Global Public Health
2012, 1–10, iFirst article

High fructose corn syrup and diabetes prevalence: A global perspective

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(*Received 1 May 2012; final version received 9 August 2012*)

The overall aim of this study was to evaluate, from a global and ecological perspective, the relationships between availability of high fructose corn syrup (HFCS) and prevalence of type 2 diabetes. Using published resources, country-level estimates ($n = 43$ countries) were obtained for: total sugar, HFCS and total calorie availability, obesity, two separate prevalence estimates for diabetes, prevalence estimate for impaired glucose tolerance and fasting plasma glucose. Pearson's correlations and partial correlations were conducted in order to explore associations between dietary availability and obesity and diabetes prevalence. Diabetes prevalence was 20% higher in countries with higher availability of HFCS compared to countries with low availability, and these differences were retained or strengthened after adjusting for country-level estimates of body mass index (BMI), population and gross domestic product (adjusted diabetes prevalence = 8.0 vs. 6.7%, $p = 0.03$; fasting plasma glucose = 5.34 vs. 5.22 mmol/L, $p = 0.03$) despite similarities in obesity and total sugar and calorie availability. These results suggest that countries with higher availability of HFCS have a higher prevalence of type 2 diabetes independent of obesity.

Keywords: sugar; high fructose corn syrup; global health; diabetes; obesity

Introduction

The concurrent global epidemics of obesity and type 2 diabetes constitute an alarming public health concern. A recent report estimates that 6.4% of the world population is currently diabetic, and that by the year 2030, that estimate will rise to 7.7% (Shaw *et al.* 2009). Another recent report showed that across the globe, the number of people with diabetes rose from 153 million in 1980 to 347 million in 2008 (Danaei *et al.* 2011). These increases are projected to affect developing countries disproportionately, with an estimated 69% increase in the number of diabetic adults as compared to a 20% increase in developed countries (Shaw *et al.* 2009).

The global trends in the rising prevalence of obesity and type 2 diabetes parallel shifts in dietary patterns that have resulted from an increase in processed, 'Western' style foods with high energy density, which have now become popular in many countries (Popkin and Gordon-Larsen 2004). A feature of most Western diets is the consumption of high levels of refined carbohydrate, and in particular, sugar (Cordain *et al.* 2005). Of special concern is the increase in consumption of sugar-sweetened beverages, which provide an easy vehicle for excessive sugar intake, and have been

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ISSN 1744-1692 print/ISSN 1744-1706 online

http://dx.doi.org/10.1080/17441692.2012.736257
http://www.tandfonline.com

directly linked to risk for obesity (Malik *et al*. 2006, Brown *et al*. 2008) and type 2 diabetes (Schulze *et al.* 2004, Palmer *et al.* 2008).

A growing body of evidence supports the hypothesis that in addition to overall sugar intake, fructose is especially detrimental to metabolic health and risk for type 2 diabetes (Elliott *et al.* 2002, Bray *et al.* 2004, Gaby 2005, Lim *et al.* 2010, Lustig 2010). This is of particular concern given the global changes that are occurring in the use of high fructose corn syrup (HFCS) in food and beverage production, a sweetener that in its typically used form of HFCS-55 has 10% more fructose than sucrose. In addition, our prior study that measured the sugar composition of popular sweetened beverages showed that fructose content was 30% higher than it would be if it was made with sucrose, accounting for as much as 65% of the sugar content (Ventura *et al.* 2010). Thus, dietary fructose consumption, which cannot be measured by conventional dietary methods because the fructose content of HFCS is not disclosed, may be much higher than we think based on common assumptions.

The methodological limitations related to assessment of fructose consumption have led to other studies that are based more on ecological analysis rather than individual estimates. In an ecological analysis that looked at changes in diet and type 2 diabetes in the USA from 1900 to 1999, increasing consumption of HFCS was identified as the primary nutritional factor associated with increasing prevalence of type 2 diabetes (Gross *et al*. 2004). The USA is the largest producer of HFCS and recently began exporting large amounts of this product to Mexico and to other countries (The United States Department of Agriculture Economic Research Service 2012). Although use of HFCS is increasing globally, there are many countries that do not use it. This provides the basis for cross-nation comparison of obesity and diabetes in relation to HFCS use at the country level. Therefore, the objective of the current paper was to use empirical, macro-level nutrient supply data at the country level to evaluate, from a global perspective, the relationships between HFCS availability, obesity and type 2 diabetes.

Methods

Data sources

Data on BMI by country were obtained from a recent global analysis (Finucane *et al.* 2011) that estimated mean BMI for adults over 20 years in 199 countries and territories using data from published and unpublished surveys and studies as part of the Global Burden of Metabolic Risk Factors (GBMRF) Collaborating Group. For the purposes of the current analysis we used the mean values for the years 2000, 2004 and 2007. Data on global prevalence of diabetes were obtained from two independent sources. The first source was the *International Diabetes Federation (IDF) Diabetes Atlas*, fourth edition (International Diabetes Federation 2009) that uses WHO diagnostic criteria, and the population-adjusted estimates for 2010 were used. Estimates of diabetes prevalence are based on ages 20–79 years and from detailed literature searches of published information (from 1979 to March 2009) as well as through direct contact with individual IDF member countries as detailed in the Diabetes Atlas report. Diabetes prevalence data using this source are identified throughout the text as $\text{Diabetes}_{\text{IDF}}$. The second source of data on diabetes prevalence was obtained through the global estimates reported by the GBMRF Collaborating Group (Danaei *et al.* 2011). This report analysed data from health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants and also included data on fasting plasma glucose. For the purposes of the current analysis, we used the mean values for diabetes prevalence and fasting plasma glucose for the years 2000, 2004 and 2007. Diabetes prevalence data using this source are identified throughout the text as $\text{Diabetes}_{\text{GBMRF}}$. Since the estimates of diabetes prevalence were significantly different for the two methods ($6.8 \pm 3.0\%$ for IDF and $9.3 \pm 2.9\%$ for GBMRF) and were only weakly correlated ($r = 0.48$), we used each estimate in separate analyses.

Data on food availability by country were obtained using FAOSTAT (http://faostat.fao.org/), a database from 200 countries maintained by the Food and Agricultural Organization of the United Nations. *Total caloric availability is expressed as kcals/capita/day*, and sugar and cereal availability is expressed in kg/capita/year. The category of cereals includes all cereals (e.g., popcorn, buckwheat, quinoa, fonio, mixed grain and all other categories of cereals). The category of 'other sweeteners' includes such things as *pure* fructose and maltose, maple sugar and other syrups, glucose and dextrose, lactose, isoglucose (HFCS), molasses and sugar alcohols. Total sugar was defined as cane sugar, beet sugar, centrifugal raw sugar, refined sugar, confectionery sugar and flavoured sugar. Food and Agriculture Organization (FAO) data do not provide for the isolation of HFCS as a unique variable/commodity. Limited data on world HFCS production, however, were available through two separate sources: F.O. Licht's (2012) *International sugar and sweetener report* and data on HFCS quotas for theEU countries, which were retrieved from the CAP Monitor (Informa UK Ltd. 2010). Countries using HFCS were defined by a mean value for 2000, 2004 and 2007 of >0.5 kg per capita per year (mean value in non-users $= 0.1 \pm 0.2$ and users $= 5.8 \pm 6.1$ kg/year per capita).

Statistical analyses

Independent *t*-tests were used to compare countries using HFCS and those not using HFCS for prevalence of diabetes. Subsequently, differences in diabetes estimates were compared between HFCS users and non-users using general linear models before and after adjusting for covariates including country-based estimates of BMI, as well as population and gross domestic product obtained from the International Monetary Fund tables. Significance was set at $p < 0.05$. SPSS version 18 was used for the analysis.

Results

The list of countries ($n = 43$) with data on utilisation of HFCS is shown in Table 1, and Figure 1 compares the per capita availability data. There were no significant differences in BMI or in other dietary variables, including caloric intake and total sugar intake, in those countries that use HFCS compared to those that do not. However, all indicators of diabetes were higher in countries that use HFCS as compared to those that do not (Table 2), and this trend was significant for IDF estimates of diabetes prevalence (7.8 vs. 6.3%, $p = 0.013$), and fasting plasma glucose

Table 1. Countries used in analysis of high fructose corn syrup (HFCS).

Country	HFCS (kg/ year per capita)	Total sugar (kg/ year per capita)	BMI (kg/m2)	$Diabetes_{IDF}$	$Diabetes_{GBMRF}$
India	0	20.55	20.99	7.76	10.30
Slovenia	0	22.65	26.74	7.66	8.80
Latvia	0	33.14	25.60	7.64	8.80
Uruguay	0	35.45	26.07	5.66	9.20
Ireland	0	40.98	26.80	5.19	5.40
Lithuania	0	41.10	26.10	7.64	9.40
Sweden	0	44.10	25.53	5.22	5.90
Luxembourg	0	45.24	26.43	5.26	6.10
Czech Republic	0	45.58	27.02	6.43	9.30
Austria	0	47.02	25.52	8.88	4.10
Cyprus	0	47.45	26.38	9.06	6.40
Estonia	0	51.04	25.34	7.64	7.50
Malta	0	53.29	27.14	6.85	8.30
Denmark	0	57.94	25.28	5.62	5.40
Indonesia	0.14	15.98	22.01	4.84	7.30
France	0.15	39.58	25.17	6.72	4.50
China	0.25	7.30	22.73	4.21	8.70
Australia	0.35	46.83	26.77	5.67	6.30
United Kingdom	0.38	38.37	26.78	3.62	5.70
Romania	0.40	27.63	25.00	6.87	9.00
Italy	0.41	31.56	25.48	5.88	5.00
Netherlands	0.46	46.71	25.41	5.26	3.90
Germany	0.54	48.02	26.25	8.88	6.30
Poland	0.87	44.53	26.02	7.64	7.20
Thailand	0.91	33.35	23.40	7.07	7.90
Greece	0.96	34.28	25.38	5.98	7.40
Portugal	1.10	33.29	26.19	9.70	5.30
Malaysia	1.13	39.82	24.64	11.63	10.90
Egypt	1.36	25.37	27.91	11.35	8.70
Spain	1.78	30.61	26.58	6.60	7.30
Finland	1.81	35.89	25.92	5.67	6.10
Serbia	2.79	26.41	25.86	6.87	8.10
Turkey	4.20	27.84	27.07	7.99	10.20
Mexico	5.83	51.23	27.59	10.79	14.10
Japan	6.19	29.49	22.59	5.00	4.90
Republic of Korea	6.75	35.87	23.42	7.88	6.10
Argentina	7.67	47.87	27.02	5.66	9.70
Belgium	8.32	56.77	25.78	5.26	6.00
Bulgaria	8.53	31.26	25.73	6.46	8.90
Canada	9.13	53.33	26.81	9.19	7.60
Slovakia	9.82	38.85	26.37	6.43	9.10
Hungary	16.85	45.51	26.19	6.43	8.40
United States of America	24.78	68.59	27.99	10.27	8.20

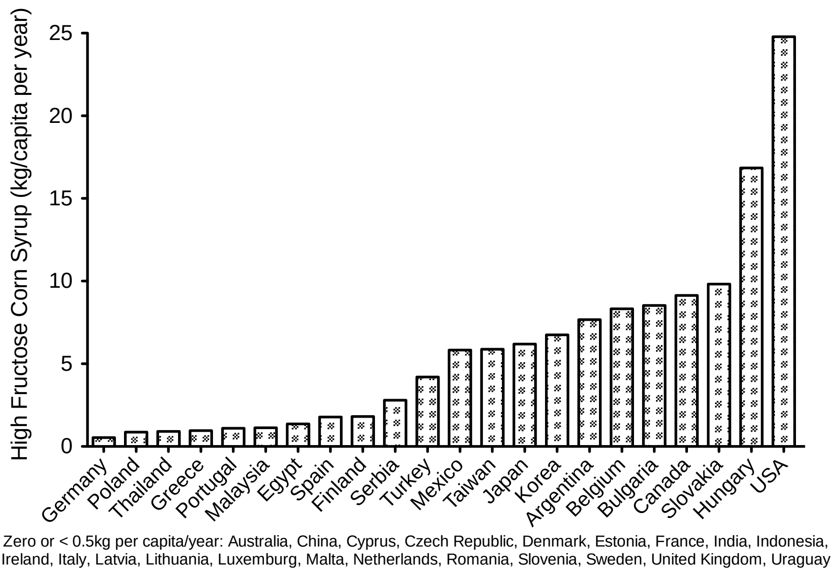

Figure 1. HFCS use by country.

(5.33 vs. 5.23 mmol/L, $p = 0.046$). As shown in Table 3, these differences were retained or became stronger after controlling for country-level estimates of BMI, total population and gross domestic product, with all estimates of diabetes being significantly higher in HFCS users: IDF estimates of diabetes prevalence (7.7 vs. 6.4%, $p = 0.03$); GBMRF estimates of diabetes prevalence (8.2 vs. 6.9%, $p = 0.03$); and fasting plasma glucose (5.34 vs. 5.22 mmol/L, $p = 0.03$).

Discussion

In the current paper, we report the results of an ecological analysis that examined whether country-level availability of HFCS was associated with global prevalence estimates of diabetes. Our analysis revealed that countries electing to use HFCS in their food supply have a diabetes prevalence that is ~20% higher than that in countries that do not use HFCS. This finding builds on a prior ecological analysis

Table 2. Comparison of countries with low vs. high availability of HFCS.

	Countries not using HFCS ($n = 22$)	Countries using HFCS ($n = 21$)	p-Value
$\text{Diabetes}_{\text{IDF}}$ (%)	6.3 ± 1.5	7.8 ± 2.1	$p = 0.013$
$\text{Diabetes}_{\text{GBMRF}}$ (%)	7.1 ± 2.0	8.0 ± 2.1	$p = 0.13$
Fasting glucose (mmol/L)	5.23 ± 0.17	5.33 ± 0.17	$p = 0.046$
BMI (kg/m2)	25.5 ± 1.6	25.9 ± 1.4	NS
Total intake (Kcal/day per capita)	3230 ± 377	3221 ± 365	NS
Cereals (kg/year per capita)	129.8 ± 30.1	137.0 ± 36.2	NS
Total sugar (kg/year per capita)	38.2 ± 12.8	39.9 ± 11.3	NS
Other sweeteners (kg/year per capita)	5.5 ± 7.1	6.1 ± 8.3	NS

Table 3. Comparison of countries with low vs. high availability of HFCS after controlling for population BMI, population and gross domestic product.

	Countries not using HFCS ($n=22$)	Countries using HFCS ($n=21$)	p-Value
$\text{Diabetes}_{\text{IDF}}$ (%)	6.4 ± 1.7	7.7 ± 1.9	$p=0.03$
$\text{Diabetes}_{\text{GBMRF}}$ (%)	6.9 ± 1.0	8.2 ± 1.9	$p=0.03$
Fasting glucose (mmol/L)	5.22 ± 0.16	5.34 ± 0.17	$p=0.03$
Total intake (Kcal/day per capita)	3282 ± 303	3167 ± 310	NS
Cereals (kg/year per capita)	127.1 ± 33.2	139.9 ± 34.0	NS
Total sugar (kg/year per capita)	40.2 ± 9.6	37.8 ± 9.9	NS
Other sweeteners (kg/year per capita)	6.6 ± 6.5	4.9 ± 6.7	NS

from data in the USA that showed that increasing consumption of HFCS in the twentieth century was the primary nutritional factor associated with increasing prevalence of type 2 diabetes (Gross *et al.* 2004).

Increased sugar intake is hypothesised to be associated with obesity and diabetes through a variety of pathways. First, adding sugar to the diet may contribute excess calories, which can contribute to excess fat accumulation, and in turn risk for type 2 diabetes, as obesity is one of the primary risk factors for diabetes. In addition, dietary sugar is related to poor beta-cell function (Davis *et al.* 2005), and over extended time could lead to beta-cell failure and type 2 diabetes, probably due to the continual requirement for insulin secretion in response to high sugar consumption (Ludwig 2002).

In addition, a growing body of literature suggests that fructose, when consumed in excess, can have a negative metabolic effect (Stanhope *et al.* 2009). Fructose and glucose are both monosaccharides, while sucrose, or table sugar, is a disaccharide composed of one molecule of fructose and one molecule of glucose. Despite their very similar chemical structure, fructose and glucose are absorbed and metabolised by different pathways. Fructose is absorbed through the GLUT-5 receptor in the gut (Douard and Ferraris 2008), and in contrast to glucose, is metabolised almost entirely in the liver by a pathway that is not dependent on insulin (Gaby 2005). Accordingly, there is evidence to show that fructose consumption does not stimulate insulin secretion or leptin production by adipose tissue (Stanhope and Havel 2008, Teff *et al.* 2009) and thereby is thought to contribute more directly to weight gain (Stanhope and Havel 2008). Also, excess fructose consumption has been shown to be more lipogenic, leading to ectopic fat accumulation including visceral adipose tissue and liver, associated insulin resistance, and thus increased diabetes risk (Stanhope *et al.* 2009). These unique detrimental properties of fructose that pose risk to metabolic health may explain the finding that countries that use HFCS had significantly increased prevalence of diabetes, independent of BMI and total sugar availability.

The manufacturing process for HFCS was developed in the 1920s (Marshall and Kooi 1957) and refined in Japan during the 1960s. It became a major part of the US diet from the 1970s onwards, when its production was an alternative use for US-grown corn at a time when its role as a source of vegetable oil was usurped by the cheaper soy bean (Putnam and Allshouse 1999). The USA is the world's largest producer of corn, and the surpluses diverted into HFCS production from the 1970s were enormous (The United States Environmental Protection Agency 2000). The consumption of total fructose in the USA increased by nearly 30% between 1970 and 2000, largely from beverages sweetened with HFCS (Bray *et al.* 2004). Between 1994 and 1998, the intake of HFCS by US citizens above the age of two years was 318 calories per day, or one-sixth of all energy intake and one-third of all carbohydrate intake (Bray *et al.* 2004). By the late 1990s, HFCS comprised 40% of all caloric sweeteners sold in the USA (Putnam and Allshouse 1999), and it became the predominant caloric sweetener in soft drinks. Though often estimated at 55% fructose, it is difficult to quantify the actual fructose content of HFCS due to lack of industry disclosure on food labels. In a recent exploratory study, we found that fructose in some US-produced soft drinks, especially the most popular, was about 20% higher than expected, suggesting that some manufacturers might be using HFCS with more fructose than previously estimated (Ventura *et al.* 2010), thus potentially driving up fructose consumption in countries that use HFCS.

Certain trade and agricultural policies have also had dramatic effects on global use of HFCS. For example, production of HFCS in the EU countries is set by quota. Current quotas were set for 2005/2006 and have been carried over till 2014/2015. However, trade in quotas between the EU countries does occur. For example, some countries do not take their assigned quotas (e.g., Sweden and the UK) while some other countries like Hungary, for example, purchase extra quotas from countries that do not take them. This explains the variation in HFCS use across the EU. In addition, the USA is the main global producer of HFCS, but has recently begun to export large amounts to Mexico. In 2002, Mexico taxed imports of HFCS from the USA to protect its sugar industry, after the World Trade Organisation rejected a petition against the dumping of HFCS by the USA to Mexico in 2001. However, political attempts to stem its flow into Mexico have largely failed. In 2008, the restrictions were removed that were previously in place regarding trade of sugar through the North American Free Trade Agreement (NAFTA). Subsequently, exports of HFCS from the USA to Mexico have increased exponentially, with most of this increase occurring since the trade restrictions were lifted in 2008 (The United States Department of Agriculture Economic Research Service 2012). The export of HFCS from the USA to Mexico was close to zero in 2004, and rose to the equivalent of 1.4, 3.1 and 7.5 kg/capita/year in the years 2006, 2008 and 2010 (The United States Department of Agriculture Economic Research Service 2012).

With consumption patterns changing due to these policy shifts, it is imperative to better understand the associated public health consequences. The increasing popularity of HFCS around the world should, therefore, be considered seriously due to its potential contribution to increases in fructose in the global food supply and its association with the global prevalence of type 2 diabetes. In our study, HFCS was associated with an approximate 20% higher diabetes prevalence even after adjusting for country-level estimates of BMI, population and gross domestic product. This effect of HFCS on higher prevalence of diabetes could be interpreted from an overall economic and health impact. For example, the health care costs of diabetes in the USA in 2007 were estimated to be $174 billion dollars per year (American Diabetes Association 2008). Countries in this study that do not use HFCS had a diabetes prevalence estimate that was 20% lower than countries that did, so the potential economic impact of HFCS on diabetes alone was estimated to be 20% of $174 billion/year, and this was equivalent to $95 million dollars per day in the USA. Given the current debate in the USA around a potential sugar tax (Brownell *et al.* 2009), these current data suggest that if each person in the USA is estimated to consume 2 servings per day of foods or beverages containing HFCS, then the required 'tax' to recuperate the additional health costs due to the diabetes burden would be approximately 10 cents per item with HFCS.

A number of limitations of this analysis should be discussed. First, our analysis is based on nutrient availability data, not individual surveys or measures, and thus represents a more ecological perspective that could be subject to ecological fallacy. Although this is a limitation, it remains the only adequate approach to examining the issue, since HFCS does not appear as a listed food ingredient or appear in nutrient databases. Thus, it is extremely challenging to obtain individual estimates of HFCS consumption. Another limitation is the major assumption in the IDF diabetes prevalence numbers that estimate prevalence for countries where no estimates are available using published reports from similar countries that are matched for factors such as ethnicity, socio-economic status and geographic location. This approach might introduce errors that might match countries similar in some aspects, but not others that might impact diabetes. In the HFCS country analysis, for example, the following countries were paired with similar estimates for diabetes prevalence: (1) countries with no HFCS use: Luxemburg and The Netherlands (diabetes prevalence = 5.26%); Latvia, Lithuania and Estonia (diabetes prevalence = 7.64%); and (2) countries with HFCS use: Slovenia and Hungary (diabetes prevalence = 6.43%). This limitation, however, was offset by the use of two separate estimates of diabetes prevalence as well as analysis of global estimates of fasting glucose at the country level, with all three estimates showing significant differences between countries using or not using HFCS.

In summary, the results from this ecological analysis suggest that countries that utilise HFCS as an alternative sweetener have increased risk of diabetes beyond the effects of sugar itself and of BMI, likely due to its contribution to higher amounts of fructose to the food supply, and the consequent negative effects of fructose metabolism on risk for diabetes. Although the sugar composition of sucrose (fructose:glucose ratio = 50:50) and HFCS are similar (fructose:glucose ratio = 55:45), the use of HFCS increases dietary fructose exposure by at least 10% and could be as high as 35% based on prior analysis of sweetened beverages (Ventura *et al.* 2010). Countries electing to use HFCS in their food supply had a 20% higher prevalence of diabetes than countries that did not use HFCS. Public health strategies aimed at diabetes prevention should incorporate efforts to limit sugar consumption and provide consumers with better labelling with regards to sugar composition, especially with regards to fructose and HFCS content. In addition, trade and agricultural policies aimed at sugar and especially HFCS supply should be considered as a means to tackle the increasing global prevalence of diabetes.

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