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The depressogenic potential of added dietary sugars

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ABSTRACT

Added sugars are ubiquitous in contemporary Western diets. Although excessive sugar consumption is now robustly associated with an array of adverse health consequences, comparatively little research has thus far addressed its impact on the risk of mental illness. But ample evidence suggests that high-dose sugar intake can perturb numerous metabolic, inflammatory, and neurobiological processes. Many such effects are of particular relevance to the onset and maintenance of depressive illness, among them: systemic inflammation, gut microbiota disruption, perturbed dopaminergic reward signaling, insulin resistance, oxidative stress, and the generation of toxic *advanced glycation end-products* (AGEs). Accordingly, we hypothesize that added dietary sugars carry the potential to increase vulnerability to major depressive disorder, particularly at high levels of consumption. The present paper: (a) summarizes the existing experimental and epidemiological research regarding sugar consumption and depression vulnerability; (b) examines the impact of sugar ingestion on known depressogenic physiological processes; and (c) outlines the clinical and theoretical implications of the apparent sugar-depression link. We conclude that the extant literature supports the hypothesized depressogenic impact of added dietary sugars, and propose that an improved understanding of the effects of sugar on body and mind may aid in the development of novel therapeutic and preventative measures for depression.

Introduction

Over the past century, sugar has become a dietary staple throughout the developed world. Americans currently derive an estimated 14% of all calories from *added sugars*[a] [1]—typically introduced to foods and beverages during their preparation and processing—the equivalent of 18 teaspoons' worth each day. These sweeteners are even found in an estimated 75% of all packaged foods [2]. The consumption of a high-sugar diet has, of course, been implicated as a risk factor for an array of adverse health outcomes, including obesity [3], cardiovascular disease [4], type 2 diabetes mellitus [5], and dental caries [6]. As a result, U.S. dietary guidelines now advise limiting the consumption of added sugars, both to promote better overall health and to help reduce the burgeoning toll of obesity [7].

Although maladaptive dietary habits pose an obvious threat to physical well-being, they also carry the potential to endanger psychological health [8]. In fact, major depressive disorder, one of the most highly prevalent and disabling forms of mental illness worldwide [9], appears particularly susceptible to unhealthy nutritional influences [10,11]. Dietary interventions, such as those designed to improve nutrition or reduce weight, have been found to reduce depressive symptoms [12]. Similarly, diets high in the consumption of fruits, vegetables, fish, and whole grains are associated with a lower risk of depression onset [13,14], whereas the frequent intake of red meats, refined grains, sweets, and other "unhealthy" foods is linked with increased depression vulnerability [13,15]. Short-term carbohydrate consumption even carries the potential to induce fatigue and decreased alertness [16]. Moreover, healthy and unhealthy diets, respectively, each appear to exert independent effects on mental health [11,17], which suggests that depressogenic processes can be affected both by the relative absence of key nutrients *and* by the excessive presence of harmful foods. Identifying the latter—the specific dietary components that contribute to depression vulnerability—will enhance our understanding of the pathology and treatment of this devastating illness.

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[a] In contrast with the natural sugars contained in whole foods such as fruits, vegetables and dairy products, *added sugars* subsume the large array of sweeteners—fructose, sucrose, maltose, dextrose, high-fructose corn syrup, cane syrup, cane juice, fruit juice concentrate, etc.—commonly added to foods and beverages during processing.

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Therefore, given the established link between excessive sugar intake and adverse health outcomes, as well as the broader association between dietary quality and mental health, we hypothesize that added dietary sugars constitute a risk factor for the onset of depression, particularly at high levels of consumption. In the following sections we examine two primary lines of evidence that lend support to the hypothesis: (a) direct investigations of the sugar-depression relationship, including observational studies and animal experiments; and (b) a voluminous literature on the depressogenic physiological effects of added sugar ingestion.

Sugar consumption and depression risk

Longitudinal cohort studies

Several large epidemiological studies have explored the sugar-depression link by tracking participants' dietary habits and health outcomes prospectively over a span of several years. The Women's Health Initiative Observational Study, for example, followed 69,954 American women over a 3-year period [18]. Investigators observed that women in the top quintile of added sugar consumption (median 79.2 g daily) were at 23% greater risk of subsequent clinical depression than those in the bottom quintile (17.8 g daily), even after accounting for other relevant dietary factors, disease markers, and demographic variables. Another large trial, the NIH-AARP Diet and Health Study, found that the regular consumption of sugar-sweetened beverages (the leading dietary source of added sugars) conferred a 20% increase in depression incidence over a 4-to-5-year follow-up period [19]. A subsequent study of 15,546 Spanish university graduates likewise observed a heightened risk of depression among the heaviest consumers of sugar over a 10-year follow-up [20], and another recent cohort study also reported a positive association between sugar intake and the onset of future depressive symptoms [21]. Conversely, two recent cohort studies failed to find the hypothesized association [22,23]: Gopinath et al. [22] did not find a statistically significant association between total sugar intake and depressive symptoms, while Vermeulen et al. [23] similarly found no relationship between symptoms and a high-sugar dietary pattern. It should be noted, however, that unlike the aforementioned supporting studies [18,19,20], the two contrary studies [22,24] did not specifically examine the impact of added sugars, per se. Instead, they utilized dietary indices that conflated sugars with other simple carbohydrates—a less precise methodology that may have limited investigators' ability to detect a potential link between added sugars and depression.

Cross-sectional surveys

Cross-sectional surveys provide additional support for the hypothesized sugar-depression relationship. For example, the incidence of depression for Australian adults was roughly 50% higher among regular versus non-regular soda drinkers [25]. Similarly, Chinese adults who reported drinking over seven ounces of soda daily were significantly more likely to report clinically salient depressive symptoms than those who consumed fewer [26]. Investigators have also found sugar-sweetened beverage intake to be positively associated with depressive symptoms among low-income obese Latino immigrants [27], and among Iranian children and adolescents [28]. Indeed, a recent meta-analysis of cohort and cross-sectional studies found that the consumption of sugar-sweetened beverages was linked to a significantly increased risk of depression [29].

Animal models

Several published studies suggest that high-sugar diets may elicit depressive behaviors in rats. In comparison with rats fed standard (low-sugar) "rat chow," those provided with free access to high-sucrose food for two days a week over the course of seven weeks displayed depressive and anhedonic behavioral shifts [30]. Rats given sugar-sweetened water for nine weeks likewise displayed depressive-like behavior in a forced-swim test paradigm [31]. Related work suggests that overfeeding sugar to adolescent rats induces subsequent depressive and anhedonic behavior during adulthood [32,33]. On the other hand, Pyndt Jørgensen et al. [34] have failed to find a relationship between sugar consumption and depressive behavior in *mice*, which suggests that the depressogenic potential of sugar may differ to some degree across species.

Depressogenic physiological effects of added sugar ingestion

Although the above-reviewed studies generally support the hypothesized association between excess sugar consumption and the risk of depressive illness, most of the relevant evidence is merely correlational in nature. It remains unclear the degree to which added sugars contribute *causally* to the experience of depression. In fact, we are aware of no well-conducted experimental manipulations of sugar intake to evaluate the sweetener's direct causal impact on human depressive symptomatology.

Nevertheless, one additional line of evidence is worthy of consideration in this context—an extensive, robust research literature on the adverse physiological consequences of excess sugar consumption. Several such pathophysiological effects also exhibit a well-documented potential to induce depression (see Fig. 1), among them: systemic inflammation, gut microbiota disruption, perturbed dopaminergic reward signaling, insulin resistance, oxidative stress, and the generation of toxic *advanced glycation end-products* (AGEs). The impact of sugar ingestion on these depressogenic processes is reviewed in the sections that follow.

Inflammation

Elevated systemic inflammation is recognized as a potent physiological trigger of depression [35]. Meta-analyses have found the concentrations of several inflammatory factors, for example, to be higher among depressed individuals than among non-depressed controls [36,37]. Inflammation is also associated with several characteristic depressive symptoms, including fatigue, sleep disruption, and appetite changes [38]. Finally, pro-inflammatory drugs carry the potential to induce depressive symptoms and to increase the risk of full-blown depression onset [39], while anti-inflammatory drugs possess antidepressant therapeutic properties [40].

Dietary sugars can elicit inflammation in both humans and non-human animals. Pro-inflammatory states, marked by elevated levels of inflammatory factors and increased expression of inflammatory genes,

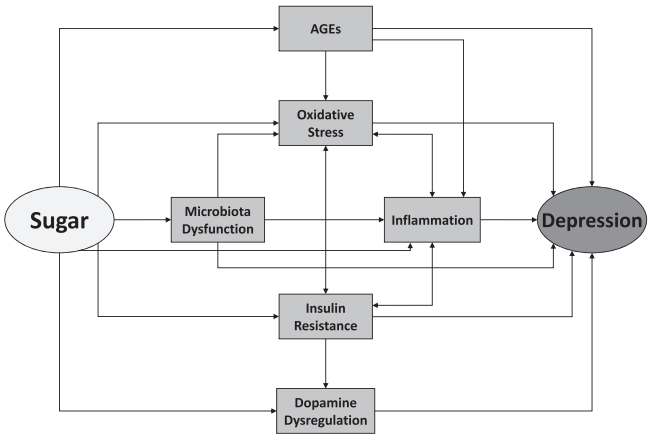

Fig. 1. Schematic overview of the physiological pathways linking sugar to depression.

characterize rats fed a high-fructose diet [41,42]. A similar pro-inflammatory response can be seen in humans following the consumption of sugar-sweetened beverages. Jameel, Phang, Wood, and Garg [43] found that participants' consumption of 50 g of dissolved fructose immediately increased levels of an important inflammatory factor, high-sensitivity c-reactive protein (hs-CRP). In fact, hs-CRP levels have been shown to double after just three weeks of daily exposure to sugar-sweetened beverages [44]. Additionally, a cross-sectional analysis of 17,689 U.S. adults found that measured hs-CRP levels significantly covaried with self-reported sugar consumption [45]. Another cross-sectional study likewise found that higher intake of added sugars was associated with higher levels of inflammation [46]. Added sugars may also trigger specific inflammatory processes localized within the brain (*neuroinflammation*), which are in turn linked with impaired cognitive function [47]. Rats exposed to high-sugar diets display impaired memory, along with increased inflammation and the expression of inflammatory genes within the hippocampus, a major brain nexus of memory consolidation and retrieval [48,49]. Significantly, cognitive deficits are a primary feature of depression, often contributing to the syndrome's characteristic psychosocial impairment [50].

In sum: added sugars have a profound effect on inflammatory processes within the body and brain, and inflammation may serve as a key mediator of sugar-induced depression onset. As discussed in the sections that follow, four additional depressive physiological pathways affected by sugar intake—disruption of the gut-brain axis, oxidative stress, insulin resistance, and the production of toxic advanced glycation end products (AGEs)—are also associated with increased inflammation.

Microbiota dysfunction

Extensive interconnections have been discovered between the human central nervous system and the collection of microbes residing within the body—the *microbiota*—and researchers have recently begun to explore the microbiota's potential role in depression and other psychological disorders [51]. The human microbiota is altered by the quantity of microbe-accessible carbohydrates in the diet, including sugars like glucose and fructose [52], and high-sugar diets are thought to permit the proliferation of harmful opportunistic organisms that contribute to *dysbiosis*, a state of maladaptive microbiota imbalance [53]. Dysbiosis, in turn, is linked to numerous physical and psychological pathologies [54].

Although knowledge of the human microbiota remains nascent, animal models suggest that high-sugar diets can disrupt microbiota balance and functioning. Rats fed a high-fructose diet display an altered microbiota, and this disruption is further related to increased disease risk [55]. Magnusson et al. [56] found that mice briefly fed a high-sugar diet also displayed distinct changes within the microbiota, in comparison with mice fed standard or high-fat diets; the sugar-fed mice also evidenced a broad pattern of cognitive impairment. Analyses of gut bacteria in mice have likewise revealed that a long-term, high-fructose diet can substantially alter microbiota composition and induce dysbiosis [57,58]. Additionally, Jena et al. [59] found that a 30-day high-fructose diet suppressed beneficial microbe species in rats. Excessive fructose consumption is also linked to intestinal bacterial overgrowth, a process in which abnormally large numbers of bacteria grow in the small intestine [60].

Sugar-induced dysbiosis may contribute to depression primarily by promoting inflammatory processes throughout the body. In fact, microbiota-induced inflammation has been posited as a primary risk factor for the development of depression [61]. There is growing evidence, for example, that sugar can increase intestinal permeability, resulting in increased passage of bacteria through the intestinal barrier and the subsequent activation of pro-inflammatory signaling pathways [62]. Higher consumption of fructose has also been linked to an increased presence of *endotoxins* (bacterially-produced poisons) in the blood of humans, indicative of increased intestinal permeability [63]. Bergheim et al. [64] provided mice with sugar-sweetened water for eight weeks, and they found that fructose-fed mice, in comparison with controls, had significantly higher levels of blood endotoxins, as well as sharply increased inflammation. Spruss et al. [60] and Sellmann et al. [65] both found a similar connection in rodents between fructose consumption and increased intestinal permeability. Added sugars may increase intestinal permeability by inhibiting microbes that maintain the intestinal barrier. Microbes of the genus *lactobacillus* have been found to decrease intestinal permeability [66,67], and this same genus seems to be suppressed by exposure to high-fructose diets [59]. There is also evidence that sugar directly affects the structure of the intestinal barrier, as high-fructose diets can interfere with the proteins necessary to maintain healthy intestinal barrier functioning [58,65].

Importantly, excessive intestinal permeability has been implicated in the pathophysiology of depression. Depressed individuals have been found to have an increased passage of bacteria through the intestinal barrier [68] and an enhanced immune and oxidative stress response against such intestinal bacteria [69,70]. Likewise, bacteria of the genus *Alistipes*, microbes associated with intestinal inflammation [71], have been found to be overrepresented in depressed individuals [72,73]. Clinical improvement of depression among patients in treatment—even among those receiving psychotherapy—is also associated with a decrease of both intestinal permeability and inflammation [68].

Dopaminergic dysregulation

The neurotransmitter dopamine (DA) plays a central role in brain circuitry that regulates reward-based behavior and key motivational processes. Signaling abnormalities that arise from chronic, stress-induced activation of dopamine-based (*dopaminergic*) pathways seem to contribute to depressive and anhedonic states through a down-regulation of dopaminergic activity [74]. Indeed, depressed humans evince significantly lower baseline dopaminergic brain activity than healthy controls [75]. Targeted interference of DA activity in mice has also been shown to induce depressive-like behavior under stressful conditions [76], and Chang and Grace [77] have demonstrated that rats exposed to chronic, unpredictable stressors manifest both depressive-like behavior and reduced DA activity.

Interestingly, acute sugar consumption tends to stimulate the DA system: even a sip of sugary beverage immediately activates rewards areas within the human brain [78,79]. In rats, Bassareo et al. [80] witnessed a significant burst of DA release in the brain's nucleus accumbens, a region centrally involved in reward and reinforcement, just ten minutes after the animals were fed sugar for the first time. Hajnal, Smith, and Norgren [81] found that DA release in the nucleus accumbens increased as a function of the concentration of ingested sugar, suggesting that added sugars have a dose-dependent impact on DA activity. Furthermore, DA antagonists have been demonstrated to block the reinforcing properties of sugar ingestion [82,83].

In addition to acutely stimulating cerebral DA activity, excessive sugar intake is associated with maladaptive changes in the structure and function of DA pathways—pathology consistent with the observed connection between DA dysregulation and depression [74]. DA in the *striatum*, a component of the brain's reward system, is particularly affected by excessive added sugar consumption. Rats chronically fed a high-sugar diet have been found to exhibit decreased concentrations of striatal DA [84] and reduced expression of the D2 dopamine receptor, which helps regulate reward-based DA activity [85]. Rodents that lose access to sugar after long-term overfeeding similarly display decreased DA levels [86,87]. Additionally, long-term high-sugar diets are associated with decreased striatal D2 receptor binding, further indicative of a sugar-induced reduction of D2 receptor density [88,89].

In sum: a substantial body of evidence suggests that chronic added sugar ingestion can interfere with intrinsic reward systems in a manner capable of inducing anhedonia and motivational deficits. Both are

hallmark symptoms and maintenance factors of depression.

Oxidative stress

Oxidative stress refers to a physiological state characterized by excess metabolic molecular by-products known as *reactive oxygen species*, which in turn induce toxic effects such as cellular destruction, inflammation, and accelerated aging [90]. Two recent meta-analyses suggest that depression is characterized by elevated levels of oxidative stress [91,92], which has been observed to normalize either with antidepressant drug treatment [92] or interventions such as vitamin D supplementation or even cognitive psychotherapy [93,94]. Notably, direct administration of a compound with antioxidant properties has also been shown to have antidepressant effects [95].

Accumulating research suggests that added sugar consumption can induce oxidative stress. Cosentino et al. [96] found that human cells exposed to high levels of glucose—a state commonly observed following acute sugar ingestion—produced elevated levels of reactive oxygen species. In fact, a heightened oxidative stress response has been observed in vivo among healthy adults immediately following high-dose glucose consumption [97]. Short-term supplementation with fructose-sweetened beverages has also increased oxidative stress in otherwise healthy overweight/obese individuals [98]. Likewise, markers of oxidative stress rapidly rose in preterm neonates after the administration of sucrose for pain management [99].

Added sugars are also associated with oxidative stress in rodents. Markers of oxidative stress are increased in rats chronically fed a high-fructose diet [41,100], while levels of antioxidants (and antioxidative enzymes) are decreased under the same dietary conditions [41,42]. Elevated production of reactive oxygen species has also been found in mice fed excessive sugar [101]. Damage related to fructose-induced oxidative stress has been viewed in the liver of rats [100]. Additionally, Lopes et al. [102] demonstrated that a single injection of fructose can exacerbate oxidative stress within the brains of rats.

In sum: oxidative stress contributes to the dysregulation of various physiological pathways associated with depressive processes. Together with inflammation, it may mediate the depressogenic impact of excessive added sugar consumption.

Insulin resistance

Insulin is a key hormone that permits glucose to enter cells for conversion to energy. *Insulin resistance* develops when receptors become less sensitive to the hormone, thereby limiting its effectiveness and in turn depriving cells of adequate fuel. Insulin receptors are present throughout the brain, and they play a central role in regulating its use of glucose for energy [103]. There is even emerging evidence (reviewed in [104]) that depression can directly arise from the brain's insulin resistance and its ensuing disruption of energy utilization. For example, adults with insulin resistance are at heightened risk for the development of future depression [105], while cross-sectional epidemiological work suggests a low- to moderate-strength association between insulin resistance and depression incidence [106].

Excessive sugar consumption is strongly implicated as a potential driver of insulin resistance. In fact, high-sugar diets are frequently used to induce insulin resistance in rodent models. Pagliassotti, Prach, Koppenhafer, and Pan [107] demonstrated that a high-sugar diet fed to rats can elicit insulin resistance in the liver and muscles within one and eight weeks, respectively. Fructose consumption has also been shown to down-regulate the expression of insulin receptors and other insulin-related proteins in rats [108]. Humans are similarly susceptible to sugar-induced insulin dysregulation. Couchepin et al. [109], for example, found that a short-term, high-fructose diet increased fasting glucose levels in healthy men and women, indicative of impaired insulin functioning. Stanhope et al. [110] likewise demonstrated that consumption of fructose-sweetened beverages decreased insulin sensitivity over the course of ten weeks. In fact, even one week of fructose overfeeding is sufficient to decrease insulin sensitivity [111,112].

Significantly, insulin resistance interacts with other depressogenic processes. Inflammation and oxidative stress are both involved in the pathogenesis of insulin resistance [113,114]. In turn, insulin has anti-inflammatory and antioxidant properties which may become disrupted following insulin resistance [115,116]. Insulin resistance is also associated with perturbed dopamine signaling in rodents [116,117]. The bidirectional relationships between insulin dysregulation and key depressive processes highlight the detrimental systemic impact of added sugar consumption.

Advanced glycation end-products (AGEs)

Advanced glycation end-products (AGEs) are toxic molecules that form when sugar molecules react with proteins, lipids (fats), or other compounds in the body. Accumulating evidence suggests that excessive added sugar consumption promotes AGE formation by increasing the availability of glucose and fructose, thereby allowing these sugars to be irreversibly converted to AGEs within the body [118]. Animal models have demonstrated that high-fructose and high-glucose diets increase the concentration of AGEs in both blood and tissue [119,120]. Once formed, AGEs are associated with a cascade of adverse biological reactions, including oxidative stress, inflammation, and neurocognitive dysfunction [121,122,123].

In light of these broadly deleterious effects, AGEs have recently been proposed as novel markers of lifestyle-related diseases [124]—a category that includes depression [125]. In fact, a recent landmark investigation by van Dooren et al. [126] lends support to the hypothesized role of AGEs in depressive illness. Among a well-characterized sample of 862 Dutch adults (Maastricht Study), those with elevated AGE accumulations in skin tissue evidenced a 42% increase in the risk of depressive disorder [126]. Study investigators also observed a significant positive association between measured AGE levels and the severity of depressive symptoms.

Although the Maastricht Study is the only large-scale investigation to date of the depressive impact of AGEs, several additional lines of evidence lend support to the finding. First, depressed individuals have been observed to have low levels of circulating protective molecules that bind and neutralize AGEs before they are able to cause damage [127,128]. Depressed individuals also appear to be deficient in the expression of glyoxalase-1, an antioxidant enzyme that helps degrade AGEs and minimize their toxic impact [129]. Further, Franklin et al. [130] demonstrated that mice without functioning AGE receptors are resistant to stress-induced depressive-like behavior. Finally, rodents exposed to high AGE levels have been found to experience impaired neuronal growth (*neurogenesis*) in the hippocampus—a central neurological feature of depression—and this reduced neurogenesis was reversed by administration of an anti-AGE drug [131]. Taken together, these findings provide substantial support for the hypothesis that AGEs exert depressogenic effects.

Conclusions and future directions

Multiple distinct lines of evidence generally converge in suggesting that the consumption of added sugars may induce depressogenic effects. The strongest evidence, by far, comes from the extensive literature on the pathophysiological consequences of added sugar ingestion, which collectively serve as candidate mediational mechanisms through which added sugars may adversely influence well-being. As reviewed, sugar intake promotes numerous maladaptive processes capable of inducing depressive symptomatology (depicted in Fig. 1): microbiota dysfunction (an altered *gut-brain axis*), disordered dopamine signaling, oxidative stress, insulin resistance, and the generation of advanced glycation end-products (AGEs). Most of these processes also promote pathological

inflammation—itself a particularly robust, well-established risk factor for depression [35]. Although the existing evidence regarding the hypothesized sugar-depression link is still neither definitive nor conclusive due to the absence of rigorous experimental manipulations of added sugar intake among sufficiently large and randomly assigned participant samples, we nonetheless regard the extant body of relevant research as persuasive.

Much more extensive investigation will be necessary, of course, to fully elucidate the sweetener's hypothesized depressogenic potential in humans. Ideally, such work would not only feature the experimental control of sugar intake at varying levels, but also the inclusion of relevant biomarkers of sugar-induced depressogenic processes. In a similar vein, it may prove valuable to evaluate the *psychological* impact of dietary interventions specifically designed to help reduce the consumption of added sugars—and thereby to reduce the occurrence of inflammation, oxidative stress, gut dysbiosis, and so on. Such interventions may carry the potential to reduce depressive symptoms (or to prevent their future occurrence), at least among the subset of patients with high baseline sugar consumption.

It is also necessary to clarify the amount ("dosage") of sugar required to induce psychopathological consequences. Gangwisch et al. [18] observed the lowest risk of depression onset among those in the lowest quintile (20%) of added sugar intake, who had a median consumption of 17.8 g daily. Notably, this amount is not far below the suggested daily limit[b] recommended by the American Heart Association [132], and we believe it serves as a reasonable placeholder guideline while additional research is conducted—particularly for those battling depression or at high risk of future onset of depressive illness. There likely also exists considerable individual variation—derived from genetic, epigenetic, and gut microbial differences—in the physiological response to added sugars. That is, some people are probably far more sensitive than others to the sweetener's depressogenic effects. The discovery of any such reliable individual differences would likely be of both clinical and theoretical importance to the field.

Finally, to the degree that the connection between added sugars and depressive illness is robustly established by further research, it may desirable to develop low-sugar dietary interventions that can be effectively implemented at a population level. Unlike existing low-carb clinical diets, which typically require the extremely limited consumption of any carbohydrates [133,134], depression-focused diets could aim specifically to reduce the intake of added sugars while simultaneously ignoring other types of carbohydrates, thereby eliminating the need for restrictive (or expensive) dietary changes that act as a barrier to adherence [135,136]. One simple change that could have a substantial impact on added sugar intake is the reduction or elimination of sugar-sweetened beverages. Such beverages are the single leading source of added sugars [137] and they have limited nutritional value, making them a prime candidate for reduction or elimination. Educational and behavioral interventions (e.g., substituting water for sodas) have been shown to successfully reduce intake of sugar-sweetened beverages in both children and adults, as have public policy strategies such as targeted sugary beverage taxation [138,139,140]. However, the long-term effectiveness and sustainability of such strategies remain largely unknown [138], as do their potential protective benefit vis-à-vis depressive illness. Other high-sugar, low-nutrition foods, such as candy, should also be considered prime candidates for reduction. Regardless of the intervention strategy, excessive restriction (e.g., the banning of all sugar products) would likely prove counter-productive, inasmuch as restrictive dietary patterns are associated with disordered eating [141]. Moreover, there is some early evidence that reducing sugar intake can actually increase its reinforcement value—an important caveat for investigators to bear in mind during the development of novel dietary interventions [142].

[b] The suggested daily limit is 25 g for women and 36 g for men.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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