Scholars LITERATURE

Journal of Food and Nutritional Health

Review Article

DOI: https://doi.org/10.47275/2692-5222-123
Volume 5 Issue 1

A Critical Review on Ultra-processed Foods - Toxic and Addictive

Ramireddy Sulekha[1*], Kota Amarnadh Reddy[2], Rishabh Parihar[3*] and Aanchal Sareen[3]

[1] Malla Reddy Institute of Medical Sciences, Hyderabad, Telangana, India.

[2] AIIMS, Mangalagiri Guntur, Andhra Pradesh, India

[3] Uzhhorod National University, Uzhhorod, Ukraine

Abstract

There have been many public health crises in the past (e.g., tobacco, alcohol, opioids, cholera, HIV, lead, pollution, venereal disease, even Coronavirus (COVID-19)) that have been addressed both individually and collectively. Healthcare professionals are well aware that noncommunicable diseases (NCDs) have their origins in our Western ultra-processed food diet, but society has been slow to take any other steps than public education, which has been ineffective because of food industry interference. By aggregating the evidence for such public health interventions, this article provides the rationale for regulating added sugar, as well as ultra-processed foods, based on four criteria set by the public health community as necessary and sufficient for regulation - abuse, toxicity, ubiquity, and externalities. Several countries have recently implemented sugar taxation policies to help ameliorate NCDs within their borders, which is to their credit. To quell this pandemic, this article also provides scientific counterpoints to food industry talking points and sample intervention strategies.

Keywords: Processed food; Nutrition; Non-communicable disease; Metabolic syndrome; Diabetes; Addiction; Policy

[*] ***Correspondence to*:** Ramireddy Sulekha and Rishab Parihar, Malla Reddy Institute of Medical Sciences, Hyderabad, Telangana, India and Uzhhorod National University, Uzhhorod, Ukraine.

Citation: Sulekha R, Parihar R (2024) A Critical Review on Ultra-processed Foods - Toxic and Addictive. J Food Nutr Health, Volume 5.1. DOI: https://doi.org/10.47275/2692-5222-123

Received: March 13, 2024; **Accepted:** May 15, 2024; **Published:** May 17, 2024

Introduction: Pandemics and Public Health

There are two pandemics going on at the same time. COVID-19 pandemic began in January 2020. In spite of media attention and warnings from scientists, many countries are experiencing a "second wave"; here in the United States (US), we never even cleared the first wave. We have no cure, at least not yet; all we can do is to mitigate the pandemic by keeping a safe distance, washing hands, and wearing face masks, all of which don't seem to work very well voluntarily [1, 2]. In the second pandemic, NCDs (type 2 diabetes, coronary heart disease, fatty liver disease, hypertension, heart attack, stroke, cancer, and dementia) have slowly built over the past 50 years. We also do not have a cure for this pandemic; all we have is education, like voluntary "diet and exercise," which does not seem to work very well either.

The number of deaths and health care dollars related to NCDs have increased to 72% in the US and 75% globally; and the morbidity, mortality, and economic costs are also increasing. As a result of both the loss of economic productivity and increased healthcare expenditures, Medicare and social security are expected to run out of money by 2026 and 2034, respectively [3-5]. Old and infirm people cannot be taken out of the system without young and healthy people paying for it. United Nation has declared NCDs a global health crisis, and the cost of these diseases is not limited to the US. In other words, each country, as well as the entire planet, faces an existential threat from NCDs [6]. A key component of mitigating NCDs is identifying their causes and implementing upstream policy measures.

Two other chronic disease pandemics have recently hit the world, ethanol, and tobacco. Both are caused by hedonic substances readily available for purchase, and both respond to public health regulatory interventions [7]. We saw a reduction in cigarette consumption and lung cancer only after the US's Master Settlement Agreement and the World Health Organization's Framework Convention on Tobacco Control. Alcohol ethanol regulations have been passed in individual countries with clear improvements in public health.

Criteria for Public Health Regulation

The question for public health officials is whether there is something specific and identifiable that could be regulated globally to help mitigate the pandemic of NCDs [3, 8]. It is possible to mandate some behaviors (e.g., mask wear), but most are left up to the individual (e.g., exercise). According to the Iron Law of Public Health, reducing the availability of a substance reduces consumption, which reduces health harms. Therefore, targeting a substance or class of causative substances would be more effective [9]. For a product to be regulated by public health, it must meet four criteria: The science and logic behind each of these criteria must be obvious and inescapable in order to generate enthusiasm for any public health regulatory effort. As a result of this treatise, the public health community and policymakers should consider ultra-processed foods, especially sugar, as targets for regulating the NCDs pandemic based on the science presented herein [10].

We must first address the "elephant in the room": the myth that calories cause obesity and obesity causes NCDs. Processed food producers could then use the mantra "any calorie can be part of a balanced diet" to deflect criticism of their products. The role of

sugar and ultra-processed foods in the pandemic of NCDs must be demonstrated by showing that obesity is not a cause of NCDs since normal-weight individuals also develop NCDs [11]. Moreover, we must demonstrate that the effects of sugar and ultra-processed food on NCDs prevalence and severity are independent of the effects of obesity on NCDs prevalence and severity (Figure 1) [12].

Obesity is a 'Marker', Not a Cause of NCDs

NCDs have been mistakenly attributed to obesity by most clinicians because of the quantity of food consumed. For five different reasons, this is not true. (a) Obesity prevalence and diabetes prevalence are not concordant. Several countries are obese without being diabetic (for example, Iceland, Mongolia, and Micronesia), while others are diabetic without being obese, such as India, Pakistan, and China (they manifest a 12% diabetes rate). (b) Diabetes and obesity are further discussed in terms of years of lost life. It has been found that up to 40 percent of normal weight adults have metabolic perturbations similar to those in obesity, including type 2 diabetes mellitus (T2DM), dyslipidemia, non-alcoholic fatty liver disease, and cardiovascular disease, while twenty percent are metabolically healthy and have normal life spans. According to recent studies, 88 percent of US adults suffer from metabolic dysfunction, as opposed to only 65% who are obese or overweight. (c) The "Little Women of Loja" are an Ecuadorian cohort who are growth hormone-receptor deficient, become obese, and are protected against chronic metabolic diseases like diabetes and heart disease. (d) Between 1988 and 2012, the prevalence of diabetes in the US increased by 25% among both obese and normal-weight individuals. (e) T2DM in children as young as 10 years old does not appear to be caused by the aging process, as these biochemical processes have been observed in children as young as 10 years old. Now children get two diseases that were never seen before in this age group — T2DM and fatty liver disease. These two diseases used to be prevalent only in the elderly, or in those who abused ethanol [13-16].

Five lines of reasoning persuade us that obesity is a "marker" for the pathophysiology of NCDs (e.g., insulin resistance), but not a primary cause, since a percentage of normal-weight people also get NCDs, while a percentage of obese people are metabolically healthy [17]. The argument could be made that "eating is addictive" if obesity causes NCDs, but that is not the case. The fact that young and normal-weight people are susceptible to these diseases suggests exposure rather than behavior is at the root of the NCDs pandemic.

Ultra-processed Food is the Cause of NCDs

The cause is rather the quality of the food. Foods with 5 or more ingredients that are ultra-processed are linked to NCDs, such as obesity, diabetes, heart disease, and cancer [18]. The prevalent, insidious, and egregious component of ultra-processed food is added sugar (i.e., fructose-containing sweeteners such as sucrose, high-fructose corn syrup, maple syrup, honey, and agave).

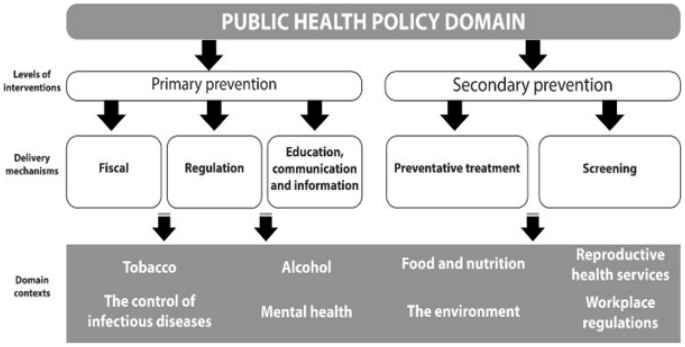

Figure 1: Population-level preventative public health policies in reducing health equalities [12].

The purpose of this article is to elaborate three related arguments using scientific and legal evidence. The food industry adds sugar to ultra-processed food specifically because of its addictive properties, and I will demonstrate that sugar makes ultra-processed food addictive. Second, I will describe how sugar causes liver damage, resulting in NCDs [19]. In conclusion, I would argue that added sugar should be considered an additive rather than a food. As a result, I will argue that added sugar meets the criteria established by the public health community for regulation of a substance (abuse, toxicity, ubiquity, and externalities).

Added Sugar is Abused

In the pandemic of NCDs, the Western diet has played a pivotal role. In the US and 19 European countries, ultra-processed food consumption correlates with body mass index (BMI) [3, 20]. During the 1990s, rapid growth in fast food sales resulted from deregulation policies, along with increases in body mass index in all countries and cultures that adopted the practice. NCDs and their resulting costs are burdened on every country that has adopted the Western diet. In spite of this, the food industry continues to promote the argument that quantity is more important than quality [21, 22]. There is no semantic argument here. The end user determines quantity, a personal responsibility issue; the manufacturer determines quality, a public health issue. What if quality changed to quantity? Therefore, those who favor one view over the other would appear justified in their positions. There seems to be a deadlock in this debate. Before any form of societal intervention can be considered, this question must be answered.

'Food addiction' vs 'eating addiction'

According to recent revelations in popular literature, the Western diet is addictive, leading to excessive consumption. There is an overlap in physiology and neuroanatomy between obesity and addiction pathways [22- 24]. Certain components of processed food, and particularly those found in "fast food," have been compared to cocaine and heroin in terms of their addictive properties. According to the Yale Food Addiction Scale (YFAS), specific foods have addictive properties, and a YFAS for children also indicates that obesity increases the likelihood of food addiction [25].

This expanded view of specific foods having addictive properties is not shared by everyone, however. NeuroFAST, a group of European academics, calls food addiction "eating addiction," rather than "food addiction" [26]. According to this group, all foods are treated similarly, and the behavior is what distinguishes eating addiction. According to these researchers, even though specific foods may induce a reward signal, they cannot be addictive because they are necessary for survival. A specific food, food ingredient, or food additive has not been shown to cause substance-based addiction in humans (the only known exception is caffeine, which can be addictive via specific mechanisms). Despite the fact that one gram of ethanol has a 7-kcal energy density, we do not consider alcoholic beverages as food in this context. Caffeine is classified as addictive by NeuroFAST but is given a pass. Despite the presence of xanthine alkaloids in many foods, caffeine is classified by the US. As a food additive, caffeine is regulated by the US Food and Drug Administration (FDA). As a drug, it is given to premature newborns with underdeveloped nervous systems to stimulate the central nervous system [27]. Ethanol is also recognized as addictive by NeuroFAST but is given a pass as well. Although NeuroFAST acknowledges that purified ethanol is not a food, natural yeasts constantly ferment fruit while still

on the vine or tree. To stop premature labor, we used to give pregnant women ethanol as a drug (Figure 2).

Using weight gain as a measure of food addiction, another European group with food industry ties studied the effects of foodstuffs on "eating dependence" in university students. Fats and sugars did not cause weight gain differently in their study. Weight gain, however, is an inherently flawed metric for measuring food addiction [28].

UCSF researchers examined the effects of food on the brain's reward pathway by studying a cohort of postmenopausal women with obesity who received the mu-opioid receptor antagonist naltrexone orally. Symptoms of craving for sweet palatable foods were correlated with cortisol amplitude and nausea generation in response to naltrexone [29]. The results suggest that naltrexone interferes with endogenous opioid peptide tone that mediates these cravings. This resulted in the discovery of the "Reward Eating Drive", which belies those obese individuals who appear to respond excessively to hedonic food cues and is associated with the opioidergic reward system of the brain, which is triggered by sweet foods. Researchers have also found that the prefrontal cortex responds to sweet tastes as being "attractive" or "unattractive" using functional magnetic resonance imaging (fMRI) [30].

Addictive potential of food components

Fast food would be the consumable class that is uniquely addictive. Are fast food's calories the only thing that makes it addictive, or is there something else? In addition to salt, fat, caffeine, and sugar, fast food contains four components with hedonic properties.

Salt

Humans have traditionally viewed salt intake as a learned preference rather than an addiction. Early in life, salty foods are likely to be preferred [31]. The sodium content of breast milk, water used to mix formula, and a baby's diet influence infants' salt preferences between the ages of four and six months. A preference for salty foods is associated with higher calorie intake since energy-dense fast foods are high in sodium, in part as a preservative to prevent depreciation [32]. A Korean study, for instance, found a connection between frequent fast-food consumption and a preference for saltier versions of traditional foods. Over 60 days, fast food intake and weight gain were significantly increased in 27 subjects withdrawing from opiates (mostly oxycodone), suggesting "addiction transfer." People can also 'reset' their preference for less salty foods, according to studies [33]. Over 8 to 12 weeks, adolescents deprived of salty pizza in school lunches and hypertensive adults retrained to consume a lower sodium diet demonstrated this effect. Additionally, salt intake at low levels is tightly regulated. Salt-losing congenital adrenal hyperplasia patients who lack the mineralocorticoid aldosterone modulate have to lose salt, modulating salt intake until fludrocortisone is supplemented. Recent public health efforts to reduce sodium intake so drastically have been criticized on the basis that sodium intake is "physiologically fixed." However, the British government conducted a secret campaign to reduce public salt consumption by 30%, which led to a 40% drop in hypertension and stroke.

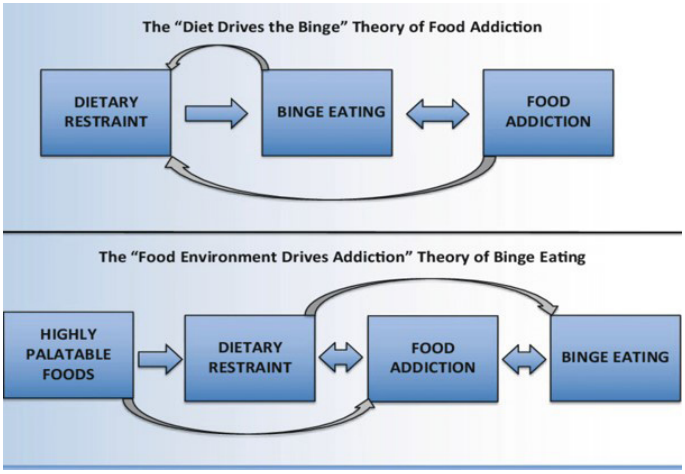

Figure 2: Models of food addiction and eating addiction/binge addiction [27].

Fat

Fast food is rewarding because of its high fat content. Among human subjects, there may be a "high-fat phenotype" characterized by a preference for high-fat foods and a weak sense of satiety after eating them, which can contribute to obesity. People typically prefer "high-fat foods" (e.g., potato chips, pizza, and cookies) that are also high in carbohydrates [34]. There is no limit for preference with increasing fat content when sugar is added to high-fat foods among normal weight human subjects. Thus, high fat combined with high sugar is likely to stimulate addictive overeating more effectively than fat alone. As low-carbohydrate, high-fat and ketogenic diets consistently result in reduced caloric intake, weight loss, and the resolution of metabolic syndrome, it appears that these rewarding properties of fat are strictly dependent on simultaneous consumption of carbs [35]. Thus, fat makes fast food more appealing, but it does not appear to be addictive in itself.

Caffeine

In children, adolescents, and adults, caffeine meets the DSM-IV and DSM-V criteria for tolerance, physiologic withdrawal, and psychological dependence. During withdrawal, headaches, fatigue, and impaired task performance have been observed [3, 36]. The majority of caffeine consumed by adults comes from coffee and tea, as opposed to soft drinks and hot chocolate. On average, these drinks contain 239 calories and a high amount of sugar. A blind comparison of caffeine-containing and caffeine-free cola shows that only 8% of frequent soda drinkers can detect the difference between the two. It is most likely that caffeine in soda increases the salience of a beverage that is already highly rewarding (high in sugar). Caffeine-dependent customers may use these drinks as a gateway to fast food restaurants.

Sugar

Sugar has the highest YFAS score, followed by caffeine. Sugar content in fast food meals increases by 10 times when a soft drink is added. An analysis of fast-food transactions reveals that only soft drink intake is related to changes in BMI, not animal fat products. Fast food eaters consume more soft drinks than people who do not eat fast food [37]. Soda consumption has been independently linked to obesity and metabolic syndrome. Neonatal circumcision has been associated with sugar's analgesic effects, suggesting a link between sugar and endogenous opioid peptide tone. Sugar withdrawal symptoms are described as "irritable", "shaky", "anxious", and "depressed" by self-identified food addicts. Psychological dependence can also be treated with sugar, according to other studies. The intensity of sugar cravings can vary widely depending on the time of day, the age, and the menstrual cycle.

Sugar is added to foods in the form of sucrose, high-fructose corn syrup, honey, maple syrup, or agave syrup. It has recently been revealed that store-bought sodas in Los Angeles contain as much fructose as 65%, even though this percentage is generally assumed to be half fructose, half glucose. The difference in reward response and toxicity between fructose and glucose may be relevant.

Correlates of addiction in animals exposed to sucrose

The acute reactant c-fos is uniquely induced in the ventral tegmental area of rodents after oral sucrose administration [38]. Furthermore, morphine and sucrose infusions directly into the nucleus accumbens reduce dopamine and opioid receptors, and fMRI studies demonstrate that craving pathways are hard-wired. Additionally, sucrose administration to rodents induces behavioral changes consistent with dependence, such as bingeing, withdrawal, cravings, and cross-sensitization to other drugs. As a matter of fact, one oft-cited rat study found that sweetness surpassed cocaine as a reward [38].

Differential effects of fructose vs glucose vs fat on the human brain

Fructose and glucose are metabolized differently despite having the same caloric content (4.1 kcal/g). The energy of life is glucose. In the absence of glucose, the liver synthesizes it from amino acids and fatty acids (gluconeogenesis) [3, 39]. However, fructose, while used as an energy source, lacks any biochemical function in any eukaryote. In our research, excess fructose intake promoted insulin resistance and resultant NCDs when the liver was unable to metabolize the fructose via the tricarboxylic acid cycle.

Physiologically, chronic fructose administration promotes fasting hyperinsulinemia and hypertriglyceridemia, which block leptin's ability to cross the blood brain barrier and inhibits leptin's ability to suppress mesolimbic dopamine signaling in rodents and humans, increasing tolerance. The stomach-derived hunger hormone ghrelin is not suppressed by fructose either. Fructose leads to overconsumption independently of energy requirements through these pathways. Comparing fructose (similar to sucrose) to glucose reveals greater risk for binging with fructose, suggesting fructose is responsible for both reward and addiction.

fMRI studies on humans have shown that acute glucose vs fructose administration affects different parts of the brain neuroanatomically. As a result of intravenous infusion of each monosaccharide, blood oxygenation level-dependent (BOLD) fMRI signals were measured in cortical areas of the brain; glucose increased the BOLD signal in cortical executive control areas, while fructose suppressed it. Additionally, rCBF was compared after glucose versus fructose consumption. Fructose reduced rCBF in the thalamus, hippocampus, posterior cingulate cortex, fusiform cortex, and visual cortex, while glucose reduced rCBF in the hypothalamus, thalamus, insula, anterior cingulate, and striatum (appetite and reward regions). Studies have shown that fructose lacks satiety or fullness in comparison to glucose, which is consistent with other studies. In addition, glucose increased the functional connectivity of the caudate, putamen, precuneus, and lingual gyrus (basal ganglia); whereas fructose increased the functional connectivity of the amygdala, hippocampus, parahippocampus, orbitofrontal cortex, and precentral gyrus (limbic system) more than glucose [40, 41]. Fructose oral intake attenuates the effects of dopamine on the nucleus accumbens in obese youth, suggesting a decrease in dopamine receptor activity. The effects of fat and sugar on fMRI signaling have been assessed both separately and together (adjusted for calories). In the insula, the Rolandic operculum, and the thalamus (gustatory regions), high-fat milkshakes increased activity while sugar increased activity in the caudate and oral somatosensory areas (postcentral gyrus, hippocampus, and inferior frontal gyrus). Furthermore, increasing sugar content increased activity in those regions, but increasing fat content did not change it. Essentially, the fat increases the salience of the sugar, but the sugar effectively recruits reward and gustatory circuits (Figure 3).

The added sugar (specifically fructose) activates reward circuitry and increases consumption both directly and indirectly, as well as downregulating dopamine receptors, requiring more and more stimulus to trigger a reward-signaling effect (tolerance), a primary component of addiction. Obesity and chronic fructose exposure downregulate dopamine receptors [42].

'Food' addiction is really 'food additive' addiction, and 'added sugar' is a food additive

Psychologists did not accept the concept of food addiction in the past. According to the DSM-IV published in 1993, "substance use disorder" requires both tolerance and withdrawal, and no food elicits withdrawal (apart from caffeine and ethanol). The definition of necessity expanded as a result of the public health challenges associated with addiction. The DSM-V published in 2013 recategorized the field to include "behavioral addictions", such as gambling (internet gaming was listed as requiring further research in the appendix). As a result, revised criteria for psychological dependence were proposed, including: Craving or a strong desire to use; Recurrent use resulting in a failure to fulfill major role obligations (work, school, home); Recurrent use in physically hazardous situations (e.g., driving); Use despite social or interpersonal problems caused or exacerbated by use; Taking the substance or engaging in the behavior in larger amounts or over a longer period than intended; Attempts to quit or cut down; Time spent seeking or recovering from use.; Interference with life activities.; and Use despite negative consequences.

DSM-V does not include a diagnosis for food addiction. In spite of this, systematic reviews of the literature demonstrate that ultra-processed foods are the most addictive due to their high sugar content. It is clear that sugar meets the DSM-V criteria of tolerance and dependence (use despite conscious knowledge and recognition of its adverse effects), regardless of whether sugar meets the DSM-IV criteria of classic tolerance and withdrawal [43].

In Bolivia, coca leaves are considered medicine, but cocaine is considered a drug and is regulated. The opium poppy is also a medicinal plant, but morphine is a controlled substance. Although coffee contains caffeine (as a medicine), concentrated caffeine is considered a drug, and is regulated. Sugar was considered a spice in ancient times. It was a condiment during the Industrial Revolution. Currently, it is a drug that has been purified. The same compound found in fruit is refined sucrose, which has been crystallized to remove the fiber. Sugar has been transformed into a drug by this process of purification. When purified and added to food, it becomes addictive, like these other addictive consumables. It is present in low doses in nature and does not exert toxic effects; however, when purified and added to food, it becomes toxic.

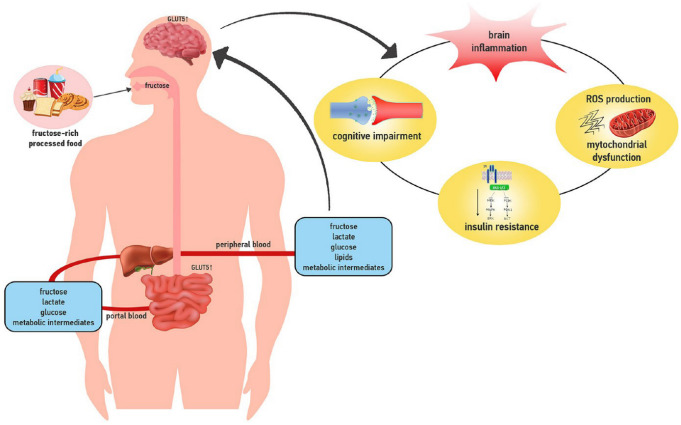

Figure 3: Effects of fructose vs glucose vs fat on the human brain [42].

Food is a necessity; drugs are a luxury. NeuroFAST asks how food, which is necessary for survival, can also be addictive? There are some "foods" that we don't need to survive. Alcohol, caffeine, and sugar are the only hedonic substances found in food that can be addictive. This is a food additive, not a food. Seventy-four percent of the food supply contains some form of sugar because the food industry knows that adding it increases sales. Nicotine levels in cigarettes, for example, were manipulated by the tobacco industry to keep users consuming, and to convert as many as possible into "heavy smokers." Ultra-processed foods have increased the percentage of calories as sugar (58%) due to similar practices in the food industry. Sugar's allure is one of the biggest reasons why the processed food industry's profit margin is now 5% (it used to be 1%). Sugar's economics also reveal its addictive nature [44]. In the case of coffee, for example, price inelasticity does not significantly affect consumption. Because of its hedonic effects, Starbucks' sales remained steady when prices jumped in 2014 due to decreased supply. In terms of consumables, soft drinks are just below fast food in terms of price inelasticity. In Mexico, when prices were raised by 10% (e.g., with taxes), consumption only dropped by 7.6%. As a result, sugar consumption is only minimally responsive to its economic or caloric value.

Added Sugar is Toxic

The term toxicity refers to the degree to which a substance can damage an organism. All calories are not toxic since such adverse effects are not caused by caloric equivalence. It is not necessary for a substance to be toxic just because it is an energy source. Despite the fact that alcohol has a caloric equivalent (7 kcal/g), humans have an upper limit on their hepatic and brain metabolism, beyond which toxicity manifests, either acutely (mental status changes) or chronically (fatty liver disease resulting in cirrhosis and insulin resistance). Calories or weight gain are not factors that make alcohol dangerous. A molecule's biochemistry in the liver confers its toxicity on alcohol; it is dangerous, therefore, because it is alcohol [45-47]. There are two mechanisms by which alcohol adversely affects liver metabolism: (1) liver mitochondrial overload with diversion of substrate to de novo lipogenesis, resulting in fat accumulation and insulin resistance in the liver; and (2) non-enzymatic binding of acetaldehyde to liver proteins, resulting in "carbonyl" stress, protein denaturation, and inflammation.

Detrimental effects of fructose on liver metabolism

Numerous investigators have documented the metabolic perturbations associated with fructose consumption without taking into account its caloric equivalent. Dietary fructose is not required for any biochemical reaction. Apart from its caloric equivalence, fructose's toxicity is determined by the same two primary molecular mechanisms as alcohol.

De novo lipogenesis

During digestion, a fructose bolus (e.g., a soft drink) is absorbed across the intestinal lining and delivered to the liver by the portal vein. As the glycolytic intermediate acetyl-CoA is delivered unregulated to the liver mitochondria, fructose is particularly lipogenic. Hepatic *de novo* lipogenesis is either exported as triglycerides (which contribute to heart disease) or is driven by fructose [48]. It is possible that the liver will overwhelm its lipid export capacity, resulting in intrahepatic lipid deposition and hepatic steatosis, resulting in insulin resistance, the cause of all NCDs. Other studies have elucidated the intermediate metabolic pathways.

Carbonyl stress — the Maillard reaction

A carbonyl stress occurs when a carbohydrate molecule's reactive aldehyde or keto-group binds non-enzymatically to its amino group, resulting in the Maillard reaction. As bananas age, they turn brown. As humans age, wrinkles also appear. To determine if their diabetes is out of control, diabetic patients check their hemoglobin A1c measurement (which is a carbohydrate molecule bound to position 1 of the globin chain). An oxygen radical is produced when this reaction occurs, which may lead to protein or lipid peroxidation, cell damage, and death if not quenched by an antioxidant.

Due to its unique stereochemistry, the ring form of fructose (a five-membered furan with axial hydroxymethyl groups) is subjected to considerable ionic strain, favoring the linear form of the molecule, which exposes the reactive 2-keto position, which participates in fructosylation of exposed amino-moieties of proteins via the Maillard reaction, seven times faster than glucose with its 1-aldehyde position [49]. An antioxidant must quench each oxygen radical generated by a Maillard reaction; otherwise, cellular damage may occur. It is unrelated to fructose's caloric equivalence that fructose causes greater cellular damage and disease progression compared to glucose.

Tying two pathophysiologic mechanisms together — methylglyoxal

Recently, our UCSF/Touro research group determined that methylglyoxal, a specific intermediate in the glycolytic pathway, is likely the nidus of both toxic phenomena in the liver. Anaerobic glycolysis produces methylglyoxal as a transient metabolic intermediate, whose production is influenced by the liver's availability of excess substrate. In contrast to glucose, nearly 100% of the fructose load is handled by the liver, so fructose is the primary cause of its formation. In addition to being a reactive aldehyde (like glucose) and a reactive ketone (like fructose), methylglyoxal is an alpha-dicarbonyl [50]. As a result, it generates 250 times more oxygen radicals than fructose and 35 times more than glucose during the Maillard reaction. D-lactate, a byproduct of methylglyoxal detoxification, is measured in the blood and is used to calculate methylglyoxal production rate. In obese adolescents, D-lactate levels are higher, and fructose restriction reduces D-lactate levels by improving *de novo* lipogenesis, liver fat content, and insulin sensitivity, all of which are unrelated to caloric equivalence or obesity. It appears that fructose is a chronic, dose-dependent hepatotoxin that contributes to the progression of NCDs.

Dissociating added sugar from its calories and effects on weight

Public health discussions are often diverted toward obesity by the food industry. Data relating sugar consumption to obesity are weak, accounting for only about 10% of the observed effects. Sugar ranks below potato chips and French fries as a cause of weight gain [51]. In this case, sugar is just one of many factors contributing to weight gain. According to a new study, the relationship between added sugar consumption and obesity among the population follows a slightly more complex function that considers both current and previous sugar consumption. Based on this model, obesity can be predicted quite accurately.

However, obesity is the wrong metric. There are countries with high diabetes rates but low obesity rates, such as India, Pakistan, and China, while their sugar consumption has increased by 15% in the past 6 years alone. Sugar consumption is more strongly associated with T2DM when weight and calories are excluded. There is no discussion on the role of added sugar in chronic metabolic diseases, excluding obesity, within the food industry at present.

T2DM is primarily caused by dietary fructose consumption, but many case-control studies don't control calories or weight. A dissociation between fructose's inherent calories and effects on weight must be performed in order to prove that fructose is specifically toxic.

In addition, cross-sectional or correlational studies without time-factor analysis cannot distinguish reverse or intermediate causality; they are like snapshots rather than movies. Last but not least, the food industry points out that most fructose studies are conducted in rodents over short periods of time, with large doses [3, 52]. An animal study shows that sugar can cause morbidity and mortality at normal levels of consumption, and a primate study shows similar effects. However, this section will focus on human studies using doses of added sugar consumed on a daily basis in order to prove toxicity.

Prospective association studies

According to three recent studies with a time analysis that controlled for calories, adiposity, and body mass index, sugar is the specific and direct causative agent of T2DM. In the European EPIC-Interact study, a prospective cohort analysis found that the consumption of sugar-sweetened beverages (SSBs) increased diabetes risk over 10 years. The multivariate modeling, which adjusted for both energy intake and BMI, showed that each SSB consumed increased the hazard risk ratio by 1.29 (95% CI 1.02, 1.63) without considering energy intake (calories) or body mass index (obesity) [53]. Our HR ratio is 1.68 since we consume the equivalent of 2.5 servings of SSBs every day in the US.

An analysis of studies isolated consumption of soda (n = 17) and fruit juice (n = 13), controlling for calories and adjusting for adiposity. Both soda and fruit juice significantly increased the relative risk ratio for diabetes (1.27 and 1.10, respectively) over time, according to this meta-analysis. Additionally, this study specifically calibrated for publication and information bias that often occurs in food industry-sponsored studies [54].

Third, our UCSF researchers examined the National Health and Nutrition Examination Survey adolescent database over three cycles 2005 - 2012, to assess nutritional consumption and dietary changes. In order to determine which aspects of the diet predicted the prevalence of metabolic syndrome, we binned subjects by added sugar consumption and controlled for caloric intake and BMI. In the first quintile (median added sugar consumption of 30 g/day), the HR ratio for metabolic syndrome was 1.0; by the 4th quintile (median added sugar consumption of 125 g/day), it was 9.7.

Econometric analyses

Over the period 1995 - 2014, an econometric analysis of 156 countries found that the global availability of sugar and sweeteners correlated with diabetes prevalence, health care costs per diabetic, and health care costs per capita; demonstrating the harm associated with sugar consumption on both a personal and societal level. As a result of this analysis, both developed and developing countries were affected by this correlation. The study did not account for calories, obesity, or any other aspect of diet.

We performed an econometric analysis at UCSF/Stanford to determine which foods were specifically implicated in altered diabetes rates. We merged three freely available databases together; (1) the Food and Agriculture Organization statistics database (FAOSTAT; a branch of the World Health Organization), which provides information on food availability per person by country, year 2000 - 2010, and by line item (Total calories, fruits without wine, meats, oils, cereals, fiber-containing foods, sugar/sweeteners); (2) The International Diabetes Federation database which lists diabetes prevalence by country by year 2000 - 2010; and (3) The World Bank World Development Indicators Database for 2000 - 2010, which expresses gross domestic product in purchasing power parity in 2005 US dollars for comparability among countries. In addition, it accounts for urbanization, aging, physical activity, and obesity. Over the past decade, what food(s) availability predicts diabetes prevalence in different countries? Using generalized estimating equations with a conservative fixed-effects approach (Hausman test), a hazard model to control for selection bias (Heckman selection test), and period effects to control for secular trends resulting from changes in diabetes detection capacity or policies for importation, we performed this analysis. Using longitudinal data between 2000 and 2010, we were able to determine which changes in diet preceded changes in diabetes prevalence (Granger causality test).

During the decade 2000 - 2010, changes in sugar availability predicted the prevalence of diabetes, independently of total calories, other foodstuffs, aging, obesity, or physical activity. For every 150 calories per day in excess, diabetes prevalence increased 0.1%, but if those 150 calories happened to be a can of soda, diabetes prevalence increased 11-fold, by 1.1% [55, 56]. Based on these data, we can draw causal medical inferences based on dose (more sugar, more diabetes), duration (more sugar exposure, more diabetes), directionality (the few countries where sugar availability decreased experienced a reduction in diabetes), as well as precedence (we observed a three-year delay between an increase in sugar availability and an increase in diabetes prevalence, and a three-year delay between a reduction in sugar availability and a decrease in diabetes prevalence in a prospective modeling study).

Two reasons have been cited for criticizing this econometric analysis. The first reason is that it is an "ecological study," which is conventionally regarded as of low quality [56]. As this econometric analysis assesses multiple points in time, discerns complex relationships between internal and external motivating factors (adjusted over time), and allows for determination of causation (Granger causality test), this analysis is more rigorous and of higher quality than all studies except randomized controlled trials. Furthermore, FAOSTAT measures country-specific food availability rather than consumption, and waste isn't taken into account. Rather than being a negative, assessing availability is a positive feature, as it is more accurate, easily quantifiable, not subject to individual recall, and independent of food wastage.

Interventional starch-for-sugar exchange

43 Latino and African American children with metabolic syndrome were studied over a 10-day period by our UCSF/Touro research group. In addition to measuring their caloric intake, we also assessed their macronutrient and fiber intake using sophisticated software. We assessed their metabolic health on Day 0 by testing their baseline analytes, oral glucose tolerance, and dual-emission X-ray absorption. After that, for nine days, we catered their meals so that they had the same caloric, fat, protein, fiber, and carbohydrate content; however, the percentage of calories from dietary sugar was reduced from 28% to 10%, and the percentage of calories from fructose from 12% to 4%. Fruit was allowed, but fruit juice was not. The scale was given to them to take home, and they were called every day [57, 58]. Weight loss was prevented by making them eat more, and we gave them extra snacks if their weight was declining. Ten days later, we re-examined them.

The metabolic health of the group improved significantly, but the weight did not change significantly. A reduction of 5 mmHg in blood pressure, a reduction of 33 mg/dl in triglycerides, a reduction of 10 mg/dl in low-density lipoproteins, a reduction of 5 mg/dl in glucose levels, a reduction of 8% in glucose area under curve, a reduction of 10 mU/L in fasting insulin, and a 25% reduction in insulin area under curve were achieved with the same calories and without weight loss [59, 60]. Moreover, liver fat was reduced by 22%, while visceral fat was reduced by 7% (due to no weight loss). Moreover, their predisposition to T2DM was reversed when insulin dynamics improved significantly.

The aforementioned studies support Koch's Postulates that added sugar is responsible for NCDs. Fructose and ethanol exert similar effects on the brain and liver, making sugar a chronic, dose-dependent liver toxin unrelated to calories or obesity [61].

Added Sugar is Ubiquitous

At the beginning of the 20th century, sugar consumption in the Western diet was 15 g/day, but by the beginning of the 21st century, it had risen to 94 g/day. The American diet now contains 56% ultra-processed food, 62% of sugar is from this category, and sugar is added to 74% of grocery store items because the food industry knows when it adds sugar, we buy more. Accordingly, world sugar consumption tripled between 1960 and 2010 while world population doubled, suggesting that added sugar consumption has increased significantly in the 50 years since NCDs became prominent. Coca-Cola consumption has been correlated with diabetes prevalence in China and Mexico over the period 1993 - 2006, for example. Sugared beverages increased 50% during this period, while food increased 25%. Since 1975, high-fructose corn syrup has reduced the cost of sugar by 50%, allowing serving sizes to increase and sugar to be added to foods that did not previously contain it. The majority of milk sales in elementary and middle schools are flavored milks (chocolate, strawberry). In addition, soda is cheaper in most developing nations than water, which has increased sugar consumption worldwide. It is extremely profitable for food marketers to market processed foods and sugared beverages to children and adolescents; in 2006, $1.05 billion was spent on marketing to children and adolescents [62].

There is a high degree of convergence between the marketing practices of tobacco companies and food companies. Throughout history, Big Tobacco and Big Food have used the First Amendment to advertise and sponsor to gain favor with the public. In the past, both companies have run aggressive advertising campaigns to recruit new users, which were only defused by regulatory agencies [63-66]. As a corporate sponsor for decades, Big Tobacco sponsored public events such as the Olympics, baseball and football games, and sporting events around the world. In addition to sponsoring global events around the world, the fast food and beverage industries engage in similar marketing practices. Food and beverage industries have followed suit (e.g., Ronald McDonald) after Big Tobacco shamelessly marketed their products to children (e.g., Joe Camel). They both use deceptive business practices to maintain increased usage among "heavy users" [67-71].

Added Sugar Exerts Externalities

Even non-users are affected by substances that cause societal harm. In terms of tobacco and alcohol control, second-hand smoke and drunken driving provided strong arguments. In light of the above data, fructose overconsumption is associated with the same long-term healthcare, human, and economic costs as NCDs.

There are 184,000 deaths worldwide caused by sugary beverages alone every year. As a result of metabolic syndrome co-morbidities, the US wastes $65 billion in productivity and $150 billion in health care resources and experiences a 50% increase in absenteeism and health insurance premiums [72]. The treatment of these diseases or their resulting disabilities consumes 75% of all health care dollars. Annually, 35 million people die from NCDs, with 80% of those deaths occurring in low- and middle-income countries, wasting precious resources. Finally, obesity has been declared a "threat to national security" by the last three Surgeons General and the Chairman of the Joint Chiefs of Staff. As of 2018, 33% of recruits are still considered "Too Fat to Fight" according to the original Pentagon report from 2012. Sugar consumption leads to Stage 3 dental caries in 43% of those recruited.

By reducing sugar consumption, we could prevent premature death, save billions of dollars for economies and improve the quality of life for millions of people around the world. By using advanced Markov modeling (using fatty liver disease as the sentinel disease), our UCSF group demonstrated that a 20% reduction in added sugar consumption (for example, through a tax) would reduce obesity, T2DM, heart disease, death rates, and medical expenditures within three years in the US, saving $10 billion in annual expenses, while a 50% reduction (e.g., following USDA guidelines) could save $31.8 billion in annual costs [73]. Morgan Stanley modeled global economic growth rates from 2015 to 2035 in low-sugar and high-sugar simulations and showed that economic growth would be sustained at 2.9% using a low-sugar scenario, while economic growth would gradually decline to 0.0% under a high-sugar scenario (e.g., the present). Consequently, added sugar consumption has direct externalities that affect everyone.

Food Industry Counters

Personal responsibility

Educating the public on "personal responsibility" over the last 30 years hasn't been effective in stemming the tide of obesity and metabolic syndrome. Educational efforts have not succeeded in reducing consumption of other substances of abuse, which is not surprising. Furthermore, 74% of the food supply is spiked with added sugar by the food industry, making it virtually impossible for most people to quit sugar outright and go "cold turkey" to reduce toxicity and dependence [74]. On the Supplemental Nutrition Assistance Program (formerly known as Food Stamps), the poor are often limited in their purchases to high-sugar processed foods. In order to make processed food more palatable, the food industry has added more and more sugar. When they do, we buy more; increasing profits reinforces the practice. Former Pepsi CEO Indra Nooyi's efforts to reduce the negative health impact of "junk food" by creating a "good for you" category (to offset their "fun for you" category) have been met with rancor by her own Board of Directors due to the $349 million reduction in profits.

As a reason to keep smoking, tobacco companies first employed the personal responsibility strategy in 1962. There are four prerequisites to this ideology.

Knowledge

Consumers buying food products at a supermarket have difficulty understanding the information on the label. In addition to the nutritional value of a product, many people will trust and buy it based on the way it is advertised. For the past 15 years, the institute of medicine in the US, as well as in the United Kingdom (UK) and the rest of Europe, has recommended that a daily intake of up to 22 teaspoons of sugar is considered healthy [75].

Access

It has become almost impossible to avoid added sugar in supermarket foods. In workplaces, gyms, and schools, processed sugary food and drinks are ubiquitous. Sugary drinks have been banned in several American hospitals (including UCSF) and the British National Health Service (NHS), as a role model for the public. A workplace ban on sugared beverages has been shown to benefit metabolic health at UCSF [76].

Affordability

Everyone should be able to afford their choice, and society must do the same. Over the next 10 years, the cost of healthy food increased by the equivalent of US $0.22 per year, compared to the cost of processed food, which increased by the equivalent of US $0.09.

Non-anarchy

In the next decade, chronic metabolic diseases caused by sugar consumption will double Medicare costs, bankrupting health care systems around the world, and the NHS is being squeezed more and more, resulting in longer waiting times. Children who are especially vulnerable to poor diet at critical developmental stages are particularly vulnerable to diet-related harm, which is ignored by the argument that your actions cannot harm anyone else [77-81].

The average American consumes 19.5 teaspoons of added sugar per day. Women should consume 6 teaspoons of added sugar per day and men should consume 9 teaspoons per day, a reduction of 2/3 to 34%. One third of these 22 teaspoon can be found in beverages, and one sixth in desserts. One-fourth of the added sugar in our diet comes from foods we didn't know contained sugar, such as salad dressing, bread, tomato sauce, ketchup, and many others. Our "sugar limit," which has been set so high by the food industry, would still be exceeded even if we eliminated all sweet drinks and desserts from our diets [82-84]. It is therefore impossible to expect relief from "personal responsibility" alone. The food industry has "adulterated" our food supply by adding sugar. The majority of sugar's 262 names are unknown to the general public. By using various forms of sugar and moving each form further down the label, the food industry can hide added sugar as the Nutrition Labeling and Education Act of 1990 requires food ingredients to be listed by mass. So, the consumer doesn't know that the food they're buying is loaded with sugar, the food industry can hide it by hiding it. A pharmacologic "fix' is not available for metabolic syndrome itself, despite the fact that each of its diseases can be temporarily delayed. The dose determines the poison, according to Paracelsus in 1537. The food industry has placed us over our limit of 25 - 37.5 grams of added sugar per day for adults and 12 g/day for children [85, 86].

To reverse the prevalence and severity of NCDs, added sugar must be reduced from the American diet. In order to prevent food-borne illnesses, public health interventions must be made to alter the food environment. However, food is a personal choice, and most people consider sugar to be "empty" calories. Why should individuals not be allowed to consume their discretionary calories as sugar? As a result of their abuse, toxicity, ubiquity, and externalities (negative impacts on society), tobacco and alcohol also pose significant societal threats [87].

Is added sugar 'food'?

Any argument for regulating added sugar will be defended by the food industry with two talking points. Sugar is a major component of fruit, and fruit has been shown to prevent NCDs. Contrary to this, fruit juice has been linked to these diseases. Glucose in whole fruit is less absorbed by the body because of the fiber, which prevents intestinal absorption. Furthermore, the industry claims that dietary sugar is on the FDA's Generally Recognized as Safe (GRAS) list, allowing it to use any amount of sugar in any food. Despite the fact that sugar had been known to cause gout from as early as the 17th century and known to raise serum uric acid levels (the mechanism of gout) in 1967, it was grandfathered into the first GRAS list as it was "natural" and had been used for generations without any obvious ill effects. A substance was included on the GRAS list prior to 1 January 1958 by either scientific procedures or experience based on common food use (requiring significant consumption by a significant number of consumers) and a reasonable certainty that the substance will not cause harm under the intended conditions of use (Food, Drugs, and Cosmetics Act (FDCA) 321(s), 21 CFR 170.30(c), 170.3(f)). Sugar consumption has increased from 2 ounces per day in 1958 to 6.5 ounces per day today. Therefore, GRAS determinations from 1958 are no longer valid. It has been proven that both trans-fats and salt, used in processed foods, are detrimental at doses above what was thought to be safe, and both are now under FDA scrutiny (despite not being removed from GRAS) [88].

The trans-fats used to be considered "food," but subsequent research has shown they can cause heart disease and other metabolic disorders. Research has shown that nitrates cause colon cancer, despite being considered a "food." Eventually, both were removed from the GRAS list and are now regulated as food additives. Alcohol has always been considered a food additive, and caffeine dosage above 0.02% (in cola drinks) is also regulated.

Adding sugar to food is legal, but does it qualify as food? The definition of "food" depends on how you use it. FDCA (1938) 321.201(f) defines "food" as (1) articles used for food or drink for humans or animals, (2) chewing gum, and (3) articles used for components of such articles. Using the word in the definition is against vocabulary rules. According to the Merriam-Webster Dictionary, "food" is a material composed primarily of protein, carbohydrate, and fat that sustains growth, repairs, and vital functions in an organism. Energy is provided by fructose, so it should be considered food [89-91]. Does it really work that way? Despite its energy content (7 kcal/g), ethanol is not a food. Eukaryotes do not require it for any biochemical reaction. It is toxic to consume ethanol chronically and in high doses, regardless of its calories or weight-related effects. Public health interventions are warranted even if not every person exposed becomes addicted. Food additives like ethanol are not foods, they are additives. Similarly, added sugar is a food additive — like ethanol, it's not essential for life, toxic in chronically high doses, and a good percentage of the population is addicted to it. Public health non-governmental organizations are currently considering removing fructose from the GRAS list [92-94].

Possible Societal Interventions

During the last 30 years, there have been four global cultural tectonic shifts in behavior to alleviate four public health problems: (a) smoking in public places; (b) drunk driving; (c) bicycle helmets and seatbelts; (d) condoms in public restrooms. Educating the public was necessary, but not sufficient, and some form of regulatory policy was also required to ensure compliance. Sugar and ultra-processed food can benefit from many lessons learned from alcohol and tobacco control policies [95].

Public education

One of the most important things we have learned from tobacco and alcohol policy research is that public education, despite being the most popular and a necessary component of prevention, does not work alone. Evidence from the US suggests that government labels warning consumers about excessive drinking health effects have no effect on alcohol consumption. However, they might have had some limited effect on risky drinking patterns, such as drunk driving. The most popular approaches – school-based health education, public information campaigns, product labeling, and government guidelines — do not work in isolation. It should be noted that education alone has not solved any substance abuse. Nonetheless, education softens the playing field, so that societal policy interventions can become acceptable and take hold (Figure 4).

The consumption of addictive substances needs to be reduced by looking at what works. Globally, research shows that regulating the pricing, marketing, and distribution of alcohol can reduce the negative consequences of alcohol consumption. The same strategy has been successful with tobacco as well. Pricing strategies (e.g., taxation), restrictions of access (e.g., blue laws), and interdiction (e.g., banning) are

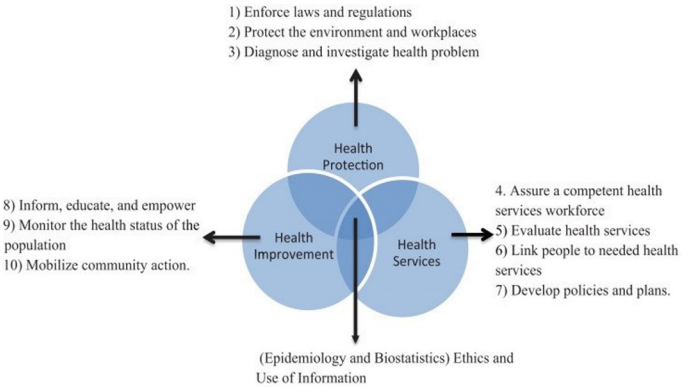

Figure 4: Domains and activities of public health practice [96].

three ways to reduce availability. There is no consensus that interdiction is a good idea - alcohol prohibition was tried and failed utterly [97, 98].

Pricing strategies – taxation

Taxation is accepted by society because it only affects those who use those products. The biggest burden on society is sugar, not tobacco or ethanol. Is there a real goal behind all of this? Is it more important to make money for the state or to reduce consumption? Reducing consumption limits revenue generation [3, 99]. Taxes on hedonic substances must hurt in order to work. It has been determined that reducing general consumption of soda would require a soda tax of at least 20%, which is higher than most soda taxes of 10%.

Six American cities and 28 countries globally have enacted sugar taxes as a result of the emerging science surrounding sugar and the inability of education to prevent the diabetes pandemic.

Pricing strategies – subsidies

Agribusinesses and farmers receive agricultural subsidies from the federal government. Their origins date back to the original Farm Bill of 1933, when cheap food was needed to feed a destitute population. Texas, Iowa, Illinois, Minnesota, Nebraska, Kansas, and North Dakota are the states that receive 45% of the subsidies in the US. At present, seven states receive 45% of the subsidies: Texas, Iowa, Illinois, Minnesota, 5.8%, Nebraska, Kansas, and North Dakota; these are the states where corn, soybeans, wheat, and rice are produced in the greatest quantities [100-103]. Food subsidies distort the market, so no economist believes in them. As a result, they make the wrong stuff more accessible while making the right stuff more expensive. Real food will remain out of reach for many as long as commodities remain cheap.

In the event that subsidies ended, what would happen? UC Berkeley's Giannini group modeled what food would actually cost, and the only two items that would increase in price are sugar and corn, which is exactly what we want. There is no surprise that these two industries are fighting to maintain the status quo. The overall price of food will rise, people will argue. The US spends the least percentage of its gross domestic product on food of all nations at 7%-because all food is derived from commodity crops. The next two fattest nations are the UK at 9% and Australia at 11%.

Restriction of access - workplace bans

It is important to recognize that the workplace is an educational opportunity. In the cafeterias at UCSF, soda and flavored coffee drinks were banned, and any vendor bringing food onto campus was forbidden from selling sugared drinks. One year after the ban was put in place, we studied 214 employees who regularly drank sugary beverages. Their daily intake at baseline was 35 ounces, while it was 18 ounces at follow-up, a 17-ounce decrease. Furthermore, waist circumference decreased by 2.1 cm. Sugared beverage reductions were associated with improvements in waist circumference, insulin sensitivity, and blood lipid levels [104-106]. Employers who implement SSB sales bans may find it difficult to implement a paternalistic workplace culture. Nevertheless, this proves that the Iron Law is indeed true.

Restriction of access – stipends

In the UK, the government offers a monthly stipend that can only be exchanged for real food. Individuals can use their stipends to vote on local food policy, promoting organic farming and local farmers.

Combination strategies - differential subsidization

Subsidizing differently is a "carrot and stick" approach combining incentives and punishments. A different subsidy system was employed in 1977 in the Nordic countries, including Sweden, Denmark, and Norway, to curb the increasing number of alcoholics. Combined, the three countries adopted two pieces of legislation: first, they nationalized liquor stores, which resulted in the same products being sold everywhere at the same price; second, they taxed high-alcohol spirits, and then used the money to subsidize low-alcohol beer. As a result, alcohol consumption was reduced as the public was encouraged to drink low-alcohol beer instead of hard spirits. The process resulted in a decrease in hospitalizations, a decline in car accidents, a decline in cirrhosis of the liver, as well as an increase in economic productivity [107].

A tax on soda and a subsidy on water could easily be used to cut sugared beverage consumption. Since they also sell water, the beverage makers won't care. In a zero-sum scheme, it's just a straight up exchange, nudging people to choose a healthier option. People will not complain if you "nudge" them into doing the right thing, and most times they won't even realize they've been nudged.

Conclusion

Public health requires a balance between personal intervention (read: rehab) and societal intervention (read: laws). The use of "personal responsibility" and railing against the "nanny state" failed to prevent tobacco, alcohol, opioids, cholera, HIV, lead, pollution, and venereal disease, and both forms of intervention were ultimately required. We do not have anything in place for added sugar and NCDs at the moment. As a result of the food industry's strategy of convincing the public that "a calorie is a calorie," that sugar is just an empty calorie, and that personal responsibility is the answer, the case for societal intervention has been lacking. It is important to educate the public about the dangers of chronic excessive sugar consumption, but education will not suffice, as has been seen with every other hedonic substance.

As with tobacco, alcohol, cocaine, and opioids, added sugar meets the public health criteria for societal regulation. There is no one-size-fits-all road map to successful intervention, but we have templates based on how tobacco and alcohol regulations have been implemented. The Iron Law of Public Health applies to tobacco and alcohol, stating that if availability is reduced, consumption will be reduced, thereby reducing health harms. Sugar consumption can be curtailed through policies that target availability, affordability, or acceptability (e.g., the Mexico sugar tax). As with the tobacco industry (e.g., Merchants of Doubt), the sugar industry, their legislative partners, and their political allies have used a variety of tools to avoid responsibility and derail policy reform. Some involve influencing science, some involve influencing public opinion, and others involve influencing legislators directly. A specific and meaningful policy measure cannot be proposed until these activities are understood and countered.

The following evidence has been provided in this article: (1) sugar is addictive and toxic without relation to calories; (2) reducing sugar confers health and societal benefits; (3) ultra-processed food and added sugar meet the criteria for regulation; (4) sugar reduction is not only possible, but necessary, to save health and healthcare, and (5) societal interventions to reduce the consumption of processed foods containing added sugar are feasible and necessary. There are likely to be geographically, politically, and culturally specific interventions (administrative, legislative, judicial); and certain policy interventions will not work everywhere.

Acknowledgements

None.

Conflict of Interest

None.

References

1. Room R, Schmidt L, Rehm J, Mäkelä P (2008) International regulation of alcohol. BMJ 337: a2364. https://doi.org/10.1136/bmj.a2364
2. Lustig RH (2016) Sickeningly sweet: does sugar cause type 2 diabetes? Yes. Can J Diabetes 40: 282-286. https://doi.org/10.1016/j.jcjd.2016.01.004
3. Lustig RH (2020) Ultraprocessed food: addictive, toxic, and ready for regulation. Nutrients 12: 3401. https://doi.org/10.3390/nu12113401
4. Sepúlveda J, Murray C (2014) The state of global health in 2014. Science 345: 1275-1278. https://doi.org/10.1126/science.1257099
5. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC (1994) Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 17: 961-969. https://doi.org/10.2337/diacare.17.9.961
6. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, et al. (2003) Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 139: 802-809. https://doi.org/10.7326/0003-4819-139-10-200311180-00007
7. Chen DL, Liess C, Poljak A, Xu A, Zhang J, et al. (2015) Phenotypic characterization of insulin-resistant and insulin-sensitive obesity. J Clin Endocrinol Metab 100: 4082-4091. https://doi.org/10.1210/jc.2015-2712
8. Abbasi F, Chu JW, Lamendola C, McLaughlin T, Hayden J, et al. (2004) Discrimination between obesity and insulin resistance in the relationship with adiponectin. Diabetes 53: 585-590. https://doi.org/10.2337/diabetes.53.3.585
9. Voulgari C, Tentolouris N, Dilaveris P, Tousoulis D, Katsilambros N, et al. (2011) Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. J Am Coll Cardiol 58: 1343-1350. https://doi.org/10.1016/j.jacc.2011.04.047
10. Araújo J, Cai J, Stevens J (2019) Prevalence of optimal metabolic health in American adults: National Health and Nutrition Examination Survey 2009-2016. Metab Syndr Relat Disord 17: 46-52. https://doi.org/10.1089/met.2018.0105
11. Rosenbloom AL, Aguirre JG, Rosenfeld RG, Fielder PJ (1990) The little women of Loja -- growth hormone-receptor deficiency in an inbred population of southern Ecuador. N Engl J Med 323: 1367-1374. https://doi.org/10.1056/NEJM199011153232002
12. Thomson K, Hillier-Brown F, Todd A, McNamara C, Huijts T, et al. (2018) The effects of public health policies on health inequalities in high-income countries: an umbrella review. BMC Public Health 18: 869. https://doi.org/10.1186/s12889-018-5677-1
13. Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, et al. (2004) Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity -- a problem that is no longer restricted to minority groups. Eur J Endocrinol 151: 199-206. https://doi.org/10.1530/eje.0.1510199
14. Biltoft CA, Muir A (2009) The metabolic syndrome in children and adolescents: a clinician's guide. Adolesc Med State Art Rev 20: 109-120.
15. Gibney MJ (2019) Ultra-processed foods: definitions and policy issues. Curr Dev Nutr 3: nzy077. https://doi.org/10.1093/cdn/nzy077
16. Moubarac JC, Parra DC, Cannon G, Monteiro CA (2014) Food classification systems based on food processing: significance and implications for policies and actions: a systematic literature review and assessment. Curr Obes Rep 3: 256-272. https://doi.org/10.1007/s13679-014-0092-0
17. Juul F, Martinez-Steele E, Parekh N, Monteiro CA, Chang VW (2018) Ultra-processed food consumption and excess weight among US adults. Br J Nutr 120: 90-100. https://doi.org/10.1017/S0007114518001046
18. Monteiro CA, Moubarac JC, Levy RB, Canella DS, da Costa Louzada ML, et al. (2018) Household availability of ultra-processed foods and obesity in nineteen European countries. Public Health Nutr 21: 18-26. https://doi.org/10.1017/S1368980017001379
19. Srour B, Fezeu LK, Kesse-Guyot E, Alles B, Debras C, et al. (2020) Ultraprocessed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective cohort. JAMA Intern Med 180: 283-291. https://doi.org/10.1001/jamainternmed.2019.5942
20. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, et al. (2019) Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). BMJ 365: I1451. https://doi.org/10.1136/bmj.l1451
21. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, et al. (2018) Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ 360: k322. https://doi.org/10.1136/bmj.k322
22. Popkin BM, Adair LS, Ng SW (2012) Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev 70: 3-21. https://doi.org/10.1111/j.1753-4887.2011.00456.x
23. De Vogli R, Kouvonen A, Gimeno D (2014) The influence of market deregulation on fast food consumption and body mass index: a cross-national time series analysis. Bull World Health Organ 92: 99-107. https://doi.org/10.2471/BLT.13.120287
24. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018) A systematic analysis for the global burden of disease study 2017. Lancet 392: 1789-1858. https://doi.org/10.1016/S0140-6736(18)32279-7
25. Ziauddeen H, Farooqi IS, Fletcher PC (2012) Obesity and the brain: how convincing is the addiction model? Nat Rev Neurosci 13: 279-286. https://doi.org/10.1038/nrn3212
26. Avena NM, Gearhardt AN, Gold MS, Wang GJ, Potenza MN (2012) Tossing the baby out with the bathwater after a brief rinse? The potential downside of dismissing food addiction based on limited data. Nat Rev Neurosci 13: 514-514. https://doi.org/10.1038/nrn3212-c1
27. Wiss DA, Avena NM (2020) Food addiction, binge eating, and the role of dietary restraint: Converging evidence from animal and human studies. In Frank G, Berner L (eds) Binge eating: a transdiagnostic psychopathology. Springer, Cham, pp 193-209.
28. Moss M (2013) Salt, sugar, fat: how the food giants hooked us. Random House. NY, USA.
29. Kessler DA (2010) The end of overeating: taking control of the insatiable American appetite. Rodale, NY, USA.
30. Volkow ND, Wise RA (2005) How can drug addiction help us understand obesity? Nat Neurosci 8: 555-560. https://doi.org/10.1038/nn1452
31. Fortuna JL (2012) The obesity epidemic and food addiction: clinical similarities to drug dependence. J Psychoactive Drugs 44: 56-63. https://doi.org/10.1080/02791072.2012.662092
32. Wang GJ, Volkow ND, Thanos PK, Fowler JS (2004) Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. J Addict Dis 23: 39-53. https://doi.org/10.1300/J069v23n03_04
33. Garber AK, Lustig RH (2011) Is fast food addictive? Curr Drug Abuse Rev 4: 146-162. https://doi.org/10.2174/1874473711104030146
34. Avena NM, Bocarsly ME, Hoebel BG, Gold MS (2011) Overlaps in the nosology of substance abuse and overeating: the translational implications of "food addiction". Curr Drug Abuse Rev 4: 133-139. https://doi.org/10.2174/1874473711104030133
35. Schulte EM, Avena NM, Gearhardt AN (2015) Which foods may be addictive? The roles of processing, fat content, and glycemic load. PLoS One 10: e0117959. https://doi.org/10.1371/journal.pone.0117959
36. Richmond RL, Roberto CA, Gearhardt AN (2017) The association of addictive-like eating with food intake in children. Appetite 117: 82-90. https://doi.org/10.1016/j.appet.2017.06.002
37. Hebebrand J, Albayrak Ö, Adan R, Antel J, Dieguez C, et al. (2014) "Eating addiction", rather than "food addiction", better captures addictive-like eating behavior. Neurosci Biobehav Rev 47: 295-306. https://doi.org/10.1016/j.neubiorev.2014.08.016

38. Ruddock HK, Christiansen P, Halford JC, Hardman CA (2017) The development and validation of the Addiction-like Eating Behaviour Scale. Int J Obes 41: 1710-1717. https://doi.org/10.1038/ijo.2017.158
39. NeuroFAST consensus opinion on food addiction.
40. Pesis E (2005) The role of the anaerobic metabolites, acetaldehyde and ethanol, in fruit ripening, enhancement of fruit quality and fruit deterioration. Postharvest Biol Technol 37: 1-19. https://doi.org/10.1016/j.postharvbio.2005.03.001
41. Markus CR, Rogers PJ, Brouns F, Schepers R (2017) Eating dependence and weight gain; no human evidence for a 'sugar-addiction'model of overweight. Appetite 114: 64-72. https://doi.org/10.1016/j.appet.2017.03.024
42. Spagnuolo MS, Iossa S, Cigliano L (2020) Sweet but bitter: focus on fructose impact on brain function in rodent models. Nutrients 13: 1. https://doi.org/10.3390/nu13010001
43. Lenoir M, Serre F, Cantin L, Ahmed SH (2007) Intense sweetness surpasses cocaine reward. PLoS One 2: e698. https://doi.org/10.1371/journal.pone.0000698
44. Lustig RH, Mulligan K, Noworolski SM, Tai VW, Wen MJ, et al. (2016) Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome. Obesity 24: 453-460. https://doi.org/10.1002/oby.21371
45. Gugliucci A, Lustig RH, Caccavello R, Erkin-Cakmak A, Noworolski SM, et al. (2016) Short-term isocaloric fructose restriction lowers apoC-III levels and yields less atherogenic lipoprotein profiles in children with obesity and metabolic syndrome. Atherosclerosis 253: 171-177. https://doi.org/10.1016/j.atherosclerosis.2016.06.048
46. Schwarz JM, Noworolski SM, Erkin-Cakmak A, Korn NJ, Wen MJ, et al. (2017) Effects of dietary fructose restriction on liver fat, *de novo* lipogenesis, and insulin kinetics in children with obesity. Gastroenterology 153: 743-752. https://doi.org/10.1053/j.gastro.2017.05.043
47. Teff KL, Grudziak J, Townsend RR, Dunn TN, Grant RW, et al. (2009) Endocrine and metabolic effects of consuming fructose-and glucose-sweetened beverages with meals in obese men and women: influence of insulin resistance on plasma triglyceride responses. J Clin Endocrinol Metab 94: 1562-1569. https://doi.org/10.1210/jc.2008-2192
48. Banks WA, Coon AB, Robinson SM, Moinuddin A, Shultz JM, et al. (2004) Triglycerides induce leptin resistance at the blood-brain barrier. Diabetes 53: 1253-1260. https://doi.org/10.2337/diabetes.53.5.1253
49. Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, et al. (2006) Leptin receptor signaling in midbrain dopamine neurons regulates feeding. Neuron 51: 801-810. https://doi.org/10.1016/j.neuron.2006.08.023
50. Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, et al. (2013) Neural correlates of stress- and food cue-induced food craving in obesity: association with insulin levels. Diabetes Care 36: 394-402. https://doi.org/10.2337/dc12-1112
51. Hill JW, Williams KW, Ye C, Luo J, Balthasar N, et al. (2008) Acute effects of leptin require PI3K signaling in hypothalamic proopiomelanocortin neurons in mice. J Clin Invest 118: 1796-1805. https://doi.org/10.1172/JCI32964
52. Teff KL, Elliott SS, Tschöp M, Kieffer TJ, Rader D, et al. (2004) Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. J Clin Endocrinol Metab 89: 2963-2972. https://doi.org/10.1210/jc.2003-031855
53. Lindqvist A, Baelemans A, Erlanson-Albertsson C (2008) Effects of sucrose, glucose and fructose on peripheral and central appetite signals. Regul Pept 150: 26-32. https://doi.org/10.1016/j.regpep.2008.06.008
54. Rorabaugh JM, Stratford JM, Zahniser NR (2015) Differences in bingeing behavior and cocaine reward following intermittent access to sucrose, glucose or fructose solutions. Neuroscience 301: 213-220. https://doi.org/10.1016/j.neuroscience.2015.06.015
55. Purnell JQ, Klopfenstein BA, Stevens AA, Havel PJ, Adams SH, et al. (2011) Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans. Diabetes Obes Metab 13: 229-234. https://doi.org/10.1111/j.1463-1326.2010.01340.x
56. Page KA, Chan O, Arora J, Belfort-DeAguiar R, Dzuira J, et al. (2013) Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA 309: 63-70. https://doi.org/10.1001/jama.2012.116975
57. Wölnerhanssen BK, Meyer-Gerspach AC, Schmidt A, Zimak N, Peterli R, et al. (2015) Dissociable behavioral, physiological and neural effects of acute glucose and fructose ingestion: a pilot study. PLoS One 10: e0130280. https://doi.org/10.1371/journal.pone.0130280
58. Jastreboff AM, Sinha R, Arora J, Giannini C, Kubat J, et al. (2016) Altered brain response to drinking glucose and fructose in obese adolescents. Diabetes 65: 1929-1939. https://doi.org/10.2337/db15-1216
59. Stice E, Burger KS, Yokum S (2013) Relative ability of fat and sugar tastes to activate reward, gustatory, and somatosensory regions. Am J Clin Nutr 98: 1377-1384. https://doi.org/10.3945/ajcn.113.069443
60. Diagnostic and statistical manual of mental disorders (DSM-5-TR). [https://www.psychiatry.org/psychiatrists/practice/dsm] [Accessed on May 09, 2024]
61. Gordon EL, Ariel-Donges AH, Bauman V, Merlo LJ (2018) What is the evidence for "food addiction?" A systematic review. Nutrients 10: 477. https://doi.org/10.3390/nu10040477
62. Lustig RH (2013) Fructose: it's "alcohol without the buzz". Adv Nutr 4: 226-235. https://doi.org/10.3945/an.112.002998
63. Ng SW, Slining MM, Popkin BM (2012) Use of caloric and noncaloric sweeteners in US consumer packaged foods, 2005-2009. J Acad Nutr Diet 112: 1828-1834. https://doi.org/10.1016/j.jand.2012.07.009
64. Andreyeva T, Long MW, Brownell KD (2010) The impact of food prices on consumption: a systematic review of research on the price elasticity of demand for food. Am J Public Health 100: 216-222. https://doi.org/10.2105/AJPH.2008.151415
65. Wayne GF, Carpenter CM (2009) Tobacco industry manipulation of nicotine dosing. In Henningfield JE, London ED, Pogun S (eds) Nicotine psychopharmacology. Handbook of experimental pharmacology. Springer, Berlin, pp 457-485.
66. Why coffee shortages won't change the price of your Frappuccino. [https://psmag.com/economics/coffee-shortages-wont-change-price-frappuccino-87107] [Accessed on May 09, 2024]
67. Colchero MA, Rivera-Dommarco J, Popkin BM, Ng SW (2017) In Mexico, evidence of sustained consumer response two years after implementing a sugar-sweetened beverage tax. Health Affairs 36: 564-571. https://doi.org/10.1377/hlthaff.2016.1231
68. Lustig RH (2010) Fructose: metabolic, hedonic, and societal parallels with ethanol. J Am Diet Assoc 110: 1307-1321. https://doi.org/10.1016/j.jada.2010.06.008
69. Onishi Y, Honda M, Ogihara T, Sakoda H, Anai M, et al. (2003) Ethanol feeding induces insulin resistance with enhanced PI 3-kinase activation. Biochem Biophys Res Commun 303: 788-794. https://doi.org/10.1016/S0006-291X(03)00407-8
70. Softic S, Cohen DE, Kahn CR (2016) Role of dietary fructose and hepatic de novo lipogenesis in fatty liver disease. Dig Dis Sci 61: 1282-1293. https://doi.org/10.1007/s10620-016-4054-0
71. Stanhope KL, Schwarz JM, Havel PJ (2013) Adverse metabolic effects of dietary fructose: results from the recent epidemiological, clinical, and mechanistic studies. Curr Opin Lipidol 24: 198-206. https://doi.org/10.1097/MOL.0b013e3283613bca
72. Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH (2010) The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. Nat Rev Gastroenterol Hepatol 7: 251-264. https://doi.org/10.1038/nrgastro.2010.41
73. Dills Jr WL (1993) Protein fructosylation: fructose and the Maillard reaction. Am J Clin Nutr 58: 779S-787S. https://doi.org/10.1093/ajcn/58.5.779S
74. Bremer AA, Mietus-Snyder M, Lustig RH (2012) Toward a unifying hypothesis of metabolic syndrome. Pediatrics 129: 557-570. https://doi.org/10.1542/peds.2011-2912
75. Mortera RR, Bains Y, Gugliucci A (2019) Fructose at the crossroads of the metabolic syndrome and obesity epidemics. Front Biosci 24: 186-211. https://doi.org/10.2741/4713
76. Rodríguez-Mortera R, Luevano-Contreras C, Solorio-Meza S, Caccavello R, Bains Y, et al. (2018) Higher D-lactate levels are associated with higher prevalence of small dense low-density lipoprotein in obese adolescents. Clin Chem Lab Med 56: 1100-1108. https://doi.org/10.1515/cclm-2017-0733
77. Erkin-Cakmak A, Bains Y, Caccavello R, Noworolski SM, Schwarz JM, et al. (2019) Isocaloric fructose restriction reduces serum d-lactate concentration in children with obesity and metabolic syndrome. J Clin Endocrinol Metab 104: 3003-3011. https://doi.org/10.1210/jc.2018-02772
78. van Buul VJ, Tappy L, Brouns FJ (2014) Misconceptions about fructose-containing sugars and their role in the obesity epidemic. Nutr Res Rev 27: 119-130. https://doi.org/10.1017/S0954422414000067
79. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB (2011) Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 364: 2392-2404. https://doi.org/10.1056/NEJMoa1014296

80. Te Morenga L, Mallard S, Mann J (2013) Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. BMJ 346. https://doi.org/10.1136/bmj.e7492

81. Bentley RA, Ruck DJ, Fouts HN (2020) US obesity as delayed effect of excess sugar. Econ Hum Biol 36: 100818. https://doi.org/10.1016/j.ehb.2019.100818

82. Gulati S, Misra A (2014) Sugar intake, obesity, and diabetes in India. Nutrients 6: 5955-5974. https://doi.org/10.3390/nu6125955

83. Deshpande G, Mapanga RF, Essop MF (2017) Frequent sugar-sweetened beverage consumption and the onset of cardiometabolic diseases: cause for concern? J Endocr Soc 1: 1372-1385. https://doi.org/10.1210/js.2017-00262

84. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010) Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation 121: 1356-1364. https://doi.org/10.1161/CIRCULATIONAHA.109.876185

85. Bray GA (2013) Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. Adv Nutr 4: 220-225. https://doi.org/10.3945/an.112.002816

86. Ruff JS, Suchy AK, Hugentobler SA, Sosa MM, Schwartz BL, et al. (2013) Human-relevant levels of added sugar consumption increase female mortality and lower male fitness in mice. Nat Commun 4: 2245. https://doi.org/10.1038/ncomms3245

87. Bremer AA, Stanhope KL, Graham JL, Cummings BP, Wang W, et al. (2011) Fructose-fed rhesus monkeys: a nonhuman primate model of insulin resistance, metabolic syndrome, and type 2 diabetes. Clin Transl Sci 4: 243-252. https://doi.org/10.1111/j.1752-8062.2011.00298.x

88. InterAct Consortium (2013) Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct. Diabetologia 56: 1520-1530. https://doi.org/10.1007/s00125-013-2899-8

89. Rodríguez LA, Madsen KA, Cotterman C, Lustig RH (2016) Added sugar intake and metabolic syndrome in US adolescents: cross-sectional analysis of the National Health and Nutrition Examination Survey 2005-2012. Public Health Nutr 19: 2424-2434. https://doi.org/10.1017/S1368980016000057

90. Castro V (2017) Pure, white and deadly… expensive: a bitter sweetness in health care expenditure. Health Econ 26: 1644-1666. https://doi.org/10.1002/hec.3462

91. Barker FG (2009) What is medical evidence? Clin Neurosurg 56: 24-33.

92. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, et al. (2009) Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 119: 1322-1334. https://doi.org/10.1172/JCI37385

93. Maersk M, Belza A, Stødkilde-Jørgensen H, Ringgaard S, Chabanova E, et al. (2012) Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. Am J Clin Nutr 95: 283-289. https://doi.org/10.3945/ajcn.111.022533

94. Bray GA (2007) How bad is fructose? Am J Clin Nutr 86: 895-896. https://doi.org/10.1093/ajcn/86.4.895

95. Vos MB, Kimmons JE, Gillespie C, Welsh J, Blanck HM (2008) Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. Medscape J Med 10: 160.

96. Karkee R (2014) Public health education in South Asia: a basis for structuring a master degree course. Front Public Health 2: 102415. https://doi.org/10.3389/fpubh.2014.00088

97. Price trends are similar for fruits, vegetables, and snack foods.

98. McGinnis JM, Gootman JA, Kraak VI (2006) Food marketing to children and youth: threat or opportunity? The National Academy Press, New York, USA.

99. Moodie R, Stuckler D, Monteiro C, Sheron N, Neal B, et al. (2013) Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries. Lancet 381: 670-679. https://doi.org/10.1016/S0140-6736(12)62089-3

100. Nutrition Labeling and Education Act (NLEA) Requirements. [https://www.fda.gov/nutrition-labeling-and-education-act-nlea-requirements-attachment-1] [Accessed on May 10, 2024]

101. Defusing the health care time bomb. [https://www.sfgate.com/opinion/article/Defusing-the-health-care-time-bomb-4168827.php] [Accessed on May 10, 2024]

102. Babor T, Caetano R, Casswell S, Edwards G, Giesbrecht N, et al. (2010) Alcohol: no ordinary commodity: research and public policy. Oxford University Press, UK.

103. Lustig RH, Schmidt LA, Brindis CD (2012) The toxic truth about sugar. Nature 482: 27-29. https://doi.org/10.1038/482027a

104. Lee Y, Mozaffarian D, Sy S, Liu J, Wilde PE, et al. (2020) Health impact and cost-effectiveness of volume, tiered, and absolute sugar content sugar-sweetened beverage tax policies in the United States: a microsimulation study. Circulation 142: 523-534. https://doi.org/10.1161/CIRCULATIONAHA.119.042956

105. How farm subsidies affect the U.S. economy. [https://www.thebalancemoney.com/farm-subsidies-4173885] [Accessed on May 10, 2024]

106. Alston JM, Sumner DA, Vosti SA (2008) Farm subsidies and obesity in the United States: national evidence and international comparisons. Food Policy 33: 470-479. https://doi.org/10.1016/j.foodpol.2008.05.008

107. Basu S, Yoffe P, Hills N, Lustig RH (2013) The relationship of sugar to population-level diabetes prevalence: an econometric analysis of repeated cross-sectional data. PLoS One 8: e57873. https://doi.org/10.1371/journal.pone.0057873