



## **A narrative review of the effects of sugar-sweetened beverages on human health: A key global health issue**

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**Submitted: 10 January 2020. Accepted: 12 February 2020. Published: 3 March 2020.**

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### **ABSTRACT**

The provision of healthy and safe food is vital for human health, and the addition of unnecessary sugars in foodstuffs is an important global issue, leading to multiple long- and short-term health issues and spiraling costs for individuals and governments alike. The negative effect of excess sugar consumption contributes to adverse health conditions, including obesity, type 2 diabetes, and poor oral health in both high and low resource settings. A key plank of governmental and health promotion bodies' nutritional guidance is to raise public awareness of "hidden" sugars, salt, and fats, such as found in processed foods and sugar-sweetened beverages (SSBs), and guide individuals to reduce their consumption. This rapid narrative review brings together some of the key issues identified in the literature around the

consumption of SSBs, including patterns of consumption, the general impact on human health and nutrition, specific effects on oral health and the oral microbiome, and strategies to address over-consumption. The range of long-term adverse effects on health is often misunderstood or unknown by the public. However, some strategies have succeeded in reducing the consumption of SSBs, including public health strategies and interventions and the imposition of taxes or levies, and this article makes recommendations for action.

**Keywords:** *effects, sugar-sweetened beverages, SSBs, consumption, tax, diabetes, cardiovascular diseases, weight gain and obesity, cancer, nutrition and diet quality, nutrition, mortality, morbidity, global health*

## INTRODUCTION

The World Health Organization (WHO) defines a healthy diet as including a diverse mix of foods and nutrients, including “staples like cereals (wheat, barley, rye, maize, or rice) or starchy tubers or roots (potato, yam, taro, or cassava); legumes (lentils and beans); fruit and vegetables; foods from animal sources (meat, fish, eggs, and milk).”<sup>1</sup> Similarly, many governments and health promotion bodies have produced nutritional guidelines emphasizing the need for people of all ages to have a balanced diet, with a mix of fresh vegetables and fruit, proteins such as meat, fish, soya, legumes, or pulses, vegetable oils, complex carbohydrates, milk and dairy products, and clean water.<sup>2,3</sup> The negative effects of excess sugar consumption are widely known around the world and contribute toward increasing health conditions (including obesity, type 2 diabetes, and poor oral health) in both high- and low-resource settings.<sup>4–12</sup> While the WHO recommends limiting added sugars to less than 10% of an individual’s total calorie consumption as part of a healthy diet and added-sugar intake to less than 5% (approximately 25 g [6 teaspoons] per day) of the total calorie consumption is healthier.<sup>13,14</sup> A key plank of health education guidance is to raise public awareness of “hidden” sugars, salt, and fats, found in processed foods and sugar-sweetened beverages (SSBs), and support individuals to change behaviors to minimize these in

their diets.<sup>1</sup> Alongside health education, multiple recent studies have found that increased taxation on SSBs improved overall health status, particularly oral health.<sup>15–19</sup> Oral diseases are the most frequently suffered non-communicable diseases (NCDs), causing morbidity and, in some cases, mortality in all age groups across the world.<sup>20</sup> The 2016 Global Burden of Disease Study estimated that around 50% of the world’s population (3.58 billion) has dental caries.<sup>20</sup> Oral health is not only affected by over-consumption of sugars but also by tobacco and alcohol use and poor diet, all of which are risk factors for the four leading NCDs: cardiovascular diseases (CVDs), cancer, chronic respiratory diseases, and diabetes. The complex interaction of various risk factors on health is not yet fully understood, but there are links, for example, an increase in type 2 diabetes is linked to an increase in periodontitis.<sup>20–22</sup>

However, certain strategies are making headway in tackling the impact of SSBs on human health. For example, an Australian study showed that a 20% increase in tax on SSBs saved A\$666 million from the healthcare budget by preventing or reducing 3.9 million decayed, missing, and filled teeth (DMFT).<sup>14</sup> Another Dutch study has found that a 20% levy on SSBs resulted in an average of 2.13 (95% uncertainty interval [UI] 2.12–2.13) caries-free tooth years per person, and on a population level, prevention of 1,030,163 (95% UI 1,027,903–1,032,423) decayed and lost teeth. From

the cost-benefit perspective, the implementation of new levy on SSBs cost €37.3 million but generated an additional €3.49 billion in revenue and saved €159.01 million (95% UI 158.67–159.35) in health-care expenditure on dental care.<sup>2</sup>

This rapid narrative review focuses specifically on SSBs and the effect of their consumption on human health, bringing together some of the key issues identified in literature, highlighting that this is a global health concern and noting strategies employed to reduce consumption of SSBs. Multiple studies have reported that the consumption of SSBs leads to several adverse health conditions such as obesity, type 2 diabetes mellitus, hypertension, and hypertriglyceridemia,<sup>23–25</sup> and, therefore, it has become a major public health issue. This article considers the effects of consuming SSBs on general health and nutrition, including the oral microbiome and oral health. The key issues identified include patterns of consumption of SSBs, the general impact on human health and nutrition, specific effects on oral health and the oral microbiome, and strategies to address over-consumption.

## MATERIALS AND METHODS

This rapid narrative review aimed to identify key topical issues, concerns, and strategies, rather than provide a comprehensive systematic review and meta-analysis. This study was conducted between March and June 2019. EBSCO, PubMed, and SCOPUS databases were searched, using the following search terms: “effects, sugar-sweetened beverages, consumption, tax, human oral microbiome, oral health, antibiotics, antimicrobials, microbial resistance, mortality, morbidity, increased healthcare costs, global health, and importance.” Google and Google Scholar were also used to identify other freely available literature. Relevant journals identified were hand-searched, and references were scanned to identify further articles.

## SUGAR-SWEETENED BEVERAGES: DEFINITIONS AND CONSUMPTION

The number and variety of SSBs have grown over the last 20 years, and they are defined in different ways. Three definitions, representative of the wider definitions of SSBs, are set out here. The Department of Health, US State of Rhode Island, defines SSBs as “drinks with added sugar including non-diet soft drinks/sodas, flavored juice drinks, sports drinks, sweetened tea, coffee drinks, energy drinks, and electrolyte replacement drinks.”<sup>26</sup> The WHO defines free sugar as “all monosaccharides and disaccharides added to foods by the manufacturer, cook, or consumer, plus sugars naturally present in honey, syrups, and fruit juices.”<sup>27</sup> SSBs contain a very high amount of sugar,<sup>26,28</sup> including highly cleaned crystalline white sugar, high-fructose corn syrup (HFCS), and other high-energy-yielding sugary compounds. The Cancer Council of Australia defines SSBs as “all non-alcoholic water-based beverages with added sugar, including sugar-sweetened soft drinks and flavored mineral waters, fortified waters, energy and electrolyte drinks, fruit and vegetable drinks, and cordials. This term does not include milk-based products, 100% fruit juice, or non-sugar sweetened beverages.”<sup>29</sup> Finally, the US Departments of Health and Human Services and Agriculture take the view that SSBs are any liquids that are sweetened with various forms of added sugars such as brown sugar, corn sweetener, corn syrup, dextrose, fructose, glucose, HFCS, honey, lactose, malt syrup, maltose, molasses, raw sugar, and sucrose.<sup>30</sup> Examples include regular soda (not sugar-free), fruit drinks, sports drinks, energy drinks, sweetened waters, and coffee and tea beverages with added sugars.<sup>30</sup>

The overall global consumption of SSBs is very high and increasing. For example, a study conducted in the rural areas of South Africa has found that the consumption of SSBs increased by

two-fold among men over 5 years,<sup>31</sup> and another national cross-sectional study of children aged  $\geq 2$ –9 years in the United States has found that consumption of SSBs increased by 135% between 1977 and 2001.<sup>32</sup> In terms of overall consumption, a systematic review and meta-analysis comprising 193 national or sub-national studies in 187 countries, including over half of the world's population and reflecting typical diet patterns, concluded that globally a high amount (8-oz. servings/day) of SSBs are consumed.<sup>33</sup> However, there are differences between countries and regions, and this study identified that consumption of SSBs was the highest in the Caribbean countries (1.9, 95%CI: 1.2, 3.0 servings/day); fruit juice intake was the highest in Australia and New Zealand ranged from 0.66 [(95%UI: 0.36, 1.13) servings/day to 0.013 (95%UI: 0.011, 0.017) servings/day]; and milk consumption was the highest in Central Latin America (1.06, 95%UI: 0.68, 1.59 servings/day). Consumption of SSBs, fruit juice, and milk was the lowest in East Asia and Oceania.<sup>33</sup> Internationally and within regions, SSBs' consumption is the highest among young people; fruit juice drinking had little correlation with age, and milk consumption was the highest in older people.<sup>33</sup> These findings are supported by other studies. For example, another global study found that children and young people have a higher consumption of SSBs,<sup>34</sup> and a US study found that children and adolescents obtained 10–15% of their total calorie consumption from SSBs and 100% fruit juices.<sup>35</sup> In some countries, sugar is added to food and drinks; for example, a recent study found that in the United States, 74% of the 85,451 available palatable foodstuffs were supplemented with extra sugars.<sup>36</sup>

While the consumption of SSBs is high around the world, their consumption, and the subsequent effect on health, varies, and is dependent on a complex interaction between familial factors, ethnicity, lower socioeconomic status, income, access to education, and level of occupation.<sup>37,38</sup> A cross-sectional study utilizing data

from the population-based “Water Campaign” study aimed to assess the correlation between familial factors, ethnic background, and children's SSBs' utilization and found that a child's age, parents' emotional standing, child-rearing practices, and parental role-modeling were strongly associated with the child's SSBs consumption.<sup>39</sup> More specifically, the accessibility of SSBs at home and school, parent's consumption of SSBs, and their approach to diet were strongly related to a child's SSBs daily intake, with ethnic variations ranging from 8.7% for children of Moroccan or Turkish ethnicity to 44.4% for Dutch children.<sup>39</sup> A survey of 990 parents and their adolescent children found that 31% of adolescents had SSBs  $\geq 1$  time/day, and 43.2% of parents consumed SSBs  $\geq 2$  times/day. The survey further found that the children's consumption was strongly related to their parent's SSBs intake and not their knowledge of health risks, with the adolescents' SSBs consumption of  $\geq 1$  time/day being related to their parents' consumption of  $\geq 2$  times/day (adjusted odds ratio [aOR] = 3.30; 95% confidence interval [CI] = 1.62–6.74).<sup>40</sup> The knowledge of adolescents and parents about the link between SSBs consumption and health issues ranged from 60.7 to 80.4%: in terms of weight increase, 75.0 and 80.4% respectively; diabetes, 60.7 and 71.4% respectively; and dental caries, 77.5 and 72.9% respectively.<sup>40</sup> There is also a strong link between people's place of residence and predominant lifestyle factors. For example, the aOR of drinking SSBs  $\geq 1$  time/day was higher among Hispanics (aOR = 1.65) than the US-born non-Hispanic whites<sup>41</sup>; however, comparing individuals who had lived in the United States for  $< 5$  years, the adjusted odds of drinking SSBs  $\geq 1$  time/day was higher among adults who had lived in the United States for 5 to  $< 10$  years (aOR = 2.72), individuals who had lived in the United States for 10 to  $< 15$  years (aOR = 2.90), and individuals who had lived in the United States for  $\geq 15$  years (aOR = 2.41).<sup>41</sup>

## SUGAR AND HUMAN HEALTH

Sugar is one of the main determinants of poor health, although public understanding of the long-term adverse effects of sugars (both overt and hidden) remains poor. Over-consumption of sugar causes many public health issues, including diabetes, obesity, hypertension, and chronic kidney diseases.<sup>42</sup> Humans have consumed an increasingly higher amount of sugar as part of their diet over the last 160 years.<sup>43</sup> The amount of sugar intake has tripled because of the promotion of fast (junk) food, processed food, and SSBs.<sup>42</sup> Very high amounts of sugar are found in SSBs, sugary snacks, candy, chocolate, sweets, and even in children's milk,<sup>44,45</sup> with food manufacturers often adding 10 categories of sugars into factory-made foods.<sup>42</sup> These added sugars include glucose, dextrose, fructose, HFCS, everyday sugar (sucrose), malt sugar (maltose), maltodextrin, and sugars found in honey, syrups, fruit juices, and fruit juice concentrates.<sup>42</sup> The food industry uses approximately 56 different names for sugar and consumers therefore often do not realize that many foods include added sugars.<sup>42,46,47</sup> This is particularly true for highly manipulated, "ultra-processed" foods (described in the NOVA [a name, not an acronym] Classification as Class 4), including SSBs, sweet and savory snacks, processed meat products, ice-cream, and many frozen ready meals, all of which include high levels of sugars, preservatives, saturated fats, and salts.<sup>48</sup>

### *Sugar-Sweetened Beverages and their Effects on Health*

SSBs are widely marketed and sold all over the world, but they are ultra-processed and provide a devastatingly high sugar load that human physiology struggles to handle, with many adverse metabolic consequences.<sup>49</sup> Sugar (like alcohol) acts more like a drug than a food, and every drug has the potential to cause harm as opposed to benefit, especially when taken in excess.<sup>50</sup> A drug is described as "a chemical substance used in the

treatment, cure, prevention, or diagnosis of a disease, or used to otherwise enhance physical or mental well-being."<sup>51</sup> The US drug authority defines a drug as "(i) any substance recognized in the official pharmacopeia or formulary of the nation; (ii) any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals; (iii) any article, other than food, intended to affect the structure or any function of the body of humans or other animals; (iv) any substance intended for use as a component of such a drug, but not a device or a part of a device."<sup>51</sup> Ingesting high amounts of sugar via SSBs and ultra-processed foods may lead to overdose-related adverse reactions and harm, particularly because sugar generates reactive oxygen-carbon (ROC).<sup>52–54</sup> SSBs are high in sugar but do not provide other nutrients such as fiber, vitamins, minerals, and other essential nutrients from plant sources that neutralize oxidative stress-induced ROC.<sup>55–58</sup> The high amount of sugar in SSBs generates much more ROC than the available antioxidant level, which could lead to atherosclerosis, hypertension, peripheral vascular disease, coronary artery disease, cardiomyopathy, heart failure, and cardiac arrhythmias.<sup>58</sup>

In addition to these general health implications from sugar, other harmful effects have been reported. One review article has reported dependable evidence for the adverse effects of SSBs on children's and teenagers' health.<sup>4</sup> This study revealed that weight gain and obesity, dental caries, insulin resistance, and caffeine-associated effects are often observed with the consumption of SSBs.<sup>4</sup> Caffeine is well-known for its addictive and dependence potential and can increase the consumption of SSBs containing caffeine in comparison to non-caffeinated SSBs.<sup>59</sup> High consumption of caffeine can lead to sleep disorders, headaches, stress, depressive symptoms, and suicidal ideation, and can increase the possibility of cigarette, marijuana, and drug addiction.<sup>4</sup>

Aside from the side-effects of caffeine, multiple systematic reviews and meta-analyses have found a positive correlation between the consumption of SSBs (particularly those high in calories) and weight gain, obesity, and metabolic syndrome.<sup>5–12</sup> The proportion of SSBs as part of overall liquid intake also influences health. A high intake of SSBs lowers the consumption of milk, calcium ( $\text{Ca}^{2+}$ ), and essential nutrients. This increases the risk of medical complications, including diabetes.<sup>6,9,12,33,60,61</sup> For example, an 8-year prospective research study of 91,249 nurses confirmed a statistically significant ( $P \leq 0.001$ ) relationship between an excessive intake of SSBs (more than three cans of cola or 450 calories per week) with the development of obesity and type 2 diabetes.<sup>61,62</sup> Another study of diabetic adults found that consuming SSBs  $\geq 1$  time/day was more prevalent among individuals who had shorter span of diabetes ( $\leq 5$  years: Prevalence Ratio [PR] = 1.47; 6–10 years: PR = 1.33 vs.  $\geq 11$  years), self-checked their glucose less often ( $\geq 0$  to  $< 1$  time/day: PR = 1.69;  $\geq 1$  to  $< 3$  times/day: PR = 1.43 vs.  $\geq 3$  times/day), and had not undertaken a self-administration of diabetes course (PR = 1.25 vs. yes).<sup>63</sup>

High consumption of SSBs can also lead to a reduction of bone mineral compactness and subsequent fractures.<sup>64,65</sup> For example, a cross-sectional study of 460 physically active teenage girls has found a high correlation (Odds Ratio [OR] = 4.94; 95% CI: 1.79, 13.62;  $P = 0.002$ ) between bone fractures and SSBs intake.<sup>64</sup> Another study amongst teenage girls has reported that the frequent consumption of SSBs was negatively associated with bone mineral content (BMC) (Pearson correlation coefficient,  $r = -0.256$ ,  $P = 0.03$ ) and decrease in  $\text{Ca}^{2+}$  ( $r = -0.227$ ,  $P = 0.05$ ).<sup>64</sup> One explanation for this is that because drinking SSBs is associated with reduced milk consumption in both sexes (boys:  $r = -0.343$ ,  $P = 0.01$ ; girls:  $r = -0.244$ ,  $P = 0.08$ ),<sup>65</sup> their overall diets might be lacking in  $\text{Ca}^{2+}$  and vitamins, which could contribute to poor bone health.

### ***The Role of Added Sugars in Appetite Regulation***

As discussed above, the high consumption of SSBs can lead to dietary imbalances with adverse health consequences, but some drinks may also more directly affect the appetite for more nutritious foods. For example, a randomized crossover study has found that temporary food intake (FI) was reduced after drinking chocolate milk (15%;  $P < 0.001$ ) and cola (11%;  $P = 0.02$ ) contrasted with water control.<sup>66</sup> However, the total calorie consumption (beverage [kcal] + test meal [kcal]) was not influenced by the beverage category. Chocolate milk and cola moderated food intake in adolescent females, although 100% (unfortified) fruit juice did not, while the aggregate food intake did not alter between different plan treatments to minimize SSBs.<sup>66</sup> Another study amongst adolescent males demonstrated a reduction in food intake ( $P < 0.001$ ) after cola ( $940 \pm 46$  kcal) and chocolate milk ( $878 \pm 41$  kcal) contrasted with water control ( $1,048 \pm 35$  kcal) and after chocolate milk contrasted with an organic drink product ( $1,005 \pm 44$  kcal). The aggregate food intake after the organic product drink was higher than water control ( $1,159 \pm 44$  vs.  $1,048 \pm 35$  kcal;  $P = 0.03$ ).<sup>67</sup> Normal appetite was not influenced by the treatment. However, the cola consumption led to a higher total food intake ( $P = 0.04$ ) and a reduction in nutrients ( $P = 0.004$ ) compared to the organic drink product.<sup>67</sup> In this study, chocolate milk and cola reduced the next-supper food intake by 60 min, while drinks made from natural products expanded the aggregate food intake (refreshment + next meal) by more than 60 min, concluding that drink synthesis is a significant determinant of reduction in food intake.<sup>67</sup>

### ***Addictive Properties of Sugar and Sugar-Sweetened Beverages***

As described above, sugar has many properties of a drug, and multiple studies have reported that people could become addicted to sugar in a similar way as becoming addicted to cocaine,

nicotine, alcohol, tobacco, or caffeine.<sup>68–73</sup> The attraction of sugar is therefore much more than its sweet taste.<sup>42,74</sup> The American Psychiatric Association defines addiction as “a complex condition, a brain disease that is manifested by compulsive substance use despite harmful consequence.”<sup>72</sup> An addicted person is highly motivated to consume a “certain substance(s), such as alcohol or drugs, to the point that it takes over their life.”<sup>72</sup> Addiction includes both psychological and physiological needs, and therefore any intervention has to focus on these aspects, exploring the underpinning issues that lead someone to over-consume substances detrimental to their health as well as helping them find ways to compensate for the physiological need. The term “addiction” is frequently used interchangeably with the word “dependence.”<sup>73,74</sup> For example, drug dependence is categorized by obsessive, from time to time irrepensible, activities that happen at the cost of other events and strengthen with frequent access to the substance of abuse.<sup>68</sup> The addict develops physical dependence as soon as the neurons become accustomed to repetitive drug exposure and then starts to work only in the presence of the substance of abuse. If the substance of abuse is stopped suddenly, many physiological responses arise, which could be mild to life-threatening.<sup>75</sup> Sugar releases physiological endogenous opioids known as endorphins, which act to both relieve pain and promote short-term euphoria (a “sugar high”).<sup>76,77</sup> As long-term over-consumption of sugars (e.g., of SSBs and industry-processed foods with high sugar content) leads to neurochemical adaptations that imitate the properties of opiates, this could lead to both psychological and physical dependence, and withdrawal signs and symptoms among people who stop or reduce their sugar consumption, particularly if this is sudden.<sup>68,78,79</sup> For example, one study has reported that when young people stopped consumption of SSBs for 3 days, they developed a strong desire for SSBs, complained of headaches, reported a reduction in inspiration, happiness, and

satisfaction, a failure to focus, and a lack of overall well-being.<sup>80</sup>

As with other addictions, although many people know well that consuming high sugary foods and drinks is unhealthy and could lead to life-threatening diseases,<sup>10,34,38,81–83</sup> it can be difficult for them to stop. The addictive properties of sugar, much of which is “hidden” in processed foods and SSBs, mean that its impact on health is not often directly understood or addressed by consumers in spite of the evidence available. As we have noted, consumption of SSBs with high sugar content could contribute to obesity, type 2 diabetes, CVDs, and cardiometabolic diseases,<sup>84</sup> and we now explore some of the more life-threatening effects of long-term and/or high consumption of SSBs.

### ***SSBs and Cardiovascular Diseases***

Multiple studies have reported that the frequent heavy drinking of SSBs (more than three cans of cola or 450 calories per week)<sup>13</sup> is correlated with coronary heart disease (CHD) and adverse deviations in lipids, inflammatory factors, and leptin in both sexes.<sup>85–87</sup> A US study involving 4,443 respondents has found a moderate positive correlation between the consumption of SSBs and dietary sodium intake ( $r = 0.35$ ,  $P = 0.001$ ).<sup>88</sup> Using an unadjusted regression model, this study found that higher SSBs consumption was associated with a 12% increased dietary sodium intake, specifically a 45-g/day consumption of SSBs was associated with an additional 390-mg sodium (Na)/day (1-g salt/day;  $P = 0.001$ ).<sup>88</sup> Another study in Australia reported that a regular intake of SSBs was positively correlated with salt intake. ( $r = 0.35$ ,  $P = 0.001$ ), that each additional 1 g/day of salt was associated with a 30-g/day higher consumption of SSBs, and that salt intake alone is responsible for 11% increase in consumption of SSBs.<sup>89</sup> Both these studies recommend that lower consumption of SSBs contributes to the recognized

benefits of lowering salt intake, including blood pressure control and childhood obesity risk.<sup>88,89</sup>

A systematic review, comprising 12 studies involving 409,707 participants, found that a continuous longstanding intake of SSBs could lead to the development of hypertension and related CVDs.<sup>90</sup> This finding is corroborated by other studies, reporting that a high consumption of SSBs (more than three cans of cola or 450 calories per week)<sup>13</sup> correlates with the development and prevalence of hypertension,<sup>91</sup> with a high low-density lipoprotein (LDL)-cholesterol level,<sup>92</sup> and a low level of high-density lipoprotein ( $P < 0.0001$ ).<sup>93</sup> Another US study, conducted among 3,683 CHD patients over 22 years of follow-up, has reported that those who consumed the lowest (Q1) quartile of SSBs had a 20% greater relative risk of CHD than those in the highest (Q4) quartile (RR = 1.20, 95% CI: 1.09, 1.33,  $P < 0.01$  [Relative Risk (RR) = 1.20, 95% CI: 1.09, 1.33,  $P < 0.01$ ]) after adjusting for age, smoking, physical activity, alcohol, multi-vitamins, family history, diet quality, energy intake, body mass index (BMI), pre-enrollment weight change, and dieting.<sup>85</sup> Another national US representative cross-sectional study of 4,867 young people aged between 12 and 18 years reported that consuming more SSBs was significantly ( $P = 0.01$ ) correlated statistically to an increasing serum uric acid and systolic blood pressure ( $P = 0.03$ ) but not related to obesity.<sup>94</sup> The consumption of SSBs is also correlated with an increased danger of “total mortality; pooled hazard ratios (95% CI) across categories (<1/month, 1–4/month, 2–6/week, 1–<2/day, and  $\geq 2$ /day) were 1.00 (reference), 1.01 (0.98, 1.04), 1.06 (1.03, 1.09), 1.14 (1.09, 1.19), and 1.21 (1.13, 1.28;  $P < 0.0001$ ).”<sup>94</sup> This study also reported correlation for “CVD mortality (hazard ratio comparing extreme categories was 1.31 (95% CL, 1.15, 1.50),  $P < 0.0001$ ) and cancer mortality (1.16 [1.04, 1.29],  $P = 0.0004$ ).”<sup>94</sup>

Artificial sweeteners, such as aspartame, sucralose, and saccharine, are generally used as

sugar substitutes to reduce calories in many types of SSBs and are often seen as a better alternative.<sup>95</sup> However, the consumption of artificially sweetened beverages is also correlated with total and CVD-related death rates when high amounts of SSBs are ingested.<sup>94</sup> The ingestion of artificial sweeteners has been linked to adverse effects such as cancer, weight gain, metabolic disorders, prematurity, bronchial asthma, type 2 diabetes, and negative modification of gut microbiota activity.<sup>96–98</sup>

Although human food does not naturally contain high amounts of fructose, fructose-containing sugars (sucrose and high fructose corn syrup) are often added to SSBs and other factory-processed foods, primarily so that they taste sweeter and thus more palatable to modern western tastes.<sup>84</sup> SSBs are a large part of this picture, with one study’s findings revealed that from 2011 to 2012, at least 46.3% of North American adult population consumed SSBs daily that yielded 213.0 kcal/day<sup>99</sup>; another study revealed that 54 kcal/day out of 83 kcal/day was obtained from SSBs.<sup>100</sup> In the United States, on average, one can of SSBs provides 150 kcal and 40–50-g sugar in the form of HFCS, which corresponds to 10 teaspoons of sucrose.<sup>101</sup> The consumption of SSBs in the United States in 24 years (1977–2001) has increased by 135%, which increased calorie intake by 83 kcal/day.<sup>32,100</sup>

### **SSBs and Fertility**

The consumption of SSBs could also affect sexual health and fertility. Pre-pubescent girls who have a heavy consumption of SSBs reach menarche much earlier than girls who have low consumption,<sup>98,102</sup> and pre-menarchal girls who consume more than 1.5 portions of SSBs daily have a 24% (95% CI: 13, 36%;  $P < 0.001$ ) higher possibility of starting their menstrual periods in the next month than girls who consume less than or equal to two servings of SSBs weekly.<sup>102</sup> Men’s SSBs consumption also affects their sexual health.<sup>103</sup> Men who consume greater than or equal to 1.3 servings of SSBs per day have 9.8% (95% CI:



1.9, 17.8) units poorer “progressive sperm motility” than men who consume less than 0.2 serving of SSBs per day ( $P = 0.03$ ).<sup>80</sup> This correlation was statistically significant ( $P = 0.005$ ) for sturdier and lean men, but no significant correlation ( $P = 0.98$ ) was observed in obese men.<sup>80</sup> Another study in US men aged 20–39 years has reported that a high SSBs intake is strongly correlated with low serum testosterone.<sup>104</sup> In this study, multivariate logistic regression found that the OR of low testosterone was significantly higher statistically with a high rate of SSB drinks in Q4 ( $\geq 442$  kcal/day vs. male participants in Q1,  $\leq 137$  kcal/day; aOR = 2.29,  $P = 0.041$ ). Secondary risks of high consumption of SSBs also exist; for example, high consumption of SSBs without corresponding exercise could lead to obesity and high BMI; high BMI is in itself a risk factor for a low level of testosterone. It was found in one study that after adjusting for possible confounding variables, research respondents with  $BMI \geq 25$  kg/m<sup>2</sup> had a lower testosterone level than those with  $BMI \leq 25$  kg/m<sup>2</sup> (aOR = 3.68,  $P = 0.044$ ).<sup>104</sup> Zero-calorie SSBs had little correlation with fecundability, thus indicating that the sugars are influential on fertility. High sugar intake can lead to obesity; for men, this could lead to hypotestosteronemia and impaired spermatogenesis, which reduce fecundability.<sup>105,106</sup> Another study found that in both sexes the consumption of SSBs was strongly correlated with a reduced fecundability (fecundability ratio [FR] = 0.81; 95% CI: 0.70, 0.94, and 0.78 for females; 95% CI: 0.63, 0.95 for males, both consuming  $\geq 7$  SSBs per week compared to none for females and males respectively).<sup>105</sup> Fecundability was further lowered in individuals who drank  $\geq 7$  servings of SSBs per week (FR = 0.75, 95% CI: 0.59, 0.95 for females and 0.67; FR = 0.67; 95% CI: 0.51, 0.89 for males) and adjusted FR (95%, CL) = 0.59 (0.28, 1.28).<sup>105</sup>

### ***Sugar-Sweetened Beverages and Nutrition***

Constant and high consumption of SSBs can affect the overall quality of a diet and lead to

essential nutritional deficiencies,<sup>107,108</sup> for example, reduction in the consumption of vegetables and fruits.<sup>109</sup> One systematic review and meta-analysis comprising 88 articles reported a clear association between the high consumption of SSBs (with a corresponding high intake of sugars, fructose, and sucrose) and a reduced consumption of milk, Ca<sup>2+</sup>, and other essential nutritional components, including vitamins, minerals, protein, fats, water, and carbohydrates, and a higher risk of medical complications.<sup>107</sup> This study also found that reduction in the intake of SSBs by 16 oz. daily correlated with the increased consumption of around 4 oz. of milk daily.<sup>107</sup> Additionally, this study reported other research that found a significant association between high consumption of SSBs and a low intake of milk and dairy products. A total of 24 studies<sup>108,110–127</sup> have revealed that consumption of high amount SSBs was significant related with low intake of milk and dairy products as well as Ca<sup>2+</sup>. Another study has estimated that the negative impact of SSBs consumption on milk and Ca<sup>2+</sup> intake was  $-0.21$  ( $P < 0.001$ ; Q5 = 23.09,  $P < 0.001$ ) and  $-0.13$  ( $P < 0.001$ ; Q4 = 15.22,  $P = 0.004$ ) respectively.<sup>107</sup>

High SSB consumption's significant correlations (Pearson correlation coefficient's  $r$ -value) with additional sugar, fructose, and sucrose were 0.18, 0.36, and 0.23 respectively.<sup>107</sup> Other studies, including a meta-analysis, have report that consumption of SSBs increases the amount of carbohydrates in diet.<sup>62,111,114,115,128–136</sup> High consumption of SSBs, coupled with an increase in carbohydrates other than pure sugars, could lead to obesity and increase the possibility of metabolic syndrome, type 2 diabetes, and hypertension.<sup>137,138</sup> High consumption of sugars harms the mitochondria, consequently affecting age vitality and could result in a type of starvation (because of leptin and insulin obstruction), increasing appetite in some individuals.<sup>135</sup> A high intake of SSBs is correlated to a reduced consumption of protein ( $r = -0.14$ ), pure fruit juice ( $r = -0.17$ ), fruit ( $r = -0.09$ ), and riboflavin ( $r = -0.12$ ).<sup>139</sup> For increase of 1 can/

day of SSBs consumption and 10 g/day increment in added sugar and fructose each, the log alanine aminotransferase (ALT) increased by 0.079 U/L (95% CI: 0.022, 0.137), 0.012 U/L (95% CI: 0.002, 0.022), and 0.031 U/L (95% CI: 0.012, 0.050), respectively, and the log aspartate aminotransferase (AST) increased by 0.029 U/L (95% CI: -0.011, 0.069), 0.007 U/L (95% CI: 0.000, 0.014), and 0.017 U/L (95% CI: 0.004, 0.030) respectively.<sup>140</sup> Women who consumed  $\geq 1.50$  can/day (12-oz. can) of SSBs versus less intake had a 0.127 U/L (95% CI: 0.001, 0.254) higher ALT level (13.5% change; 95% CI: 0.1, 28.9) and a 0.102 U/L (95% CI: 0.015, 0.190) higher AST level (10.8% change; 95% CI: 1.5, 20.9).<sup>140</sup> SSBs were also related to higher serum ALT and AST-fixation values among physically fit pre-menopausal women, demonstrating that even moderate ongoing consumption of SSBs could evoke hepatic lipogenesis.<sup>140</sup> In general, there is no correlation (all  $RS < 0.01$ ) between drinking SSBs and fat or vitamin, such as vitamins A and B<sup>12</sup>, intake.<sup>141</sup>

A systematic review and meta-analysis,<sup>142</sup> comprising 30 and 38 randomized control trials and prospective cohort studies (PCS), respectively, have established that a reduction in the consumption of SSBs reduces body weight (0.80 kg, 95% CI: 0.39–1.21;  $P < 0.001$ ) whereas increased SSBs consumption leads to a comparable weight increase (0.75 kg, 95% CI: 0.30–1.19;  $P = 0.001$ ). Additionally, the meta-analysis found that children who consumed a higher amount of SSBs had a 55% (95% CI: 32–82%) greater risk of obesity compared to children who consumed less SSBs.<sup>142</sup> Another meta-analysis, comprising eight PCS involving 310,819 research respondents and 15,043 patients of type 2 diabetes, has established that a daily intake of SSBs was associated with a 26% (95% CI: 12–41%) higher possibility of developing type 2 diabetes compared with an infrequent consumption of one SSB per month.<sup>9</sup>

### ***The Effects of Caffeine***

As mentioned above, caffeine is perhaps the most regularly consumed pharmacologically active ingredient globally. Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid found in coffee beans, tea leaves, cocoa beans, cola nuts, and other plants, and is available in SSBs, chocolate, and cocoa. Women of reproductive age and growing children have been identified as more at risk of damage due to caffeine-containing drinks.<sup>143</sup> This study suggested that caffeine consumption must be limited to a level of 300 mg/day, equivalent to 4.6 mg/kg body weight per day in 65-kg women who are planning to conceive or are pregnant. The maximum level of caffeine drink for children must be 2.5 mg/kg body weight per day to avoid the risk of caffeine-related adverse effects.<sup>143</sup> Another study has reported that people who sleep for 5–6 h daily consume more caffeine-containing SSBs than those who sleep for 7–8 h; such variances were not detected for consumption of SSBs without caffeine.<sup>144</sup> This study<sup>144</sup> has additionally reported a dose-dependent association with the total consumption of SSBs, finding that there was a 21 and 11% more pronounced sleep disturbance effect during 5-h and 6-h sleep, respectively, in comparison to 7–8-h sleep.<sup>144</sup>

### ***The Effects of Sugar-Sweetened Beverages on Oral Health***

#### *The importance of oral health to human health*

The WHO defines oral health as “a state of being free from chronic mouth and facial pain, oral and throat cancer, oral infection and sores, periodontal (gum) disease, tooth decay, tooth loss, and other diseases and disorders that limit an individual’s capacity in biting, chewing, smiling, speaking, and psychosocial wellbeing.”<sup>145</sup> Although the WHO declares that oral health-care is a fundamental health right, access to dental care is often unavailable, particularly in poor and marginalized communities, and noticeable

discrepancies and disparities in the management of dental-associated diseases have been reported in both low- and high-resource countries.<sup>20,136,146–150</sup> Oral diseases are a critical public health issue around the world, affecting people of all age groups in high-income and low- and middle-income countries (LMICs), causing pain, distress, disfigurement, dental deformity, and even death.<sup>20,136,146–148</sup> In 2016, the WHO reported that around 3.58 billion people frequently suffer from oral infectious and non-infectious diseases<sup>20</sup>; therefore, implementing good oral health is central to improving overall global health.<sup>147</sup>

Although treatment strategies for oral conditions are now very advanced, many of these are unavailable to communities who struggle for access to dental care in both high-income and LMICs.<sup>132</sup> For example, in the United States, dental caries, periodontal diseases, tooth loss, dry mouth, oral cancer, chewing problems, pain, or discomfort among all age groups are the most poorly addressed public health issues, and these oral conditions are frequently associated with general health difficulties.<sup>150</sup> Many LMICs have a major shortage of well-trained oral health professionals, and therefore in all countries better prevention policies and strategies are required so that the need for dental treatment is reduced.<sup>151</sup> Health education and promotion activities for maintaining oral health and preventing oral diseases are needed in both LMICs and marginalized groups and poor communities in high-income countries.<sup>148</sup> Such activities are to be underpinned by research to develop sustainable oral health policies and improve capacity-building around the world<sup>148</sup> to promote better oral healthcare, which includes psychological factors as well as biomedical and clinical issues.<sup>152</sup> Oral healthcare must consist of operational research studies aimed at developing a better understanding among health professionals for putting into

practice the knowledge about biomedical and clinical science of oral diseases.<sup>153</sup> Alongside this, educational interventions aimed at updating knowledge of both prevention and treatment strategies among healthcare professionals and other stakeholders are required.<sup>145</sup>

#### *SSBs and oral health*

As we have noted, SSBs have a very high sugar and acid content, and greatly contribute to dental caries and poor oral health in many countries, including the United States,<sup>154</sup> South Korea,<sup>155</sup> and Poland.<sup>156</sup> This has been known for many years. For example, in the United States, the term “mountain dew mouth” was coined relating to an “epidemic” of oral disease among many children in the state of Kentucky. The children did not often brush their teeth because of gum inflammation and pain, had cavities and fillings, with some toddlers pulling out their own decaying teeth with pliers.<sup>154</sup> The State had the highest percentage of the US population without teeth before attaining the age of 65 years.<sup>154</sup> Such findings led to calls for excluding all SSBs from the diet to improve oral and general health. However, adherence to such a holistic approach was frequently low, hence there was a need to develop a range of flexible policies and strategies which could reflect local culture and practices.<sup>157</sup>

The special relationship with “oral health problems and diet and new-generation soft drinks, such as energy, sports drinks, and flavored waters is a real concern as these beverages are marketed as a beverage of choice for adolescents,”<sup>158</sup> and are often seen as healthy. An Australian study of 3,671 teenagers found that consuming one cup or more of SSBs daily was consistently related to a higher odds of poorer oral health when compared with drinking less than 1 cup/day of diet soft drinks, sports drinks, flavored water, and energy drinks.<sup>159</sup> Besides sugar, one of the main problems of SSBs is their

acidity. SSBs, in general, have a pH level of 2.4–3.3<sup>160,161</sup> or a pH below 4.<sup>162</sup> The pH of the mouth cavity is 6.75–7.25,<sup>163</sup> and that of saliva is 6.7–7.4.<sup>164</sup> A pH below 6 leads to dentine erosions and carries formation starts when the pH level drops to 5.5.<sup>163</sup> Sugars attach to the external enamel surface of the teeth, and the longer they are attached, the more opportunity microbes get to ferment sugar molecules to produce acid, which leads to dental caries.<sup>165–167</sup> Furthermore, a low pH promotes the growth of aciduric microorganisms, such as *Streptococcus mutans* (and related species) and *Lactobacillus* species. These are not typically found, or only available in the sub-threshold level of dental plaque<sup>163,168,169</sup> and are considered to have the highest impact on dental caries formation.<sup>170–173</sup> Another study amongst adults in Poland<sup>156</sup> aimed to determine the correlation between the intake of SSBs and oral fungal infection; 38% of the research respondents consumed an amount higher than the recommended SSBs (less than three cans of cola or 450 calories per week).<sup>61</sup> 68% of the Polish study population were infected with seven different types of *Candida* (*Candida albicans*, *C. tropicalis*, *C. guilliermondii*, *C. famata*, *C. lusitaniae*, *C. humicola*, and *C. lipolytica*) in the oral cavity.<sup>156</sup> There was a statistically significant correlation between the amount of fungal infections and consumption of SSBs with high sugars (correlation coefficient 0.5395), with 76.3% of those with high consumption of SSBs having infections.<sup>156</sup> In addition, positive statistically significant correlations ( $P = 0.004$ ; correlation coefficient 0.9691) were found with a high intake of coffee and tea with sugar, leading to the conclusion that added sugar promotes a significant escalation of fungal colonization in the oral cavity.<sup>156</sup>

SSBs are a principal source of added sugars among the US population.<sup>174</sup> The US dietary guidelines recommend that below 10% of total calorie intakes are derived from pure crystalline

sugar<sup>175</sup>; nonetheless, most of the US population has a much higher intake of sugar.<sup>174–178</sup> As with the general population, the high consumption of SSBs has a negative impact on children's general and oral health,<sup>179–183</sup> and the consumption of milk is significantly reduced. Milk is considered as the primary resource of Ca<sup>2+</sup>, K<sup>+</sup>, vitamin D among US children and adolescents<sup>184–186</sup> and a lack of these impacts on not only oral health (e.g., caries and oral diseases<sup>187</sup>) but also leads to low bone mass and density, fractures and minor injuries.<sup>188,189</sup> Another US study conducted among children between 8 and 9 years of age found that they regularly consumed around two servings (average preserving SSBs 140–150 calories and 35–37.5 g of sugar per 12-oz. serving)<sup>34</sup> of SSB daily (1.7, 95% CI: 1.6–1.8) and 52% suffered from oral and dental diseases.<sup>190</sup> After adjusting for population-related and parental factors (in particular the mothers' oral health), this study found a 22% adjusted PR = 1.2, 95% CI: 1.1, 1.3 increase in the possibility of caries for every additional consumption of SSB daily<sup>190</sup> and recommended a restriction on SSBs consumption to reduce dental diseases, obesity, and to promote overall better health. A Finnish study found a positive correlation in 4-year old children between SSBs consumption and an augmented proportion of DMFT, but no significant association with socio-demographic and behavioral profiles.<sup>191</sup> In adults, the consumption of 1–2 and 3+ SSBs per day, compared with those not consuming any SSBs, had a 31% incidence rate ratio (IRR): 1.31; 95% CI: 1.02–1.67 and 33% IRR: 1.33; 95% CI: 1.03–1.72 increase in DMFT respectively, concluding that there is a positive dose-response relationship between dental and oral diseases and the consumption of SSBs. The high occurrence and frequency of oral diseases in American children (for example, one study found that 51% of the US children aged 6–11 years had oral and dental infectious diseases<sup>192</sup>) has made it a public health

concern as dental caries often cause other health issues such as tooth loss, poor quality of life, impairs mastication and digestion, and/or promotes infectious diseases that could lead to death.<sup>193,194</sup>

#### *Effects of sugar-sweetened beverages on oral microbiome*

The health status of the oral cavity often represents an individual's overall health.<sup>195</sup> The human oral cavity is normally inhabited by abundant and disparate microbes of bacterial, viral, and fungal species,<sup>196,197</sup> variously termed as oral microflora, oral microbiota, or the oral microbiome.<sup>198–200</sup> Every one or two hours, every person's mouth develops almost six billion new microbial communities.<sup>201,202</sup> The word "microbiome" was coined by Dr. Joshua Lederberg as "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease."<sup>203</sup> The microbiome plays a vital role in building the human immune system, helps prevent the growth of pathogenic microbes, and contributes in maintaining health and combating disease.<sup>204–210</sup>

The human oral microbiome is a highly researched area and plays a dynamic responsibility in the conservation of oral health.<sup>211</sup> It contains a total of 770 species, which include: officially named (57%), yet not named but cultivable (13%), and uncultivated (30%) phylotypes.<sup>212</sup> A diet containing a high level of carbohydrates (and high sugar content) has the highest impact on the oral ecological microbial community,<sup>213–215</sup> and multiple studies have reported that the consumption of sugary foods stimulates acidogenic and aciduric microorganisms to flourish, particularly lactobacilli and *Streptococcus mutans* present in SSB consumers' mouth cavities, which are highly associated with the development of dental caries.<sup>107,213,216–222</sup>

## STRATEGIES FOR REDUCING CONSUMPTION OF SSBs

The consumption of SSBs contributes to the development of several long-term, life-limiting conditions. This has enormous implications on public health in both low- and high-resource settings, and requires strong public health interventions.<sup>223,224</sup> As noted, many recent studies have highlighted that the consumption of SSBs is correlated with the development of obesity, dental caries, type 2 diabetes, insulin resistance, CVDs, and sexual health.<sup>4,85–87,98,103,104,128,223</sup> Several public health strategies, including health education and promotion, have been employed to address the issues raised by the addition of sugar and other products to foods and beverages. Alongside these, various governments have tried through legislative and taxation controls to limit the addition of unnecessary ingredients. The notion of additional levies on food and drinks to preserve and promote public health dates back to 1776, when the Scottish economist, philosopher, author and "father of economics," Adam Smith wrote one of his two classic works *An Inquiry into the Nature and Causes of the Wealth of Nations*. In this essay, the author promoted imposing additional levies on tobacco, rum, and sugar as none of these products was considered essential for life.<sup>141,225</sup>

However, more recently, multiple studies also have demonstrated that imposing levies or duties on SSBs and unhealthy foods is successful in reducing their consumption, thus helping to improve public health.<sup>226–230</sup> A recent systematic review found that not only was consumers' intended consumption of SSBs significantly reduced when tax on them were increased but consumers also reported an intention to buy healthy beverages instead thus reducing calorie and sugar intake.<sup>231</sup> Another systematic review concluded that an additional levy on SSBs is an effective policy and has the potential to cut SSBs' drinking.<sup>232</sup> Furthermore, this review has found

that while additional duty on SSBs reduces their consumption in both high- and low-income groups, it has a greater positive effect among the low-income group,<sup>232</sup> which in turn would improve the overall health of the population. A study conducted in Berkeley, CA, USA has found that after 1 year of implementation, SSBs' sales came down and their excise levy was achievable. Although the research was inconclusive as to whether the fall in sales of SSBs was due to the increased price or other health-related promotional programs,<sup>233</sup> a follow-up study in the same location found that after 3 years of implementing a higher levy, there was a sustained reduction in SSBs consumption.<sup>234</sup>

Following these findings and, as a response to the rise in obesity and other non-communicable health conditions, several countries in the last decade have introduced high levies on SSBs and unhealthy foods, especially those containing high salt, fat, and/or sugar.<sup>225</sup> These countries include Mexico,<sup>235,236</sup> France, Hungary, Finland, Latvia,<sup>237</sup> Barbados, Belgium, Brunei Darussalam, Chile, Kiribati, Norway, Samoa, Saudi Arabia, Spain, Vanuatu, Mauritius, French Polynesia,<sup>238</sup> Fiji and Tonga, Samoa, Nauru,<sup>239</sup> South Africa,<sup>240,241</sup> and the United Kingdom.<sup>242</sup> The marketing strategies of SSBs are being monitored strictly using regulatory measures. It has been suggested specifically that television and Internet advertising of SSBs should be controlled, as very aggressive advertising influences their increased usage, particularly among children and young people.<sup>240</sup> Any controls on the sales and advertising of SSBs should be a part of national strategy about food and nutrition, because well-planned and implemented food policies can have a huge impact on improving the diets (and thus the health) of individuals and communities.<sup>243</sup> Policymakers must involve community representatives and leaders and consider behavioral, socioeconomic, and demographic factors relating to specific communities to develop meaningful customized food policies.<sup>244</sup>

## CONCLUSIONS

The provision of healthy and safe food is vital for human health, and the addition of unnecessary sugars in foodstuffs is an important global issue, leading to multiple long- and short-term health issues and spiraling costs for both individuals and governments. Compelling evidence indicates that the regular consumption of SSBs has a significant adverse impact on people's health. The worldwide demand of SSBs has proliferated over the last decades, spurred on by intensive marketing and promotion by global corporations. There is an urgent need, therefore, to develop strategies to ensure public safety by reducing the consumption of SSBs and other foods with high sugar content. A combination of policy and strategic approaches is required, including health education and promotion about the risks of consuming SSBs for parents and children in schools and other institutions, thus encouraging change in individual behavior; limiting access of vulnerable groups to SSBs; promoting and giving access to oral healthcare; lobbying governments, interest groups, and large corporations; and legislation and taxation.

### *Recommendations*

The following recommendations are put forward:

- A multi-pronged approach has to be taken to addressing the issue of “hidden” sugars in processed foods and SSBs.
- This should involve national and local governments, large corporations, and health and education providers.
- Widespread public health and health education programs should be developed and implemented to inform the public about the risks of overconsumption of SSBs and provide support for parents and other vulnerable groups to change behaviors.

- Alongside prevention, targeting increased provision of and access to dental care is essential to prevent long-term adverse effects on oral health.
- More research needs to be carried out to measure the long-term effects of the over-consumption of SSBs.

### *Key Findings*

- While ethnic and cultural variations exist, the adverse effects of SSBs on human health is a global concern in both low- and high-income countries.
- Over-consumption of SSBs is increasing, and it leads to several health conditions, including malnutrition, obesity, type 2 diabetes, CVDs, and oral diseases.
- Sugar has addictive properties, and SSBs often have high amounts of sugars, which lead individuals to reduce their intake of foods and drinks with higher nutritional content.
- The range of long-term adverse effects on health by over-consumption of SSBs is often misunderstood or unknown by the public.
- Successful strategies for reducing consumption of SSBs include public health strategies and interventions as well as imposition of taxes or levies.

### **AUTHOR CONTRIBUTIONS**

MH, JM, and MS were responsible for the conceptualization and methodology of the study. MH, JM, MS, NS, SZH, and MAB made contributions to the original draft preparation, supervised the study and were responsible for project administration. MH, JM, and MS reviewed and edited the article.

### **CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

### **FUNDING**

This review manuscript received no financial support.

### **ACKNOWLEDGMENTS**

The principal authors are very grateful to the UPNM library for its support in providing the manuscripts which are not part of open access.

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