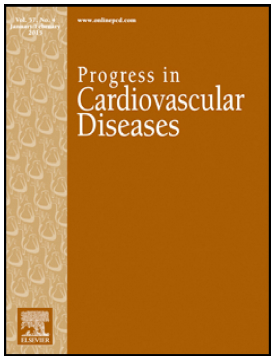
In Defense of Sugar: A Critique of Diet-Centrism



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Abstract

Sugars are foundational to biological life and played essential roles in human evolution and dietary patterns for most of recorded history. The simple sugar glucose is so central to human health that it is one of the World Health Organization's Essential Medicines. Given these facts, it defies both logic and a large body of scientific evidence to claim that sugars and other nutrients that played fundamental roles in the substantial improvements in life- and health-spans over the past century *are now suddenly* responsible for increments in the prevalence of obesity and chronic non-communicable diseases. Thus, the purpose of this review is to provide a rigorous, evidence-based challenge to '*diet-centrism'* and the disease-mongering of dietary sugar. The term '*diet-centrism'* describes the naïve tendency of both researchers and the public to attribute a wide-range of negative health outcomes exclusively to dietary factors while neglecting the essential and well-established role of individual differences in nutrient-metabolism. The explicit conflation of dietary intake with both nutritional status and health inherent in '*diet-centrism'* contravenes the fact that the human body is a complex biologic system in which the effects of dietary factors are dependent on the current state of that system. Thus, macronutrients cannot have health or metabolic effects independent of the physiologic context of the consuming individual (e.g., physical activity level). Therefore, given the unscientific hyperbole surrounding dietary sugars, I take an *adversarial position* and present highly-replicated evidence from multiple domains to show that 'diet' is a necessary but trivial factor in metabolic health, and that anti-sugar rhetoric is simply diet-centric disease-mongering engendered by physiologic illiteracy. My position is that dietary sugars are not responsible for obesity or metabolic diseases and that the consumption of simple sugars and sugar-polymers (e.g., starches) up to 75% of total daily caloric intake is innocuous in healthy individuals.

Key Words: Sugar; diet; metabolism; obesity; nutrition; public policy

Abbreviations:

NCDs- Non-communicable diseases

PA-Physical activity

SSBs-Sugar-sweetened beverages

T2DM-Type II diabetes mellitus

US –United States

WHO-World Health Organization

Introduction

"…the subject of nutrition seems to have a special appeal to the credulous, the social zealot and, in the commercial field, the unscrupulous. This fact makes the solid advancement of nutritional science particularly difficult… [and will] *strike despair in the hearts of the sober, objective scientists." Ancel Keys*[1]

History demonstrates that when demonstrably false information is widely disseminated, scientific progress is impeded, research resources are misdirected, and public health is placed in jeopardy.[2-6] Thus, the purpose of this review is to provide a rigorous, evidence-based challenge to the current disease-mongering of dietary sugar and the simplistic notion that 'we are what we eat'. Herein, I demonstrate that it contravenes a large body of highly-replicated scientific research to claim that sugar and other nutrients (e.g., saturated fats) that played essential roles in both human evolution[7-10] and the substantial improvements in public health over the past century,[11-14] *are now suddenly* responsible for causing obesity and chronic non-communicable diseases (NCDs).

In this review, the term 'diet-centrism' describes the naïve tendency of researchers and the public to attribute a wide-range of negative outcomes exclusively to dietary factors while neglecting the essential role of individual differences in nutrient-metabolism and health. The explicit conflation of diet with both nutritional status and health inherent in diet-centrism contravenes the fact that the human body is a complex biologic system in which the effects of dietary factors are entirely dependent on the current state of that system (e.g., metabolic phenotype, nutrient-energy status). Thus, because the effects of sugar consumption are dependent of the physiologic context of the consumer, prescriptive, population-level dietary recommendations are both unscientific and futile: *one size does not and cannot fit all.*

Several arguments are presented to counter the logical and scientific errors induced via diet-centrism. Table presents a summary. For clarity, herein the term 'sugars' refers to both mono and disaccharides (e.g., glucose, fructose, and sucrose). The term 'sugar-polymers' (or 'glucose-polymers') refers to polysaccharides, such as starches, glycogen, and other molecules (e.g., cellulose) formed from the simple sugar glucose. Within the context of the human diet, starches (e.g., rice, potatoes) and glycogen are sources of sugar (glucose) to meet metabolic demands.

While all sugars and sugar-polymers are carbohydrates, not all carbohydrates are relevant to the present review. As such, the more precise terms sugar and sugar-polymers will be used.

Table

Evidence Contrary to the 'Diet-Centric' Disease-Mongering of Dietary Sugars
Without Sugar, we die: biological life depends on sugar in its many forms.
Dietary sugars and sugar-polymers were the predominant source of nutrient-energy for most human populations since the invention of agriculture.
Sugar (glucose) is so vital to human health and well-being that it is one of the World Health Organization's (WHO) Essential medicines.
Diet-centrism is based on physiologic illiteracy: *one size does not and cannot fit all.*
Physical activity (PA) is the major modifiable determinant of energy intake, energy expenditure, nutrient-energy partitioning, and concomitant metabolic health. Diet is merely a necessary but trivial component.
The consumption of dietary sugars up to 80% of total energy intake is entirely innocuous in active populations.
There is a strong, positive association between sugar availability/consumption and health.
Diet-Centrism Relies on Pseudoscientific and Inadmissible Data
Obesity and T2DM: Blood Sugar, not Dietary Sugars Matter
Diet-centric reductionism led researchers, policy-makers, and the public seriously astray, and led to biased and unscientific research and policy recommendations. The consequence has been a general 'fear of food' and the disease-mongering of dietary sugars and fats.

Without Sugar, We Die

Sugar is a Fundamental Component of Life

Sugar, in its many forms, is an essential constituent of all biological life from the construction of nucleic acids (e.g., DNA[15]) to organismal structure (e.g., cellulose) and cellular respiration (e.g., a metabolic fuel). Nearly all bacteria, plants, non-human and human animals can metabolize the simple sugar glucose (a hexose monosaccharide), and nearly all biological ecosystems depend on photosynthesis, which is the conversion of sunlight to sugar. Thus, sugars and sugar-polymers are the most important organic compounds on Earth.

The Necessity of Sugar for Human Life

In humans and other mammals, sugars and the sugar-polymer glycogen are essential for basal metabolic processes and physical activity (PA). The failure to consume or synthesize sufficient sugar to maintain an adequate supply to glucose-dependent tissues (e.g., neurons, red blood cells) results in rapid death.[16] For example, the cells of the central nervous system require a large, finely regulated, and continuous supply of sugar (glucose),[16, 17] and cell death occurs rapidly with sugar deprivation (e.g., neuroglycopenia).[17] Stated more simply, if we do not eat enough sugar or sugar-polymers, or our bodies do not produce enough sugar, we die.

Sugar and Sugar-Polymers: The Major Sources of Nutrient-Energy for Humans

Given the importance of sugars and sugar-polymers in biological life processes and their essential role in energy metabolism,[18, 19] it is not surprising that these nutrients played critical roles in both human evolution[7-9, 20] and dietary history.[21-26] For example, sugars and sugar-polymers are major nutritive constituents of many foods and beverages including breast milk, dairy products, fruit, fruit juices, honey, sucrose (i.e., table sugar; a disaccharide of glucose and fructose), sugar-sweetened beverages (SSBs), rice, beans, potatoes, wheat, corn, quinoa, and other cereal grains. As such, sugars and sugar-polymers were the major source of nutrient-energy (calories) for most of the global population throughout human history,[7-9, 21, 23-26] and now account for 45-70% of both total energy intake[18, 26] and expenditure (as metabolic fuels[18]).

Given these facts, it is illogical to posit that foods and beverages that were a substantial part of human dietary patterns since the dawn of recorded history are *now suddenly* responsible for the increasing global prevalence of obesity and NCDs. As explained in following sections, PA is the

major modifiable determinant of metabolic health, and therefore, increments in the prevalence of obesity and NCDs are not caused by unhealthy diets, but are metabolic conditions driven by non-genetic evolutionary processes engendered by physical inactivity over multiple generations.[27-34]

Sugar is an Essential Medicine

Sugar Saves Lives

Malnutrition and diarrheal diseases are responsible for ~50% of deaths of children under five, [35, 36] and dietary sugars play essential roles in nutritional rehabilitation. Sugar in the form of glucose is one of the World Health Organization 's (WHO's) Essential Medicines,[37] and the treatment of malnutrition and dehydration was recently characterized as "*A liter of water. A fistful of sugar. A half-teaspoon of salt*."[38] Treatment begins with feedings of "*sugar water…every 2 hours round-the-clock.*"[39] During recovery, the WHO prescribes a diet that is more than five times the current WHO recommendations for sugar consumption.[36, 40] It was estimated that 90% of all diarrheal mortality could be prevented if sugar-based prescriptions were used in 100% of cases.[38] In other words, sugary sweetened beverages save lives. The contradiction between the WHO's prescription and proscription of dietary sugars is an exemplar of diet-centrism in public policy, and why ignoring the physiologic context of the individual is both naïve and unscientific.

A 'Sweet' Thought-Experiment

Imagine you are a physician in a rural village in which the prevalence of malnutrition and wasting in children is high. For nutritional rehabilitation, you have a large supply of sustainably grown, organic kale and quinoa, and a large supply of soda (i.e., SSBs).

Clinical Dilemma

It is generally assumed that kale and quinoa are much "healthier" than SSBs, and kale was described as a "superfood."[41] More importantly, as an educated clinician you read a myriad of allegedly scientific papers, books, and newspaper articles by physicians, journalists, and researchers describing 'added sugars' and SSBs as "poison" and

"toxic."[42-44] In fact, a prominent science writer quoted an eminent pediatric endocrinologist using these exact terms.[43]

Clinical Questions

Question #1: Do you supplement the diets of the malnourished, stunted children with the locally and sustainably grown, organic kale and quinoa or do you prescribe the consumption of SSBs every two hours?

Question #2: Which treatment is more palatable?

Extra Credit Question: Are more foodborne illnesses and deaths in the United States (US) directly attributed to the consumption of fruits, nuts, and vegetables or SSBs?

Answers

Answer #1: If you supplement the malnourished children's diet with kale and quinoa, your patients will die. If you supplement their diet with SSBs or some other form of 'added sugars' (e.g., sugar water), your patients may recover. If 'healthy' is defined at a minimum as maintaining basic vital functions and survival, in this context SSBs are 'healthier' than organic, sustainably and locally-grown kale and quinoa.

Answer #2: The nutritional rehabilitation with SSBs is better tolerated and leads to better outcomes because it is more palatable, more energy-dense, and the sugars improve rehydration.[36]

Answer to Extra Credit Question: 46% of all foodborne illnesses and a sizeable number of foodborne deaths in the US from 1998-2008 were directly attributed to the consumption of fruits, nuts and vegetables. Leafy vegetables caused more illnesses (22%) than any other commodity and were responsible for 6% of deaths. No foodborne illnesses or deaths were directly attributed to SSBs.[45]

Summary of the "Sweet' Thought-Experiment

This thought-experiment illustrates the elementary but often ignored fact that the physiologic context of the consuming individual is the most important consideration in the effects of diet on

health. Thus, 'health' is a property of an individual and not an inherent property of foods or beverages. Therefore, the dichotomy of "healthy" versus "unhealthy" when referring to foods and beverages that are safe to consume (i.e., relatively pathogen-free) is not valid, scientific, or logical. The illiterate nature of this false dichotomy was revealed by a recent New York Times article[46] in which neither the public, dieticians, researchers, nor policy makers could agree on which foods were 'healthy' and which were 'unhealthy'. Thus, the diet-centric myth that "we are what we eat" is misleading to health professionals, patients and the public because it ignores the reality of physiologic context and individual differences. In summary, the use of disease-mongering terms such as 'unhealthy', 'toxic' and 'poisonous' when referring to dietary sugar is simply unscientific.

The Physiologic Illiteracy of Diet-Centrism: One Size Does not and cannot Fit All.

The term '*diet-centrism'* describes the naïve and physiologically illiterate tendency of researchers and the public to attribute a wide-range of negative health outcomes exclusively to dietary factors while neglecting the essential and well-established role of individual differences in nutrient-metabolism. The explicit conflation of 'diet' with nutritional status and health in *diet-centrism* contravenes the fact that the human body is a complex biologic system in which the effects of dietary factors are dependent on the current state of that system. Thus, it is a fact that macro- and micronutrients cannot have health or metabolic effects independent of the physiologic context of the consuming individual (e.g., metabolic phenotype). For clarity, an individual's metabolic phenotype is characterized by myriad factors such as body cellularity (i.e., the ratio of high to low metabolically active cells), PA and fitness levels, age, sex, reproductive status, illness, and the energy status of the systems responsible for metabolic control (e.g., skeletal muscle, liver).[47-52]

The Necessity of Increments in Serum Energy Substrates

Diet-centric researchers and policy makers erroneously assume that population-level dietary recommendations on sugar and fat consumption are valid because the increments in serum

energy substrates (i.e., blood sugars and lipids) induced by sugars and/or other dietary constituents (e.g., sugar-polymers, proteins, fats) lead to obesity, metabolic dysfunction, and NCDs (e.g., see [40, 53, 54]). This demonstrably false belief ignores the fact that the rise in serum and tissue energy substrates concomitant with eating and drinking are *essential for health and survival*. In other words, if an individual's habitual caloric intake is not sufficient to increase serum sugars and/or lipids to the level necessary to meet chronic metabolic demands, that individual will die. For example, the transient positive energy-balance of the post-prandial period induced via the consumption of dietary sugars causes increments in the storage of the nutrient-energy (e.g., glycogen) necessary for basal metabolic processes and PA during the post-absorptive (i.e., inter-meal) period.

As detailed in subsequent sections, diet-induced increments in serum energy substrates are not pathological. Rather, it is the failure of skeletal muscle- and hepatic-cells to dispose of serum nutrient-energy substrates and return blood sugar and lipids to post-absorptive levels. Stated more simply, it is not 'what one eats' (i.e., 'diet') that causes obesity and NCDs, but 'what one's body does with what is eaten' (i.e., nutrient-energy physiology). This fact was recognized, replicated, and refined for thousands of years,[49, 55-57] and explains why identical diets consumed by different individuals result in divergent metabolic and health effects.[47, 49, 57] Consequently, detailed, prescriptive, population-level dietary recommendations are futile because *one size does not and cannot fit all.*

PA, not Diet, is the Major Modifiable Determinant of Metabolic Health

The metabolic health of an organism is determined by the flow of energy through its constituent population of cells (i.e., metabolic-flux).[27, 28] Significant disturbances to metabolic-flux such as starvation (i.e., insufficient energy-intake relative to metabolic demands), exhaustion (i.e., excessive metabolic demands relative to energy intake), and physical inactivity (i.e., insufficient metabolic demands relative to energy intake) increase morbidity and mortality.[29, 58-62] While it is well-established that the greatest drivers of both energy intake and expenditure across populations are basal metabolic processes,[63, 64] the only major modifiable (i.e., behaviorally-mediated) determinant is PA.[30, 59, 61, 64-67] Unlike dietary factors, PA has major effects on nearly

every facet of nutrient-energy metabolism from ingestive behaviors to nutrient partitioning and the control of blood sugars and lipids. These effects are due to dose-dependent alterations in energy intake,[59-61, 67-72] skeletal muscle- and hepatic-cell metabolic-flux and concomitant alterations in peripheral and central insulin sensitivity, and nutrient-energy partitioning.[27, 28 47, 48, 50-52, 73-100] Stated more simply, PA affects both sides of the energy balance equation, and by doing so determines metabolic health. The evidence for this is both rigorous, comprehensive, and unequivocal.[28, 29, 47, 48, 50-52, 59-61, 65-67, 70, 73-101]

Because metabolic health depends on PA and the maintenance of the reciprocal relationship between energy expenditure and the consumption of nutrient-energy, it is not surprising that disturbances of this relationship via large decrements in PA and consequent declines in both fitness and PA energy expenditure over the past century[29, 31-33, 101-105] led to increases in the prevalence of obesity and NCDs.[27, 29, 73, 101, 106, 107] This large body of evidence and the role of skeletal muscle-cell metabolic flux are often underappreciated by diet-centric researchers.[108]

The Physiologic Mechanism of PA and Metabolic Health

A detailed description of the mechanisms by which PA determines metabolic heath is beyond the scope of this review. Nevertheless, a summary is necessitated given the widespread lack of understanding of the role of PA in metabolic health. Briefly, PA induces contractions of skeletal muscle-cells that are metabolically costly and reduce stored energy (e.g., glycogen, lipids) in a dose-dependent manner (i.e., frequency, intensity, duration, and mode/type of PA). The decrement in stored energy causes increments in the uptake of both blood sugar and lipids via insulin-dependent and insulin-independent (e.g., contraction-induced) mechanisms.[82, 86]

The increased disposal of serum nutrient-energy substrates by skeletal muscle-cells leads to a decline in blood sugar that stimulates hepatic-cells to synthesize sugar (glucose) via glycogenolysis and gluconeogenesis to maintain blood sugar levels. The energy expended via these endogenous sugar-producing processes reduces hepatic nutrient-energy stores (e.g., glycogen and lipids) and causes concomitant increments in the uptake of blood sugar and lipids by hepatic-cells, and over time increments in energy intake.[72] The metabolic costs of gluconeogenesis explain the effects of PA on nonalcoholic fatty liver disease.[109, 110]

In summary, PA induces glycogen and lipid depletion/repletion cycles (i.e., metabolic-flux) in both skeletal muscle- and hepatic-cells. These cycles determine metabolic health by maintaining insulin sensitivity and inducing the partitioning of nutrient-energy to metabolically active tissues thereby reducing the availability of blood sugar and lipids for other processes (e.g., adipogenesis, *de novo* lipogenesis).

PA and Nutrient-Energy Intake

PA unequivocally affects appetite[65, 69, 98] and is the major modifiable determinant of energy intake.[59-61, 67-72, 111] Thus, PA affects both sides of the energy balance equation (i.e., 'energy-in' and 'energy-out'). The relationship between PA and energy intake was described millennia ago when Aristotle wrote that the defining characteristic of animals was the necessity of bodily movement (i.e., PA) in order to eat (i.e., energy intake), and contrasted the daily PA of animals with that of plants, which have the luxury of energy acquisition and survival despite stasis.[112] Yet the specific effects of PA were not demonstrated until ~60 years ago by Mayer and colleagues.[59, 60, 66, 68] These results were replicated more recently with both observational and rigorous experimental designs.[61, 67, 69-72] As depicted in Figure 1, these studies demonstrated a curvilinear relationship between chronic PA, body-weight, and energy intake in both humans and non-human animals.[59, 61] This inter-species parallelism is expected in evolutionarily conserved relationships.

When individuals decrease their PA below a metabolic tipping point, (denoted as *'Sedentary'* in Figure 1), energy intake is dissociated from energy expenditure causing more calories to be consumed than expended. The resulting positive energy balance leads to increments in nutrient-energy storage and body-mass.[59, 61] The increased body-mass initiates a positive feedback-loop that decreases strength-to-weight-ratios that further depresses PA (i.e., heavier/larger bodies move less[30, 113]) and leads to further decrements in insulin sensitivity in both peripheral and central tissues. Thus, physical inactivity drives the overconsumption that leads to metabolic diseases.

Given that skeletal muscle-cells are responsible for 75 to 95% of whole body glucose uptake,[74] any decrement in the insulin sensitivity of these cells will adversely affect metabolic health. As described by De Franco, the loss of skeletal muscle cell insulin sensitivity and concomitant

insulin resistance is the primary defect in type II diabetes mellitus (T2DM).[80] The mechanisms for the progression from the loss of insulin sensitivity to T2DM are quite simple. As low PA and high sedentary behaviors drive increased energy-intake in concert with decrements in skeletal muscle- and hepatic-cell insulin sensitivity, the ability of pancreatic beta-cells to compensate for the reduced disposal of blood sugar results in insulin resistance. Over time, T2DM develops as pancreatic-beta cells become exhausted and/or lose their sensitivity to increments in blood sugar.[50, 78, 80] Therefore, as depicted by the *'Sedentary'* tipping point in Figure I, there is a minimum amount of PA (and concomitant glycogen and lipid depletion-repletion cycles) necessary to maintain both insulin sensitivity and metabolic health.[47, 114] This dose varies by metabolic phenotype (e.g., body cellularity[27, 28]). Conversely, as active individuals increase PA, energy intake increases in parallel, and these individuals remain in neutral energy balance because the increments in energy intake are partitioned and stored in metabolically active tissues (e.g., skeletal muscle- and hepatic-cells).[47, 48, 61, 75-77] This explains why increases in exercise have little effect on body weight in moderately active individuals. As discussed below, given the necessity to increase caloric consumption to meet the metabolic demands of PA, sugar and sugar polymers are the dietary choice of highly-active individuals (Figure 1).

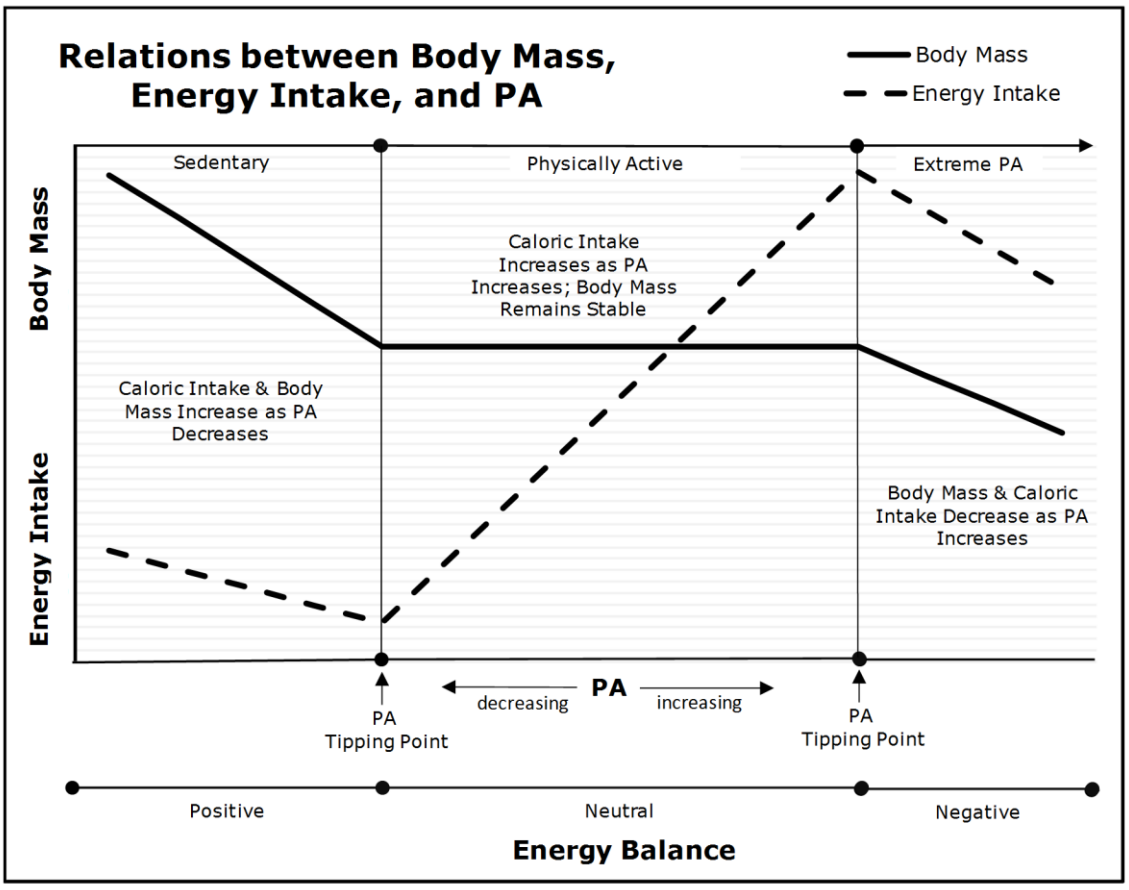

Figure 1: Relations between PA, Body Mass, and Energy Intake

Text Description: As PA declines below the metabolic tipping point into the *'Sedentary'* range, energy intake and energy expenditure become dissociated due to insufficient depletion/repletion cycles, and body mass begins to increase as energy balance becomes positive and insulin sensitivity is lost.

The Necessity of Sugar for PA

In addition to their essential roles in the maintenance of basal metabolic processes (e.g., brain function), sugar and sugar-polymers (i.e., glucose and glycogen) are also requisite energy substrates for PA.[115] While at rest, skeletal muscle-cells are a major determinant of fatty acid oxidation,[116-118] but as the dose of PA increases, the oxidation of blood sugar and glycogen

increases exponentially.[117, 118] The energy demands of PA behaviors are variable[30, 119] and can exceed that of basal metabolism.[30, 120] The increased demands of high levels of PA require that large amounts of dietary sugar and/or sugar polymers be consumed. Thus, as described in the following section, numerous organizations recommend diets that are high in sugar and/or sugar polymers for recovery, health, and performance.

Recommendations for Elevated Sugar Consumption

Given the necessity of dietary sugars and/or sugar-polymers for PA and athletic performance, medical and health organizations such as the American College of Sports Medicine and the American Dietetic Association recommend a high sugar and/or high sugar-polymer diet for recovery and performance enhancement in highly-active individuals.[121] These evidence-based guidelines explicitly recognize the importance of individual differences and recommend sugar and sugar-polymer consumption ranging from 6 to 10 grams per kilogram per day depending on the total daily energy expenditure, sex and training status of the individual, mode of training, and the environmental conditions during exercise.[121] These recommendations vastly exceed the diet-centric recommendations (e.g., see [40, 53, 54]) that ignore individual differences in metabolic phenotype.

Sugar Consumption Is Entirely Innocuous in Active Populations

Given the large energy demands of PA, it is not uncommon for active individuals and populations to consume more than 70% of their energy needs in some form of sugars,[9, 122, 123] and/or sugar-polymers.[25, 124, 125] Anthropologic research shows that modern hunter-gatherers seasonally consumed 20-80% of their total energy intake as 'added sugar' (i.e., honey,[122, 123] a disaccharide of glucose and fructose) while increasing their glycemic and fructose loads via the intrinsic sugars in fruits and tubers.[8, 9, 122] This is 5-8 times greater than current recommendations. Despite the massive consumption of sugar and high glycemic loads, these populations have some of the lowest NCD risks ever recorded.[119, 126, 127] For example, modern hunter-gathers have a very low prevalence of hypertension, low body mass index, low total cholesterol, and unlike inactive Americans, these health metrics do not vary with age.[126]

The extremely low-prevalence of obesity and NCDs in these populations in concert with massive sugar consumption[119, 126, 127] can be explained by their high PA levels and concomitant levels of skeletal muscle and hepatic-cell metabolic-flux. Hill et al. described one modern hunter-gatherer population as*, "a healthy robust population that maintains a high* [physical] *activity profile*",[123] and Raichlen et al. stated, "*the Hadza engage in over 14 times as much MVPA* [moderate to vigorous PA] *as subjects participating in large epidemiological studies in the United States. We found no evidence of risk factors for cardiovascular disease in this population (low prevalence of hypertension across the lifespan, optimal levels for biomarkers of cardiovascular health).*"[119]

Epidemiologic Evidence: A Positive Association between Sugar Consumption and Health

In addition to anthropologic evidence, epidemiologic evidence demonstrates that highly-active individuals and athletes exhibit high levels of metabolic health throughout their lifespan.[128, 129] These individuals maintain high insulin sensitivity in concert with low levels of body fat and low levels of metabolic disease[130-133] while consuming diets rich in simple sugars and using SSBs to enhance athletic performance.[134-137] For example, a survey conducted at the US Professional Championship Road Race demonstrated that more than 50% of the cyclists drank SSBs during the race,[138] and marathoner Frank Shorter credited his 1972 gold-medal marathon performance to his use of SSBs.[136] Research demonstrates that glucose and fructose are the sugars of choice "*to restore muscle glycogen deposits after exercise*"[134] and "*sucrose should continue to be regarded as one of a variety of options available to help athletes achieve their specific carbohydrate-intake goals*."[135] Thus, the consumption of dietary sugars at doses many times diet-centric recommendations are entirely innocuous in active individuals.

While some erroneously argue that despite their similar chemical composition that not all 'added sugars' are alike, Raatz et al. demonstrated that the effects of the disaccharides honey, sucrose, and high-fructose corn syrup on glycemia, lipid metabolism, and inflammation were similar within participants.[139] Thus, it is logical to posit that the only reason sugar consumption appears to be deleterious in industrialized nations is that PA levels and skeletal muscle- and hepatic cell metabolic-flux are simply too low to support metabolic health.[31-33, 58, 73, 101, 103]

Food Availability Data: A Positive Association between Sugar Consumption and Health

From a historical perspective, the greatest increases in sugar availability in the US occurred from the late 19th century until World War II and remained relatively flat until 1980. During this period, sugar availability increased from less than 10 lbs per capita to more than 100 lbs per capita per year; an increase of more than 1 lb. per person per week.[14] Given that the US population experienced large improvements in every health metric examined over the period from 1880 to 1980,[11, 12] it is unequivocal that sugar consumption has a positive association with health and well-being. In 1979, the availability of sugar in the American food supply had never been higher and the US Surgeon General's report on Health Promotion and Disease Prevention began with the unequivocal statement that, "*The health of the American people has never been better.*"[140] If sugar were harmful, large increments in the availability of dietary sugars should not have occurred in confluence with decade-by-decade improvements in public health. Clearly, a century of increased sugar availability did not have the deleterious dose-dependent effects that the diet-centric rhetoricians claim.

Similarly, the United Kingdom experienced increments in health and wellbeing in lockstep with increases in sugar availability as it rose from less than 10 lbs per capita at the turn of the 19th century to over 100 lbs before the Second World War. As in the United States, this substantial increase is sugar availability was linked to better, not worse health. For example, "*Significant positive correlations exist between the secular increase in brain weight of adults in London born between 1860 and 1940, and the secular trend in sugar consumption in the United Kingdom*."[141] Clearly, these data do not support a negative effect of increased sugar consumption on health and wellbeing.

A Natural Experiment: Increased Sugar Consumption = Improved Health

With the fall of the Soviet Union in the 1980s, Cuba was forced to rely on domestic crops such as sugar cane. While overall sugar production declined,[142] domestic sugar utilization increased from 530 metric tons in 1980 to 637 in 1995.[143] Concomitant with that increase in sugar use was a large and significant increase in PA and significant declines in obesity, T2DM, and NCDs.[144]

These results suggest that increments in both PA and dietary sugar lead to improvements in metabolic health.

Diet-Centrism Relies on Pseudoscientific and Inadmissible Data

Diet-disease relations were posited early in recorded history,[56] and it is now widely established that an individual's health may be severely affected by his or her dietary intake. For example, if an individual chronically fails to consume sufficient nutrient-energy to meet metabolic demands, that person will die (i.e., starve to death). Similarly, if a person does not consume adequate levels of micronutrients, he or she will suffer diseases specific to the dietary deficiency (e.g., pellagra from insufficient niacin, or scurvy from insufficient Vitamin C). It is important to note that the established causal effects of diet are limited exclusively to disease-specific deficiencies and starvation (i.e., protein-energy malnutrition).

Yet, beginning in the mid-20th century nutrition researchers began speculating that the overconsumption of specific macro-nutrients, foods, and beverages were responsible for a wide variety of NCDs and obesity. Despite the fact that these speculations were not supported by the extant evidence[2] and failed to meet many of Bradford Hill's criteria (e.g., strength, consistency, biological gradient, and specificity),[145] they immediately gained wide-spread political support.[2] Given the substantial evidence to the contrary,[2] diet-centric investigators began employing a demonstrably pseudoscientific method to collect dietary data. These methods, known as Memory-Based Dietary Assessment Methods (M-BMs; e.g., food frequency questionnaires),[4, 146, 147] were based on the naïve notion that a person's usual diet could be measured simply by asking what he or she remembered eating and drinking.

Despite the credulousness necessary to employ M-BMs and the unfalsifiable (i.e., pseudo-scientific) nature of the data produced, epidemiologists used it to produce thousands of influential publications that dominated the empiric landscape and significantly altered the perception of diet-disease relations. Nevertheless, when the highly publicized nutrition claims derived from M-BMs (e.g., see [148, 149]) were tested using objective study designs, they were found to be false.[150-154] For example, Young and Karr examined over 50 nutritional claims and

demonstrated that *"100% of the observational claims failed to replicate"* and some were statistically significant "*in the opposite direction*."[155] These results suggest that M-BMs are invalid and the vast majority of diet-disease relations are spurious.

Given the lack of support for diet-disease relations, my colleagues and I published a series of scientific, policy, and popular media articles,[2, 4-6, 146, 147, 156-167] with the express purpose of ending the use of M-BMs in scientific research and public policy formation. Our work empirically and theoretically refuted the validity of M-BMs and demonstrated that self-reported dietary data were physiologically implausible (i.e., meaningless numbers),[4, 5, 146, 147, 163] *"incompatible with life",*[150 p.347] and were repeatedly demonstrated to have little relation to actual nutrient and energy consumption.[150, 168-171] Furthermore, we showed that because there was no way to ascertain if the reported foods and beverages matched the respondent's actual intake, the measurement errors associated with self-reported data were non-quantifiable and non-falsifiable (i.e., pseudo-scientific). More importantly, these non-quantifiable errors were systematically propagated when the self-reported foods and beverages were pseudo-quantified via the assignment nutrient and energy values to create estimates of consumption. Our conclusions were that M-BMs were *"pseudo-scientific and inadmissible…* [and] *…constituted an unscientific and major misuse of research resources."* [4p. 911] These conclusions were supported by 60+ years of highly replicated evidence (for reviews please see[4, 146]). Nevertheless, the authors of the 2015 Dietary Guidelines for Americans,[172] a major report from the National Academies of Sciences, Engineering, and Medicine,[173] and other influential research papers[53, 174, 175] failed to cite, address, or even acknowledge our critiques and empirical refutations. Thus, many investigators and public policy architects remain uninformed about the lack of validity of M-BMs.

Most importantly, when the pseudo-scientific M-BM data, results, and conclusions are removed for the scientific discourse, there is little evidence to support diet-centric speculations or population-level dietary recommendations on dietary sugar consumption. Meta-analyses and reviews of randomized control trials demonstrated that the assumed negative effects of dietary sugars are due to positive energy balance and not the consumption of sugars *per se*.[176-182] Thus, the anti-sugar narrative has little support, and as presented herein, there is a large body of evidence to the contrary.

Obesity and T2DM: Blood Sugar, not Dietary Sugars Matter

Recent research strongly suggests that obesity and T2DM are not diet-related diseases but are metabolic conditions caused by the positive energy balance (i.e., over-nutrition) driven by the confluence of physical inactivity and nongenetic evolutionary processes known as *'accumulative maternal effects'*.[27, 28, 34, 183, 184] Stated simply, over the past few generations, PA and fitness levels declined precipitously in both children and adults.[29, 31-33, 58, 102, 104, 105] Given that PA is the major determinant of metabolic health, these trends led to decrements in metabolic control across the population,[185] with concomitant increments in the prevalence of pathological metabolic phenotypes such as acquired (i.e., adult-onset) obesity and T2DM. (For reviews of these trends please see [27, 28]).

Maternal Effects: Why A Mother's Blood Sugar Matters

The term *'maternal effects'* describes the nongenetic evolutionary process by which a mother's phenotype (i.e., her characteristics; e.g., body mass and behavior) alters both pre- and post-natal development, independent of genotype. Maternal effects significantly influence the survival and health trajectories of her offspring,[27, 28] and in humans and other mammals, it is well established that a mother's prenatal metabolic control is the major determinant of the birth weight and metabolic phenotype of her offspring (e.g., ratio of skeletal muscle to fat cells).[27, 28, 186-190] Thus, as mothers became increasingly physically inactive and sedentary in the latter half of the 20th centruy,[31-33] the loss of metabolic control increased the availability of sugar (glucose) and lipids to the intrauterine milieu. Because the availability of sugar (glucose) is a major determinant of adipocyte (fat-cell) number and pancreatic beta-cell development,[27, 28] the children of inactive mothers were born increasingly predisposed to inherited (i.e., pediatric) obesity and T2DM. With each passing generation, these '*maternal effects*' accumulated and led to the twin-epidemics of both obesity and T2DM.[27, 28, 34, 191, 192]

The Physiologic Illiteracy of Diet-Centric Public Health Recommendations

By design, detailed, prescriptive population-wide dietary recommendations on the consumption of dietary sugars (e.g., see [40, 53, 54]) ignore individual differences and the physiologic context of

the consumer. These diet-centric sanctions erroneously assume that the effects of sugar consumption are uniformly deleterious across the population. This error is based on the failure to understand that it is not the consumption of nutrient-energy, nor the rise in serum and tissue energy substrates that lead to metabolic disease, but rather the inability of skeletal muscle- and hepatic cells to control energy intake and re-establish metabolic homeostasis in the post-prandial and post-absorptive periods by disposing of serum sugars and lipids. Thus, it is not 'what you eat' that causes obesity and NCDs, but what your body does with what is eaten.

As detailed herein, the chronic overconsumption of nutrient-energy and concomitant elevated serum and tissue energy substrates that lead to metabolic diseases *can only be achieved* via physical inactivity in current and/or past generations. Therefore, our present state of poor metabolic health is not because our diets are unhealthy or that we consume sugars, it is because we are physically inactive.[27, 29-34, 58, 73, 101-103, 193-195]

Conclusion

In this review, I presented evidence to challenge *diet-centrism* and demonstrate that diet-centric reductionism has led researchers, policy-makers, and the public seriously astray. The consumption of dietary sugars is entirely innocuous in healthy populations and essential for many highly-active individuals. Thus, the only reason sugar consumption now appears deleterious in industrialized nations is that PA levels and metabolic-flux are too low to support metabolic health. Until the pathologies of physical inactivity and high sedentary behaviors are corrected, our population's metabolic health will continue to decline. As such, current diet-centric hyperbole surrounding sugar consumption impedes progress in medical science by diverting attention and research resources from the true causes of obesity and metabolic diseases: low levels of PA and reduced metabolic-flux.

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