4 years (1.2 lb/year), respectively. Those individuals with the greatest decrease ($\geq$1 drink/day to $\leq$1 drink/week; n = 1107) or increase ($\leq$1 drink/week to $\geq$1 drink/day; n = 765) in their sugar-sweetened beverage consumption gained an average of 0.15 kg/4 years (0.1 lb/year) and 4.20 kg/4 years (2.3 lb/year), respectively. Those in the "Other" category gained an average of 2.10 kg/4 years (1.2 lb/year) and included 16% of the cohort population.	low-low (consistent at $\leq$1 drink/week), high-high (consistent at $\geq$1 drink/day), and high-low ($\geq$1 drink/day to $\leq$1 drink/week) consumption categories ($P < 0.001$). The low-high consumption category only contained about 2% of the study sample. About 75% of the study sample was located in the low-low consumption category, and about 5% of the study sample was located in the high-high consumption category. The results of the study suggest that those individuals in the high consumption category could benefit by reducing their consumption to $\leq$1 drink/week and that those individuals in the low consumption category could benefit by limiting their increase to no more than 2–6 drinks/week. Smaller changes in sweetened beverage consumption did not show any differences in weight gain.
Janket et al., 2003.	Longitudinal/RCT Women's Health Study (WHS) Cohort of 38,480 female health professionals aged $\geq$45 years Only included participants from the WHS who had completed FFQs and had no history of diabetes at baseline Examined the relationship between risk of type 2 diabetes and intakes of total caloric sweeteners, sucrose, fructose, glucose, and lactose During follow-up, 918 cases of type 2 diabetes were identified.	After controlling for age, smoking, BMI, vigorous exercise, alcohol use, history of hypertension and high cholesterol, post-menopausal hormone and vitamin use, and family history of type 2 diabetes, the authors found no association between the lowest versus highest consumption categories of total caloric sweeteners, sucrose, fructose, glucose, or lactose and risk of type 2 diabetes.	Neither fructose nor glucose—the main components of HFCS—were related to the risk of developing type 2 diabetes. Sucrose, which has a F:G ratio very similar to that of HFCS, was also not related to the risk of developing type 2 diabetes. The data are not nationally representative. The study used self-reported data that may be subject to measurement error.
Mrdjenovic and Levitsky, 2003.	RCT Examined the effects of excessive sweetened drink consumption [defined as >12 oz (>370 g)/day] on total energy intake and weight gain among 30 children aged 6–13 years attending the Cornell Summer Day Camp in 1997 All children consumed home-prepared foods during the first week of camp.	Children who consumed >16 oz/day (>492 g/day) of sweetened drinks gained more weight (1.12 ± 0.7 kg) than did children who consumed between 6 and 16 oz/day (186 and 492 g/day) of sweetened drinks ($0.32 - 0.48 \pm 0.4$ kg). In addition, children who consumed >12 oz/day (>370 g/day) of fruit juice gained more weight (3.3 ± 1.95 kg) than did	Average daily intake of total energy did not exceed the Recommended Daily Allowance (RDA) for any of the age groups in the study. Children in the highest and lowest sweetened drink consumption categories had daily total energy intakes of $91\% \pm 5\%$ and $82\% \pm 5\%$ of the RDA, respectively. In addition, children between the ages of 6

(Continued on next page)

Table 3 Review of longitudinal epidemiologic studies on the association between HFCS and weight gain *(Continued)*

Study	Type of Analysis	Summary of Results	Remarks
	From the second week of camp to the end of the study, each child was provided meals and snacks prepared by study administrators for consumption at camp (breakfast, lunch, and two snacks) or at home (dinner). Three beverage categories were included in the analysis—milk (fluid milk and milk shakes), 100% fruit juice, and sweetened drinks (carbonated fruit-flavored drinks, noncarbonated fruit-flavored drinks, less than 100% fruit juice, sodas, and tea). Daily beverage consumption was divided into four categories—0 [no drink consumed (0 g/day)], 1 [no more than 6 oz (186 g)], 2 [between 6 and 12 oz (186 and 370 g)], 3 [>12 but <16 oz (>370 but <492 g)], and 4 [>16 oz (>492 g)]. Daily dietary intakes were collected over 4 to 8 weeks. Body weights and heights were measured either after the first week of camp or on the first day the child joined the study. Second weight measurements were recorded during a child's final week at camp and were not obtained for all study participants (n = 21). The study authors did not discuss or include second height measurements in their study.	children who consumed <6 oz/day (<186 g/day) of fruit juice (0.5 ± 0.4 kg). None of these differences was statistically significant, and the authors observed that "the sample size was too small (n = 21) to provide sufficient power for the observed difference in weight gain to be statistically significant." Mrdjenovic and Levitsky, 2003. It is also possible that the observed difference in weight gain was not significant due to the absence of a relationship between sweetened drink consumption and weight gain.	and 13 years are increasing in height as well as weight. BMI, which accounts for the relationship between height and weight, would have been a better measure of the relationship between sweetened drink consumption and weight gain due to increased adiposity. The models did not control for physical activity. The study had a small sample size (n = 30 total, n = 21 for a second weight measurement) that was not nationally representative.

during which daily caloric sweetener consumption increased by 74 kcal/person. They attributed about 82% of the increase in caloric sweetener consumption to GNP and urbanization shifts. They credited the remaining 18% increase in caloric sweetener consumption to unmeasured factors, such as changes in food production and/or consumer behavior. No assessment of the relationship between caloric sweetener consumption and overweight and obesity was undertaken.

Table 4 Review of randomized controlled trials on the association between HFCS and weight gain

Study	Type of Analysis	Summary of Results	Remarks
James et al., 2004	Cluster RCT Focused educational intervention program on carbonated drink consumption and overweight and obesity in 644 children aged 7–11 years The children were recruited from six primary schools in southwest England and assigned to one of the 29 study clusters which were each randomly assigned to the intervention or control group. Children in the intervention clusters participated in a program designed to emphasize the consumption of a balanced healthy diet and to discourage the consumption of both sweetened and unsweetened "fizzy" drinks. Included anthropometric measurements taken at six-month intervals and 3-day dietary records (two weekdays and one weekend) obtained at baseline and at the end of the trial.	Observed a decrease in carbonated drink consumption of 0.6 glasses/3 days (50 ml/day) in the intervention group with an increase in carbonated drink consumption of 0.2 glasses/3 days (17 ml/day) in the control group. Mean percentage of overweight and obese children decreased by 0.2% in the intervention group and increased by 7.5% in the control group. The percent difference of overweight and obese children between the intervention and control groups was statistically significant (7.7%; 95% CI = 2.2% to 13.1%). Differences in average BMI values (0.1 kg/m^2; 95% CI = -0.1 $kg/m^2$to 0.3 kg/m^2) and z-scores (0.04; 95% CI = -0.04 to 0.12) between the intervention and control groups were not statistically significant.	Because only the United States produces carbonated drinks sweetened with HFCS, the sweetened "fizzy" drinks in this study were most likely sweetened with sucrose. The data are not nationally representative.

Summary of the Ecological Studies

None of the reviewed ecological studies investigated the relationship between HFCS availability in the food supply and population BMI values. Gross et al. also inappropriately used the term "corn syrup" in their analysis. HFCS, composed mainly of fructose and glucose, is a sweetener derived from corn that is widely used in commercial food production. The term "corn syrup," which many individuals equate with Karo® Syrup, is an entirely glucose-based corn sweetener that was developed for use in the home. Other glucose-based corn sweeteners are produced for use in commercial food production. However, unlike HFCS, their per capita consumption has remained relatively unchanged since 1966 (USDA, 2004). Harnack et al. examined trends in the availability of corn sweeteners, which presumably included the glucose-based corn sweeteners in addition to HFCS, but they did not examine the relationship between corn sweeteners and BMI. Nielsen and Popkin analyzed soft drink and fruit drink consumption trends and did not examine their relationship with BMI. Popkin and Nielsen investigated caloric sweeteners, which could include sucrose, glucose, fructose, HFCS, and other saccharides, but did not estimate the relationship between caloric sweeteners and BMI.

Current ecological studies neither support nor invalidate a hypothesized relationship between HFCS availability and BMI. The increase in BMI values in the U.S. population since the 1970s may have originated from any number of concurrent trends, such as, but not limited to, changes in energy intake from a variety of food sources (Harnack et al., 2000), an increase in sedentary occupations (Lakdawalla and Philipson, 2002), an increase in workforce participation among women (Anderson et al., 2003; Crepinsek and Burstein, 2004), and a decrease in physical education (PE) classes and extracurricular sports programs in schools (Andersen et al. 1998).

EPIDEMIOLOGIC EVIDENCE

Overview

Epidemiological research can include longitudinal, cross-sectional, and case-control studies. Each type has well-known strengths and limitations (Coggon et al., 1997, 1997, 1997). Our literature search found longitudinal and cross-sectional studies that directly or indirectly examined the relationship between HFCS consumption and the prevalence of overweight and/or obesity. No case-control studies on this relationship were found.

Many studies described in this section use the term "sugar-sweetened" soft drinks or beverages. Sugar is often considered synonymous with sucrose, and this creates the potential for confusion. We have continued to use the terminology chosen by the study authors, but it is important to note that most of the beverages in the United States are not actually sweetened with sucrose. The beverages may use a variety of caloric sweeteners, the most common of which is HFCS-55. In other countries, sucrose remains the primary sweetener used in beverages.

Literature Review of the Cross-Sectional Studies

Forshee and Storey (Forshee and Storey, 2003) found that BMI had a statistically significant and positive relationship with diet carbonated soft drink (DCSD) consumption for both boys ($p < 0.05$) and girls ($p < 0.05$). Since DCSD contain little, if any, energy, these beverages were most likely a marker, not a cause, of higher BMI values among study participants. Overweight children are more likely to consume DCSD in an attempt to control or decrease their weight. BMI did not show an association with regular carbonated soft drink (RCSD) or fruit drink/ade consumption.

A study by Forshee et al. (Forshee et al., 2004) found that the consumption of DCSD was positively associated with BMI for females using 24 hr data. Neither RCSD nor fruit drinks/ades were associated with BMI for females or males. In the FFQ, consumption of DCSD was also positively associated with BMI for females. No relationship was observed between any other beverage consumption category and BMI for either females or males.

French et al. (2003) analyzed soft drink consumption trends among children aged 6–17 years. These authors found that the overall prevalence of soft drink consumption among children aged 6–17 years was 48% higher in 1994–96, 98 than in 1977–78. Mean soft drink intake increased from 5 to 12 oz/day (155 to 370 g/day). The relationship between soft drink consumption and BMI was not examined.

Giammattei et al. (2003) investigated the relationship between BMI, television viewing, and regular and diet soft drink consumption among 305 non-diabetic sixth and seventh grade students from 3 different schools in Santa Barbara County, California. They discovered that 17.9% of the students were at-risk of overweight, while 17.4% of the students were overweight. Only the number of hours of television viewing on a school night and the total number of soft drinks consumed per day were significantly associated with BMI. When regular and diet soft drinks were analyzed separately, BMI z-scores and percent body fat remained positively and significantly associated with diet soft drink consumption only. BMI z-scores and percent body fat were not significantly associated with regular soft drink consumption.

Grant et al. (2004) studied the relationship between anthropometric status and macronutrient intake among Pacific Island children aged 2–5 years living in New Zealand. After adjusting for age and gender, the obese children consumed significantly more total energy than did the non-obese children. The obese children consumed more of all types of foods, not just more of specific foods, than did the non-obese children.

Nicklas et al. (2003) analyzed the relationship between BMI and food consumption patterns among 1562 African-American (AA) and Euro-American (EA) 10-year-olds. The

authors found that EA males and EA females showed positive associations between overweight and consumption of sweets and sweetened beverages. For EA males and EA females, positive associations were also found between overweight and consumption of total foods and beverages, particularly from low-quality foods. AA females showed negative associations between overweight and consumption of fruits/fruit juices and fruit/fruit juices/vegetables, total number of meals consumed, and consumption of the breakfast meal. The total model explained about 4-8% of the variance in BMI for the various ethnic-gender groups, and soft drink consumption alone explained approximately 1% of the variance in the model.

Rajeshwari et al. (2005) assigned sweetened beverages to one of the following categories: soft drinks, fruit drinks, iced tea with sugar, and coffee with sugar. Study participants were categorized as non-consumers, low-consumers, medium-consumers, or high-consumers of sweetened-beverages. Between 1973 and 1994, mean BMI significantly increased for each of the four sweetened-beverage consumption categories. However, Rajeshwari et al. found no differences in mean BMI among any of the four consumption categories.

In their study of snacking trends among individuals aged 19–29 years, Zizza et al. (2001) found that sweetened beverages (regular soft drinks, diet soft drinks, and fruit drinks) were one of the major contributors of energy from snacking occasions. The relationship between snacking and BMI was not examined.

Summary of the Cross-Sectional Studies

The overall evidence for a positive association between consumption of soft drinks (HFCS proxy) and overweight and/or obesity is limited. Of the six cross-sectional studies that directly or indirectly investigated the relationship between soft drink consumption and prevalence of overweight and/or obesity, only Giammattei et al. and Nicklas et al. found a positive association. Two of the reviewed studies, French et al. and Zizza et al., did not include an analysis of the relationship between soft drink consumption and BMI.

In Giammattei et al., the association appears to be between the consumption of diet drinks and BMI. The reported association between regular soft drinks and BMI was not significant. Furthermore, Giammattei et al. found that only the sixth- and seventh-grade children who were consuming $\geq$3 soft drinks/day were more likely to have BMI values $\geq$85th percentile. This level of soft drink consumption is relatively large compared to the average soft drink consumption among children within this age group.

We conducted an original analysis to estimate the average consumption of soft drinks and the percentage consuming $\geq$3 soft drinks/day among the age group used in the Giammattei et al. study. We analyzed the most recent nationally representative data available—NHANES 1999–2002 (CDC, 2005)—and found that the mean combined consumption of regular fruit drinks/ades and RCSD for children aged 11–12 years is 450 g/day (95% CI = 397 to 503 g/day), or about 1.2 12-oz servings/day. We found that only those children above the 90th percentile consumed $\geq$3 soft drinks/day.

Nicklas et al. discovered that soft drink consumption explained approximately 1% of the variance in the model. The authors hypothesized that overweight status is not the result of a single eating pattern.

Four of the six studies do not support a relationship between consumption of a specific type of beverage (Forshee and Storey; Forshee et al.; Rajeshwari et al.) or a specific macronutrient (Grant et al.) and prevalence of overweight and obesity. Because sucrose and HFCS contain similar F:G ratios, the results from the Grant *et al.* study are relevant to the HFCS debate.

Literature Review of the Longitudinal Studies

The expert panel examined seven longitudinal studies that assessed the relationship between soft drinks—often utilized as a proxy for HFCS—and BMI of pre-schoolers, children, adolescents, and adult women.

Berkey et al. (2004) analyzed the relationship between BMI and intakes of sugar-added beverages, milk, fruit juices, and diet soda in a cohort of more than 10,000 males and females aged 9–14 years in 1996. These authors found a positive association between BMI and sugar-added beverage consumption for boys, but the association was not statistically significant for girls. When total energy was included in the model, the associations were not significant for either boys or girls.

In a cohort of 8203 girls and 6774 boys aged 9-14 years in 1996, Field et al. (Field et al., 2004) investigated the association between BMI and the intake of various snack foods, including sugar-sweetened beverages. No relationship was found between the snack food intake and the annual change in BMI for either girls or boys. According to these authors, "[w]hen servings per day of sugar-sweetened beverages were included as snack foods the association between snack food intake and change in BMI z-score was similar to the main findings" (Field et al., 2004).

Ludwig et al. (2001) examined the relationship between BMI and consumption of sugar-sweetened drinks among a cohort of 548 ethnically diverse schoolchildren aged 11–12 years enrolled in Massachusetts public schools. Over 19 months, the average sugar-sweetened drink consumption increased from 1.22 to 1.44 servings/day—a difference of 0.22 servings/day. There was a positive association between sugar-sweetened drinks and BMI with a magnitude of a 0.24 kg/m^2 increase in BMI for each additional serving/day increase in sugar-sweetened drink consumption. For the average increase in sugar-sweetened drink consumption (0.22 servings/day), this model predicted a BMI increase of 0.05 kg/m^2 assuming all other variables in the model remained constant. Nielsen and Popkin (2004) reported that between 1977 and 1996, the mean consumption of sweetened beverages increased from 2.02 to 2.55 servings/day for a mean increase of 0.53 servings/day. Using the Ludwig et al. estimate, the

predicted increase in BMI would be 0.13 kg/m^2 for an increase of 0.53 servings/day of sugar-sweetened drink consumption.

Newby et al. (2004) explored the relationship between beverage consumption and changes in BMI in a cohort of 1345 children aged 2–5 years. These authors found no significant relationships between any of the beverages analyzed and BMI.

Schulze et al. (2004) examined the relationship between sugar-sweetened beverage consumption, weight change, and risk of type 2 diabetes among women aged 24–44 years at study initiation in 1989. More than half of the respondents were excluded from the Schulze et al. analysis because of various exclusion criteria. Those individuals with the greatest increase ($\leq$1 drink/week to $\geq$1 drink/day) in their sugar-sweetened beverage consumption experienced a greater weight increase than other respondents. Those individuals with the greatest decrease ($\geq$1 drink/day to $\leq$1 drink/week) experienced a smaller weight increase than other respondents. There was no difference in weight gain between those individuals who were consistently low consumers, consistently high consumers, or who made a smaller change in their consumption of sweetened beverages.

The low-high ($\leq$1 drink/week to $\geq$1 drink/day) consumption category only contained about 2% of the study sample. About 75% of the study sample was located in the low-low (consistent at $\leq$1 drink/week) consumption category, and about 5% of the study sample was located in the high-high (consistent at $\geq$1 drink/day) consumption category. The results of the study suggest that those individuals in the high consumption category could benefit by reducing their consumption to $\leq$1 drink/week and that those individuals in the low consumption category could benefit by limiting their increase to no more than 2–6 drinks/week. Smaller changes in sweetened beverage consumption did not show any differences in weight gain.

Janket et al. (2003) examined the relationship between risk of type 2 diabetes and intakes of total caloric sweeteners, sucrose, fructose, glucose, and lactose among a cohort 38,480 female health professionals and found no association between the lowest versus highest consumption categories of total caloric sweeteners, sucrose, fructose, glucose, or lactose and risk of type 2 diabetes. Neither fructose nor glucose—the main components of HFCS—were related to the risk of developing type 2 diabetes. Sucrose, which has a F:G ratio very similar to that of HFCS, was also not related to the risk of developing type 2 diabetes.

Mrdjenovic and Levitsky (2003) examined the effects of excessive sweetened drink consumption [defined as >12 oz (>370 g)/day] on total energy intake and weight gain among 30 children aged 6–13 years attending the Cornell Summer Day Camp in 1997. They found that children who consumed >16 oz/day (>492 g/day) of sweetened drinks gained more weight than did children who consumed between 6 and 16 oz/day (186 and 492 g/day) of sweetened drinks, but none of these differences was statistically significant. The authors observed that "the sample size was too small (n = 21) to provide sufficient power for the observed difference in weight gain to be statistically significant" (2003). It is also possible that the observed difference in weight gain was not significant due to the absence of a relationship between sweetened drink consumption and weight gain.

Summary of the Longitudinal Studies

Of the four longitudinal studies examining growing children or adolescents, Berkey et al., Newby et al., and Mrdjenovic and Levitsky showed no association between BMI and the consumption of soft drinks. Only Ludwig et al. showed a significant increase of 0.24 BMI units over the previous 19 months for every additional serving increase in sugar-sweetened drink consumption. Berkey et al. estimated a non-significant increase of 0.019 and 0.015 BMI units from the previous year for each serving of sugar-added beverages consumed per day for girls and boys, respectively. Because of the large sample size in GUTS, this is a relatively precise estimate (95% CI = −0.008 to 0.046 for girls; 95% CI = −0.014 to 0.044 for boys, based on our calculations). We calculated the confidence intervals using Stata "p2ci" program which calculates a confidence interval based on the reported coefficient and p-value.

Janket et al. found no relationship between intakes of various caloric sweeteners and the risk of type 2 diabetes. Schulze et al. found that after four years, women who increased their consumption of sugar-sweetened beverages from $\leq$1/week to $\geq$1/day had higher BMI values by 0.47 kg/m^2 than did women who consistently consumed $\leq$1/week. Only 2% of the women in this study increased their sugar-sweetened beverage consumption from $\leq$1/week to $\geq$1/day, while 75% of the study participants consistently consumed $\leq$1/week. Overall, the mean BMI for the 96% of women who did not move from one extreme consumption category to another (low-high or high-low) was statistically indistinguishable regardless of the quantity of sweetened beverages consumed.

Field et al. did not report the estimated associations between sugar-sweetened beverage consumption and BMI.

Estimating the Relationship between Current RCSD Consumption Patterns and BMI

The potential impact of reducing RCSD consumption on BMI is a function of the strength of the association between the two and the amount of RCSD currently consumed. To assess this potential impact, we conducted an original analysis and applied current RCSD consumption patterns to estimates of the association between soft drink consumption and BMI from the longitudinal studies.

We obtained RCSD consumption data from NHANES 1999–2002 (CDC, 2005)—the most recent nationally representative survey available—for females and males aged 20+ years. These data show that the majority of survey participants consume only modest amounts of RCSD. We represented the full distribution of RCSD consumption via kernel density plots, which show the distribution of a variable by approximating the probability density function of consumption (Silverman, 1986). Similar to a

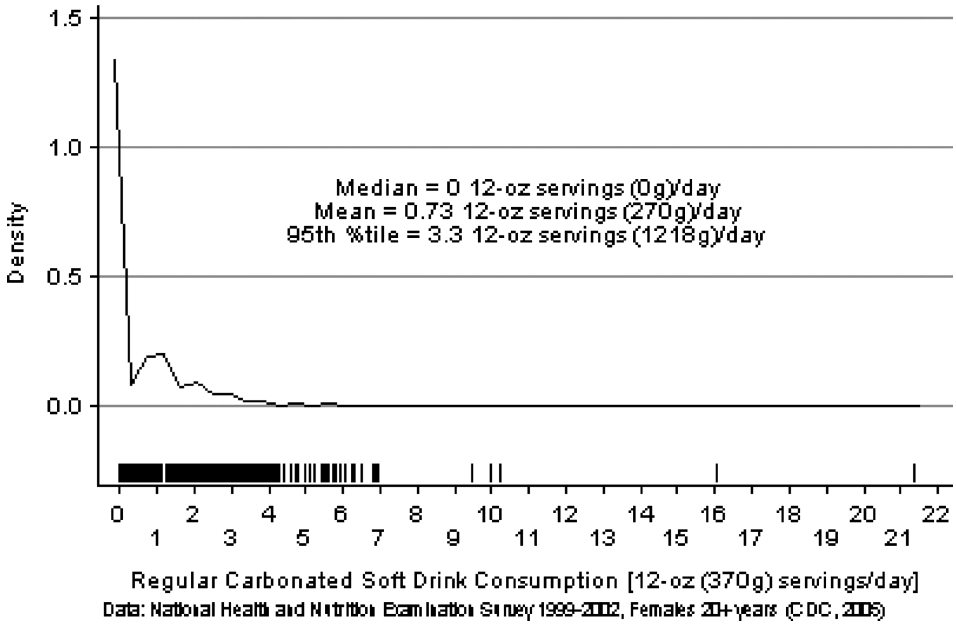

Figure 3 Kernel density distribution plot of regular carbonated soft drink (RCSD) consumption from NHANES 1999–2002 among females 20+ years. RCSD consumption is shown as the number of 12-oz servings consumed per day, and each 12-oz serving is equivalent to 370 g. The line graph represents the kernel density function for RCSD consumption. The kernel density function is an extension of the histogram and uses a "sliding window" to approximate the probability of consuming a given amount of RCSD across the entire distribution. Below the kernel density plot is a rug plot. Each vertical "pipe" in the rug plot represents a unique value for RCSD consumption. Rug plots are useful for visualizing extreme values in a data set. Figure produced by authors.

histogram, the height of the line is proportional to the percentage of respondents at any given level of consumption.

Kernel density plots of RCSD consumption for females and males show that the most commonly consumed amounts of RCSD are modest (Figs. 3 and 4). For both adult females and males, the most common amount is at 0 12-oz servings/day (0 g/day). Another, much smaller, peak is at 1 12-oz serving/day (370 g/day); a third, still smaller, peak is at 2 12-oz servings/day

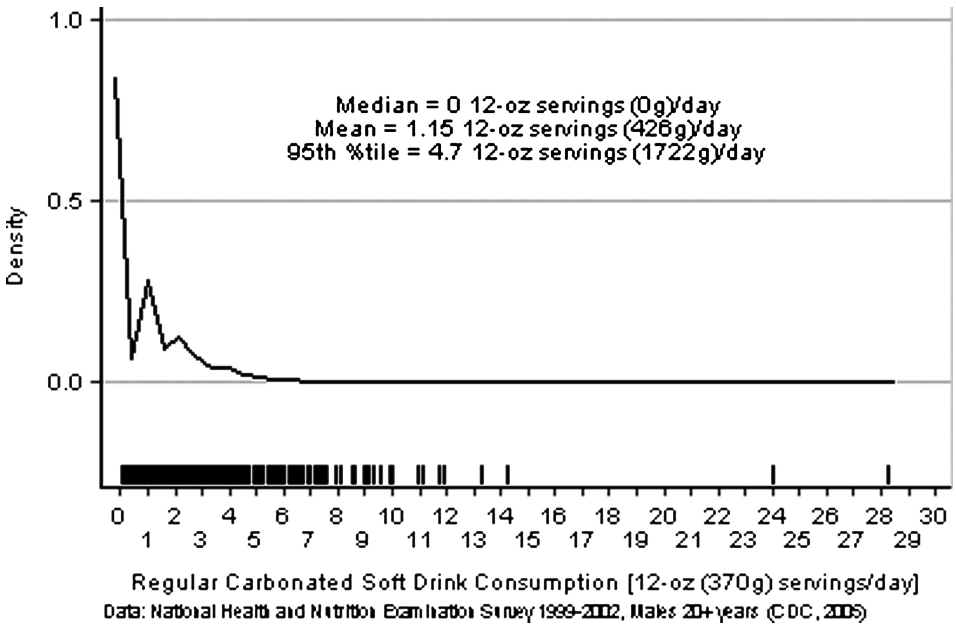

Figure 4 Kernel density distribution plot of regular carbonated soft drink (RCSD) consumption from NHANES 1999–2002 among males 20+ years. RCSD consumption is shown as the number of 12-oz servings consumed per day, and each 12-oz serving is equivalent to 370 g. The line graph represents the kernel density function for RCSD consumption. The kernel density function is an extension of the histogram and uses a "sliding window" to approximate the probability of consuming a given amount of RCSD across the entire distribution. Below the kernel density plot is a rug plot. Each vertical "pipe" in the rug plot represents a unique value for RCSD consumption. Rug plots are useful for visualizing extreme values in a data set. Figure produced by authors.

(740 g/day). The curve then asymptotically approaches zero with small upticks at whole numbers of servings. Beneath each kernel density plot is a rug plot to better visualize the extreme values in the data, particularly the handful of respondents with very high reported RCSD consumption levels. Each vertical line, or "pipe," represents a unique value for RCSD consumption. Above about 10 12-oz servings/day (3700 g/day) the rug plot becomes extremely sparse.

On the day of the 24HR, 59% of the females and 50% of the males aged 20+ years did not consume any RCSD. The mean consumption of RCSD was 0.73 12-oz servings/day (270 g/day) for females and 1.15 12-oz servings/day (426 g/day) for males. In the 95th percentile of RCSD consumption, females and males consumed 3.3 and 4.7 12-oz servings/day (1218 and 1722 g/day), respectively.

One limitation of NHANES 1999–2002 is that the dietary data are self-reported and may be subject to bias, particularly under-reporting. The upper percentiles of consumption observed in a 24 hr are generally known to be higher than the upper percentiles observed from either longer-term measurements of dietary intake or statistical estimates of usual intake (Tran et al., 2004; Nusser et al., 1993; Carriquiry et al., 1992).

Estimates of the relationship between soft drink consumption and BMI from longitudinal studies and our estimates of current RCSD consumption provide some parameters by which to approximate the impact that eliminating RCSD consumption would have on overweight and obesity rates in the United States. The estimates of the association between soft drink consumption and BMI in the longitudinal studies ranged from non-significant to a maximum of a 0.24 kg/m^2 change in BMI for each one serving/day change in soft drink consumption over 19 months. Using the Ludwig et al. (maximum) estimate, a female at the 95th percentile of soft drink consumption who eliminated soft drinks from her diet would reduce her BMI by about 0.825 kg/m^2. Using the Berkey et al. (non-significant) estimate—a 0.02 kg/m^2 change in BMI for each one serving/day change in soft drink consumption—the same female at the 95th percentile of soft drink consumption would reduce her BMI by only 0.066 kg/m^2.

A limitation of the discussion in this section is that it does not consider any possible long-term, cumulative changes in BMI as a result of changes in soft drink consumption. Extrapolating beyond the time frames used in the studies reviewed is difficult. Such extrapolation requires an assumption that the change increases proportionally with time. Rarely do we observe such simple proportional relationships over time. Changes often decelerate with time or even turn around completely. Therefore, in the absense of more direct evidence we can only offer vague speculation about what might happen over greater lengths of time and safely draw conclusions about what happens during the duration of our studies.

While it is impossible to rule out that weight change may continue beyond the time frames of the studies reviewed, the current models do not allow accurate projections beyond the original time frames.

RANDOMIZED CONTROLLED TRIALS

Overview

Randomized controlled trials (RCTs) are often considered the "gold standard" in research because they are not susceptible to confounding and are less susceptible to other forms of bias than are other types of studies (Coggon et al., 1997). We found only one RCT reported in the literature on the relationship between soft drinks and either BMI or weight gain.

Literature Review of the Randomized Controlled Trials

James et al. (James et al., 2004) performed a cluster RCT to study the effect of a focused educational intervention program on carbonated drink consumption and overweight and obesity in 644 children aged 7–11 years. Children in the intervention clusters participated in a program designed to emphasize the consumption of a balanced healthy diet and to discourage the consumption of both sweetened and unsweetened "fizzy" drinks (most likely sweetened with sucrose). James et al. observed a decrease in carbonated drink consumption of 0.6 glasses/3 days (50 ml/day) in the intervention group with an increase in carbonated drink consumption of 0.2 glasses/3 days (17 ml/day) in the control group. Mean percentage of overweight and obese children decreased by 0.2% in the intervention group and increased by 7.5% in the control group, and this difference was statistically significant. However, differences in average BMI values (0.1 kg/m^2; 95% CI $= -0.1$ kg/m^2 to 0.3 kg/m^2) and z-scores (0.04; 95% CI $= -0.04$ to 0.12) between the intervention and control groups were not statistically significant.

Summary of the Randomized Controlled Trials

There are no RCTs examining the direct relationship between HFCS consumption and overweight and obesity. The sweetened "fizzy" drinks studied by James et al. were almost certainly sweetened by sucrose, not HFCS, given that the study was conducted in Great Britain. Furthermore, James et al. did not show any difference in carbonated drink consumption and BMI between the treatment and control groups.

THEORIZED MECHANISMS

Overview

Three hypotheses have been proposed to support the argument that HFCS plays a unique role in weight gain compared with other caloric sweeteners. These hypotheses include:

1. HFCS increases the F:G ratio in the food supply, causing adverse metabolic effects that either directly or indirectly lead to weight gain.

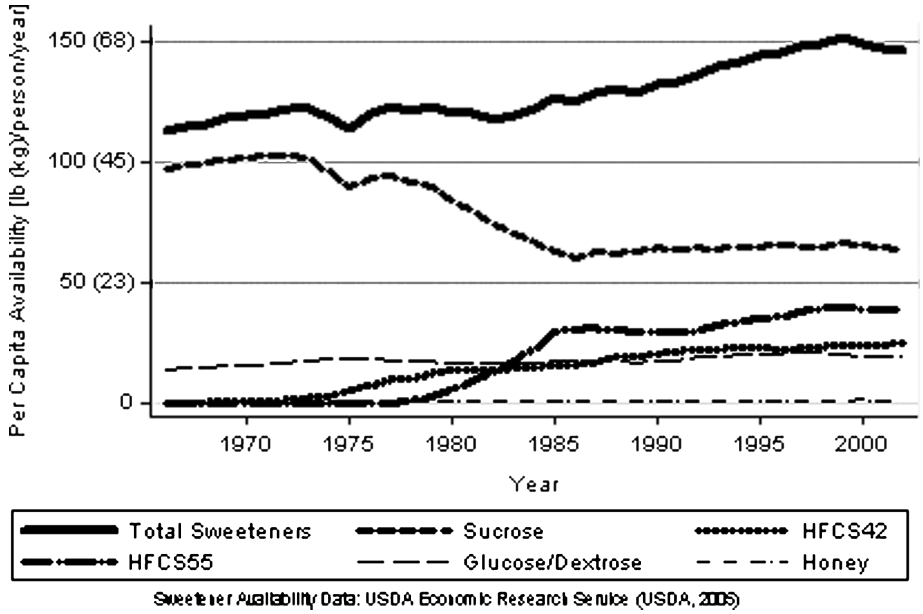

Figure 5 Per capita availability [lb (kg)/person/year] of total sweeteners, sucrose, HFCS-42, HFCS-55, glucose (dextrose), and honey in the U.S. food supply from 1966 to 2002. The various line graphs represent the per capita availability of the different types of sweeteners in the U.S. food supply based on USDA ERS food availability data. Figure produced by authors.

2. HFCS is "sweeter" than sucrose, leading to over-consumption of foods containing HFCS and weight gain.
3. Consumption of beverages, which are almost exclusively sweetened with HFCS, does not stimulate satiety signals, leading to over-consumption and weight gain.

HFCS Increases the F:G Ratio in the Food Supply

The term "high fructose corn syrup" has generated some confusion. HFCS is high in fructose compared to the original dextrose-based corn syrups, which contain no fructose. HFCS is compositionally similar to sucrose, which contains a F:G ratio of 50:50.

The confusion over the meaning of "high fructose" has led some researchers to speculate that the introduction of HFCS has increased the F:G ratio in the U.S. food supply. Fructose metabolism studies show that fructose absorption from the gut is dependent on the presence of glucose (Riby et al., 1993; Ravich et al., 1983). Unabsorbed fructose is either fermented in the colon or excreted in the feces. However, some researchers propose that an increase in free fructose in the food supply has contributed to adverse metabolic changes that have led to increased overweight and obesity rates.

To address this question, we conducted original research to calculate the changes in total glucose and fructose availability and the F:G ratio in the food supply since the introduction of HFCS-42 in 1966. There are serious limitations to the USDA Economic Research Service (ERS) food availability data, particularly if one needs to make inferences about associations at the individual level. Our purpose here is only to assess the trends in fructose and glucose availability and their ratio. This provides more information than is currently available about the impact that the introduction of HFCS has had on the relative amount of fructose and glucose in the food supply. This analysis is subject to the same limitations discussed earlier regarding ecological data. Ideally, the analysis should be conducted at the individual level by examining the associations between fructose and glucose consumption and BMI. Unfortunately, such data are not currently available.

Many caloric sweeteners in the food supply contain various formulations of fructose and glucose. Data for per capita sweetener availability (Fig. 5) were obtained from the USDA ERS disappearance series (USDA, 2005). Using the percentage of fructose and glucose for each of the major sweeteners, we calculated the total fructose and total glucose available from caloric sweeteners in the U.S. food supply (Fig. 6). Data for the fructose and glucose composition of sweeteners were obtained from Hanover and White (Hanover and White, 1993). The data in Fig. 6 do not include the glucose that is available from other carbohydrate sources (e.g. starches, maltodextrins, etc.) or the fructose that is naturally available in certain fruits and vegetables.

Until the mid-1960s, sucrose was the primary sweetener in the American diet. A 1993 study by Park and Yetley (1993) noted that HFCS had replaced sucrose in many foods and beverages. These scientists remarked that "from the standpoint of fructose metabolism the source of fructose, whether free or from sucrose, is not important because bound fructose is readily liberated in the food product and in the small intestine. The total fructose in the diet is the most important consideration." (Park and Yetley, 1993) Although the type of sweetener used in the U.S. food supply has changed over the last few decades, the total amount of

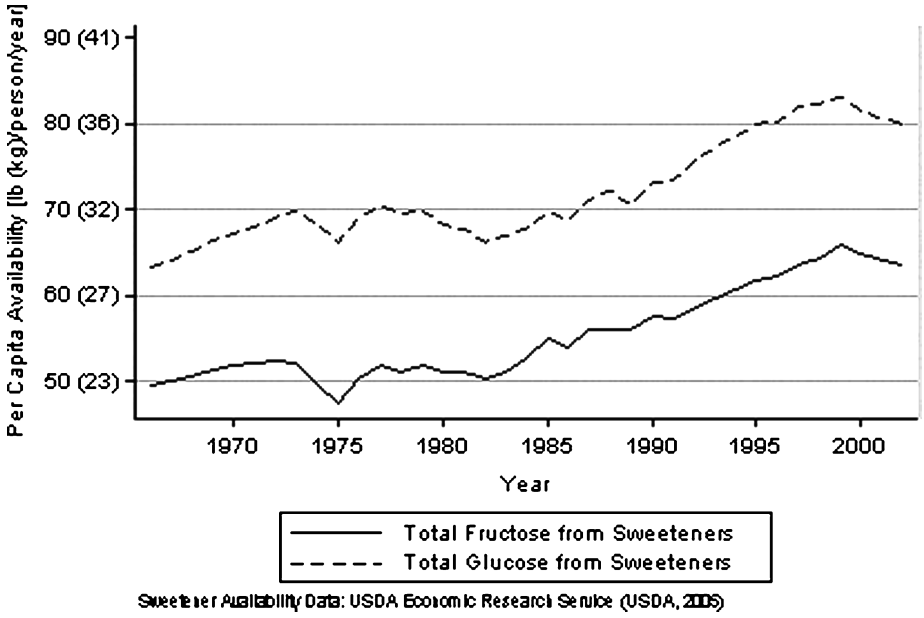

Figure 6 Per capita availability [lb (kg)/person/year] of total fructose and total glucose from caloric sweeteners in the U.S. food supply from 1966 to 2002. The solid line graph represents the per capita availability of total fructose from all sweetener sources, and the dashed line graph represents the per capita availability of total glucose from all sweetener sources. Both graphs are based on USDA ERS food availability data. Sweetener availability calculations do not include glucose available from other carbohydrate sources (e.g. starches, maltodextrins, etc.) or fructose naturally available in certain fruits and vegetables. Figure produced by authors.

fructose (free and bound) from sweeteners has remained relatively constant according to Park and Yetley. Since the F:G ratio of sucrose and HFCS are nearly identical, replacing the free and bound fructose from sucrose with the free fructose from HFCS had virtually no effect on the availability of the total amount of fructose from sweeteners. In the decade since the Park and Yetley paper was published, however, soft drink (RCSD and fruit drinks/ades) consumption has increased.

Data from the USDA ERS show that sweetened beverage consumption increased between the late 1970s and mid-1990s. In addition, Yen and Lin (2002) reported that the percentage of children and adolescents who drink carbonated soft drinks rose from 44% in the 1970s to 49% in the 1990s. Average consumption increased for children aged 6–11y and adolescents aged 12–17y.

There have been significant changes in the total availability of caloric sweeteners in the U.S. food supply. From 1966 to 1999, the total per capita sweetener availability increased, despite some temporary declines in the 1970s and 1980s. Since 1999, however, the total per capita sweetener availability has declined by 5 lb (2.3 kg)/person/year. The mix of sweeteners has also changed. Sucrose availability fell substantially during the 1970s and early 1980s before stabilizing in the mid–1980s. HFCS-42 began to be incorporated into the food supply around 1970 and has since steadily increased. HFCS-55 began to be utilized in the mid-1970s, increased rapidly in the early 1980s, and continued to gradually increase until 1999.

We conducted a new analysis of the USDA ERS food availability data to examine the ratio of fructose to glucose since 1966. Throughout this time period, the availability of glucose was more than 10 lb (4.5 kg)/person/year higher than the availability of fructose, and the trends in total fructose and total glucose are very similar (Fig. 7). For each year, the total available fructose was divided by the total available glucose to create a ratio. For reference, we included a line at 1.0 to indicate what the ratio would be if only sucrose were used in the food supply. The F:G ratio has been substantially less than 1.0, and has stayed in a narrow range between 0.71 and 0.80. From 1966–1975, the F:G ratio actually fell as HFCS-42 (42:53 ratio) was replacing sucrose (50:50 ratio) in some foods. With the introduction of HFCS-55 (55:42 ratio), the F:G ratio began returning to its previous level before the introduction of any HFCS product. In 2002, the F:G ratio was 0.79 compared to 0.78 in 1966.

These trends contradict the hypothesis that the introduction of HFCS increased the F:G ratio in the U.S. food supply. Moreover, most RCT studies of fructose consumption have used F:G ratios well above 1.0. For example, in Swanson et al. (1992) subjects in the fructose treatment consumed 100 g of fructose, 10 g of sucrose, and 23 g of "other" carbohydrates. Even if all 23 g of "other" carbohydrates are assumed to be glucose, the F:G ratio for these subjects would be 3.75, which is more than 4 times the largest F:G ratio typically observed in the food supply.

HFCS is "Sweeter" than Sucrose

The monosaccharides—fructose, glucose, and galactose—and the disaccharides—lactose, sucrose, maltose, and trehalose—have varying degrees of sweetness. Of the monosaccharides, crystalline fructose imparts the "sweetest" taste with

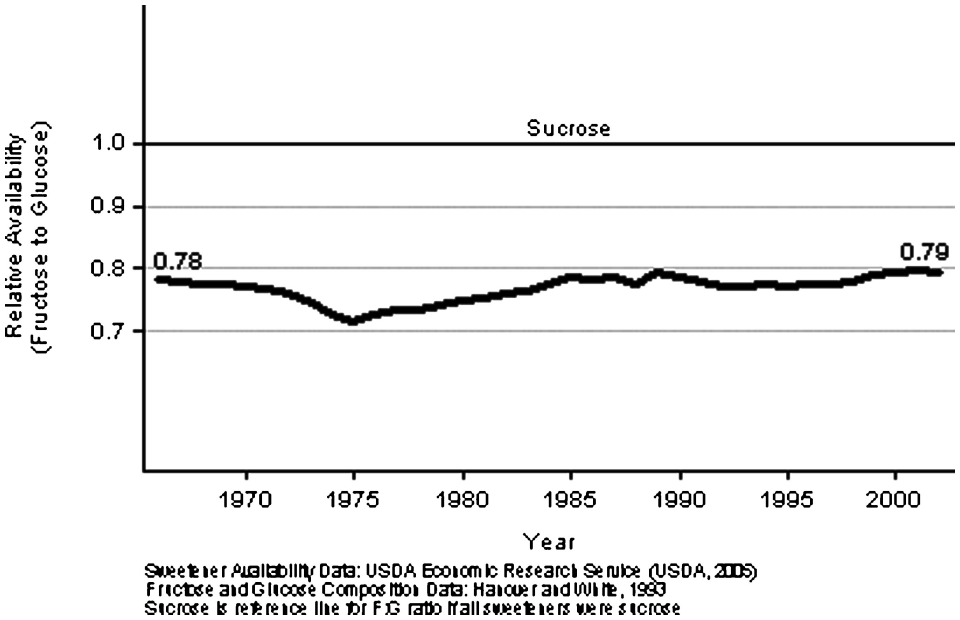

Figure 7 Relative availability of fructose:glucose (F:G) in the U.S. food supply from 1966 to 2002. The line graph represents the ratio of per capita availability of fructose from all sweetener sources and per capita availability of glucose from all sweetener sources based on USDA ERS data. The straight line at 1.0 represents the theoretical F:G ratio if sucrose were the only sweetener available in the food supply. Figure produced by authors.

a relative sweetness of 173 compared with crystalline sucrose, which has been designated as the reference and set at 100. Glucose, galactose, and lactose are less sweet than sucrose with relative sweetness scores of 74, 33, and 16, respectively (Biology, 2004).

Bray et al. (2004) hypothesized that HFCS-55 is much "sweeter" than sucrose. They conjectured that a corresponding increase in the sweetness of the food supply created cravings that induced people to over-consume sweetened beverages, leading to a positive energy balance and weight gain. Unfortunately, the authors miscalculated the relative sweetness of HFCS-55 by using the sweetness value of crystalline fructose rather than aqueous fructose. Expert sensory panels have confirmed that an aqueous solution of fructose at 10% dry solids and room temperature has a relative sweetness of 117 (Hanover and White, 1993). Calculating the relative sweetness of HFCS-55 using the sweetness value of aqueous fructose yields a sweetness value almost identical to the aqueous sucrose standard. Moreover, a recent study concluded that temperature had little effect on sweetness intensity (Schiffman et al., 2000). Therefore, the hypothesis that HFCS-55 is "sweeter" than sucrose and creates cravings that induce over-consumption and weight gain seems implausible.

Beverages, a Major Source of HFCS, do Not Stimulate Satiety Signals

Although the underlying factors contributing to weight gain are multiple and complex, it is widely acknowledged that weight gain generally occurs because of a long-term imbalance between energy consumed and energy expended. Some scientists hypothesize that overweight and obesity rates have dramatically increased for both children and adults because soft drink consumption (HFCS proxy) has increased since the 1970s. Although weight gain can be linked to various patterns of over-consumption, liquid calories are thought by some researchers to be less satiating than calories obtained via consumption of solid foods. The lack of satiety produced by soft drinks then leads to over-consumption and weight gain.

Several mechanisms may account for liquid calories being less satiating. The mastication of solid foods may stimulate a satiety signal that is not activated when liquids are consumed. Initial pancreatic exocrine and endocrine responses to oral stimulation are greater for non-liquids than they are for liquids; initial pancreatic responses that include insulin release may modulate postprandial metabolism. This includes glucose tolerance with possible hunger and eating effects (DiMeglio and Mattes, 2000).

Satiation refers to the reduction in the amount of energy consumed at a particular meal, whereas satiety refers to the reduction in the amount of energy consumed at a subsequent meal or meals (Almiron-Roig et al., 2003). The total volume of a solid or liquid appears to contribute to satiety; that is, consumption of a large volume of foods or beverages at a particular meal or eating occasion (snack) reduces the amount of energy consumed at future meals or eating occasions.

Studies conducted by Rolls and colleagues show that high-volume/less-energy-dense liquids, such as soups, vegetable juices, and milk, are satiating because of their high water content (Bell et al., 2003; Rolls et al., 1999; Rolls et al., 1990). Other researchers contend that solid foods are more satiating (DiMeglio and Mattes, 2000).

An RCT with 24 women aged 20–37 years with a mean BMI of 22.6 kg/m^2 examined the effects of three isoenergetic

(1128 kJ) preloads on satiety and subsequent food intake (Rolls et al., 1999). Participants consumed breakfast, lunch, and dinner at the study site on four separate test days with at least one week separating each test. Three of the test days included the consumption of a preload prior to the lunch meal, while no preload was consumed on the remaining test day (control). The three preloads included chicken and rice casserole, chicken and rice casserole with a glass of water, and chicken and rice soup.

Mean energy consumed during the control lunch meal (no preload) was significantly greater (2693 $\pm$ 166 kJ) than mean energy consumed during the lunch meals preceded by either the casserole (1639 $\pm$ 148 kJ; $p < 0.05$), the casserole with water (1657 $\pm$ 148 kJ; $p < 0.05$), or the soup (1209 $\pm$ 125 kJ; $p < 0.05$) preloads. In addition, after adding the energy obtained from the preload to the energy consumed during the subsequent lunch meal, Rolls et al. found that the women consumed significantly less energy (16%) with the soup preload than with either the casserole or the casserole with water preloads. Since energy intakes during the dinner meal were similar regardless of the preceding lunch condition, the women did not compensate for the reduced energy intake from the lunch meal with the soup preload.

DiMeglio and Mattes (2000) conducted a study examining the effects of supplementing the diets of 15 free-living individuals with 450 kcal/day from either jelly beans (solid load) or carbonated soft drinks (liquid load). The duration of each treatment was four weeks with a four-week washout period between treatments. For each four-week treatment period, the participants were instructed to increase their total consumption by ingesting the required amount of jelly beans [approximately 4 oz (113 g)/day] or carbonated soft drinks [approximately 3.2 12-oz servings (1184 g)/day]. Twenty-four hour dietary recalls of food consumption were randomly conducted six times during the four-week treatment periods. The study included one hunger rating experiment lasting 180 minutes.

Although participants were instructed to increase their caloric consumption by 450 kcal/day over each four-week treatment period (12,600 kcal total), physical activity did not increase significantly. The study reported a 118% compensation for the solid load, but a -17% compensation for the liquid load. However, there was no significant difference in hunger ratings. Mean body weight increased by 0.3 kg and 0.5 kg during the jelly bean and carbonated soft drink treatment periods, respectively. Mean BMI increased by 0.1 kg/m^2 during both treatment periods. Although the mean body weight and BMI increased after each treatment period, the increases were significant only for the liquid treatment period ($P \leq 0.05$ for both). However, the change in mean body weight and BMI was not statistically significant between the two treatments.

More rigorous research focused on the satiety and satiation differences of liquids versus solids is needed. Controlled, metabolic feeding studies are also needed to refute or confirm epidemiologic studies and to examine possible differences in absorption, metabolism, and utilization of HFCS versus sucrose. Additional RCTs examining associations between weight gain and consumption of sweetened beverages, various sweeteners, and total energy, as well as studies designed to increase the understanding of food intake behaviors, are needed. These RCTs should include analyses of individual differences in blood lipids, glucose tolerance, and certain hormones and peptides (i.e. insulin, ghrelin, leptin, glucagon-like peptide, etc.) in response to the consumption of various sweeteners. Currently, there are no studies that directly compare biological responses of HFCS versus sucrose consumption.

RESEARCH GAPS

The expert panel identified several research gaps. No studies examined whether HFCS is metabolized differently than sucrose. This is a critical research gap and should receive the highest priority for future research on this question. While it appears likely that the biological effects of HFCS and sucrose are similar, it is premature to conclude whether or not there are any differences in the mechanisms by which sucrose and HFCS are metabolized in the absence of this important research. The results from fructose studies can not be extrapolated to HFCS because the typical F:G ratio found in these fructose studies is much higher than the F:G ratio found in HFCS.

Updating the USDA food composition and nutrient databases for key food groups should be the second priority. HFCS levels in most food products have not been quantified, and no information concerning individual-level consumption of HFCS is currently available. This is an important data need that prevents crucial epidemiological research. Fructose levels in food products and actual fructose consumption are also largely unknown. Without data on the HFCS and fructose concentrations of foods, it is impossible to identify the high consumers of fructose and develop epidemiologic models of their relative risk for overweight and obesity or other health endpoints. Furthermore, no analytical chemistry methods exist to distinguish naturally-occurring dietary fructose from the fructose added by manufacturers either as sucrose or HFCS.

One specific research need is a more detailed investigation of the vulnerabilities of sub-populations. Some sub-populations may be particularly susceptible to overweight and obesity due to the over-consumption of caloric sweeteners, but there are no studies addressing this possibility. Individuals with strong family histories of overweight and obesity and/or those who are entering life stages that are associated with weight gain need particular attention.

Some more general research gaps should also be addressed. Increased access to federally-funded longitudinal datasets is needed in order to replicate the findings of other researchers.

Additional studies are needed to better measure energy expenditure and its relative importance to weight control and prevention of weight gain.

OVERALL STRENGTH OF THE EVIDENCE

The evidence that HFCS consumption uniquely increases the risk of weight gain is very weak. Few studies directly explore

the relationship between HFCS, body weight, and BMI. The only evidence directly linking HFCS consumption and weight gain is ecological data. Ecological data are widely recognized as insufficient for establishing cause-effect relationships.

The prospective observational studies typically utilized soft drinks as a proxy for HFCS. Three of the four studies of youth reviewed in this manuscript found no association between soft drinks and BMI while the third found a significant association of 0.24 kg/m^2 for each one serving/day change in consumption.

Cited mechanisms proposing a positive relationship between HFCS consumption and weight gain have major gaps. The hypothesis that the increasing levels of HFCS in the food supply has increased the F:G ratio is not supported by the USDA ERS food availability data. The F:G ratio actually fell after the introduction of HFCS-42, rose slightly after the introduction of HFCS-55, and is now currently only .01 higher than it was before the introduction of HFCS-42. The claim that HFCS is "sweeter" than sucrose is not supported by expert sensory panels. This claim appears to be the result of incorrectly calculating the relative sweetness of HFCS-55 based on the relative sweetness value of crystalline fructose instead of the relative sweetness value of fructose in solution.

CONCLUSIONS

The impact of HFCS consumption on BMI must be put in context with other broad economic and societal changes during the past several decades. Many other plausible explanations for rising overweight and obesity rates exist, including a decrease in smoking (Janzon et al., 2004; Rodu et al., 2004; Koh-Banerjee et al., 2003); an increase in sedentary occupations (Lakdawalla and Philipson, 2002); an increase in two-income households and single-parent households (Anderson et al., 2003; Crepinsek and Burstein¸ 2004); transportation and infrastructure changes that discourage physical activity (Bell et al., 2002; Lanningham-Foster et al., 2003); a decrease in PE classes and extracurricular sports programs in schools (Andersen et al., 1998); an increase in sedentary forms of entertainment (i.e. TV/movie viewing, video games, etc.) (Sternfeld et al., 2004); demographic changes (i.e. aging population, immigration, etc.) (Hedley et al., 2004; USD-C, 2002; Guzman 2001); a decrease in food costs with increase in food availability (Lakdawalla and Philipson, 2002); and changes in food consumption patterns (Diliberti et al., 2004; Binkley et al., 2000).

The expert panel concluded that the currently available evidence is insufficient to implicate HFCS per se as a causal factor in the overweight and obesity problem in the United States. However, there are significant knowledge gaps and weaknesses in existing research, so further research is warranted. Nevertheless, in a society that is experiencing unhealthy weight gain, it is necessary for many individuals to reduce their energy intake, including, but not limited to, energy provided from calorie-dense foods and beverages. Many individuals also need to increase their level of physical activity to help achieve and maintain a healthy weight and to reap the other health benefits of physical activity (USDA, 2005).

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