Clinical Studies

Clinical studies confirming Sweet Nothing's active ingredient, is safe and effective for significantly reducing the desire for sweet foods, reducing appetite for all foods, and reducing total calorie consumption.

General Information

Adigam is a liana or climbing plant with stems up to 8 m in length. It grows in open woods and bushland at an altitude of 100-1000 m in India, China, Indonesia, Japan, Malaysia, Sri Lanka, Vietnam and South Africa. Both the leaf and root are used in Ayurvedic medicine. On account of its property of abolishing the taste of sugar it was given the Hindi names of Gurmar and Madhunashini meaning 'sugar destroying.' The sweet taste suppressant property of Adigam was revealed to a British officer by the inhabitants of a northern Indian village in the mid-19th century. The herb is traditionally used for the treatment of diabetes and Adigam extracts are sold in Japan for the control of obesity.

Clinical Summary

Actions
Antiobesity, Antidiabetic, hypoglycaemic, hypocholesterolaemic

Therapeutic Indications
• Hyperglycaemia, insulin-dependent and non-insulin-dependent diabetes mellitus (prolonged administration required).

Dosage & Administration

For sweet-craving and sweet taste depression 1 to 2 mL per day of liquid extract or 2.6 g tablet form is all that is necessary. This should be applied in divided doses directly to the tongue by dropper and rinsed off after one minute. This can be done at 2- to 3-hour intervals.

Adverse Reactions: None known

Contraindications & Cautions: None known.

Traditional Uses

Adigam has been described in Hindu Materia Medica as a stomachic, diuretic and antiperiodic (e.g. to treat a periodic illness such as malaria). In Ayurvedic medicine indications for Adigam include glycosuria, urinary disorders and diabetes mellitus.2 Adigam has been used in the treatment of diabetes mellitus in India for over 2000 years.4

Scientific Studies

Constituents

Adigam leaf contains 4 to 10% of a group of more than 20 saponin glycosides of the oleanane-type including gymnemic acids I-XVIII and gymnemasaponins I-V.5-7 Some of the gymnemic acids are acylated (contain an acyl group), while the gymnemasaponins are non-acylated. Acylation affects pharmacological activity.

Dammarane-type saponins8 and a polypeptide consisting of 35 amino acid residues called gurmarin and other oleanane-type saponins (gymnemasins) have also been isolated.

Pharmacodynamics

'Gymnemic acid' referred to in the literature is often not chemically defined and most likely refers to the crude saponin fraction of Adigam (i.e. all the saponins) or to a mixture of the gymnemic acids.

Sweet Taste Suppression (Antisweet Activity)

The antisweet principles of Adigamin include gymnemic acids,11 gymnemasaponins6 and gurmarin.12 Gymnemasaponins completely inhibited the perception of sweetness induced by a 0.1 M sucrose solution. This is about half the activity exhibited by the gymnemic acids. (Hence the structure of the saponin affects the magnitude of the sweetness inhibition. Acylation of the saponin, as occurs (naturally) in the gymnemic acids, produces greater inhibition.)6 The reduced sensitivity to sweet substances produced by Adigammight result from the competition at the receptor sites between glycosides and the sweet substances.13 An electrophysiological study on taste responses in rats suggests that gurmarin acts on the apical side of the taste cell, possibly by binding to the sweet taste receptor protein.14

In humans and chimpanzees, gymnemic acids suppress the sweet taste of all sweeteners but had no effect on taste receptors sensitive to bitter or salty substances in chimpanzees.15 The sweet suppressing activity of Adigamextract in humans has been verified by measurement of gustatory evoked potentials.16 In experimental models the degree of suppression produced by gymnemic acid (measured by nerve response) varied from complete abolishment (aspartame, saccharin) to about 50% reduction (xylitol). Gymnemic acid had no effect on the responses to nonsweet (bitter, salty or sour) compounds. These results parallel psychophysical and electrophysical findings in humans.17

A gymnemic acid rinse used by human volunteers reduced the intensities of sucrose and aspartame to 14% of their pre-rinse levels.18 Over a recovery interval of 30 minutes these values increased linearly to 63% of the pre-rinse levels. A study involving human volunteers observed that a period of at least 30 seconds was required after tasting Adigaminfusion for the full sweet suppression effect to appear.19

Pretreatment with Adigam extracts reduced the sweetness of sweeteners by an average of 77% in volunteers. There was no evidence for a differential effect across the range of sweeteners (3 concentrations each of acesulfame K, aspartame, sodium cyclamate, fructose, glucose, sucrose, stevioside and xylitol). The percentage reduction in sweetness was constant across the low, medium and high concentrations. Such results suggest that a receptor occupancy or blocking mechanism is unlikely. A type of 'mixed' inhibition involving an effect on the breakdown of the stimulus/receptor complex is more likely.20

For further antisweet activity demonstrated in humans see below in Clinical Studies (Weight Loss).21

Hypoglycaemic Activity

Pharmacodynamic and clinical studies suggest that the hypoglycaemic activity of Adigam may be mediated through stimulation of insulin release (and possibly by pancreatic regeneration or repair), stimulation of enzymes responsible for glucose uptake and utilisation and/or inhibition of intestinal absorption of glucose.22-25

Adigam extract and some isolated constituents have inhibited glucose uptake in isolated small intestinal tissue.26,27 Adigam extract and gymnemic acids inhibited the intestinal absorption of glucose in humans and rats.28,29 In evidence of this, two fractions obtained from Adigam(containing gymnemic acids) suppressed potassium-induced contraction of isolated ileal longitudinal muscle, interfered with the increase in transmural potential difference induced by glucose and inhibited the elevation of blood glucose in vivo (route unknown).30 Two gymnemic acids suppressed the contraction of smooth intestinal muscle, most likely by inhibiting glucose uptake.28

Oral administration of Adigam extract reduced post-prandial serum glucose and improved glucose tolerance in mildly diabetic rats. Pancreas weight and content of insulin were not changed.31 Adigam corrected hyperglycaemia in mild alloxan-diabetic rats and significantly prolonged lifespan in severe alloxan-diabetic rats (i.e. with completely destroyed pancreatic tissue). The authors suggested that the prolonged survival time was due to the adaptogenic activity of Gymnema.32

Feeding with Adigam leaf powder regulated blood sugar levels in alloxan-diabetic rabbits and increased the activities of enzymes which facilitate the use of glucose by insulin-dependent pathways (phosphorylase, gluconeogenic enzymes and sorbitol dehydrogenase). Uptake of glucose into glycogen was increased in liver, kidney and muscle. Adigam treatment also increased the incorporation of glucose into the protein components of these tissues.22 The hypoglycaemic activity of Adigam occurs in a slow and steady manner: in rabbits with mild alloxan-diabetes between 12 and 24 weeks of treatment was required.4

Blood sugar levels in normal and diabetic rats were lowered 2 hours after oral administration of a Adigam concentrate (50-400 mg/kg, 19.5:1), but Adigam was 6 times less potent than oral tolbutamide in the diabetic animals.33 Two Adigam extracts returned fasting blood glucose levels to normal after 20 to 60 days of oral administration to diabetic rats. A rise in serum insulin towards normal fasting levels occurred and the number of beta cells within pancreatic tissue increased.23 This suggests a restorative effect on pancreatic tissue.

The crude saponin fraction of Adigam and gymnemic acid IV reduced blood glucose levels in streptozotocin-diabetic mice when administered by injection. Gymnemic acid IV also increased plasma insulin levels.34 Gymnemoside b and gymnemic acids III, V and VII (route unknown) produced some inhibitory activity on glucose absorption after oral glucose loading in rats, but gymnemic acid I and gymnemasaponin V were inactive.35

Appetite & Weight Loss

The effect of Adigam on body weight, glucose absorption and lipid metabolism was examined by using a breed of fatty rats with genetic obese-hyperglycaemia. Simultaneous feeding with Adigamaqueous extract decreased body weight in fatty and lean rats (4.2% and 6.1% respectively) compared to animals consuming only the test diet (high carbohydrate-low fat) over a 21-week period. Plasma glucose was lower by 18% in the Gymnema-treated animals compared to controls. The plasma glucose increase following an oral glucose tolerance test was almost normalised in the Gymnema-treated group without any alteration in serum insulin levels. Hypertriglyceridaemia, but not hypercholesterolaemia, was also improved in the treated group.36

Two fractions of Adigam extract (containing 160-360 mg/g of gymnemagenin) decreased body weight gain and food intake dose-dependently when given orally (0.05-1.0 g/kg) to rats for 22 days. Administration of a Adigamfraction (1.0 g/kg) containing 363 mg/g of gymnemagenin increased faecal excretion of cholesterol, total neutral steroids, total bile acids and cholic acid-derived bile acid. These increases correlated with faecal gymnemagenin levels.37

Other Activity

Adigam ingestion produced a significant lowering of cholesterol in a hypertension model, but did not lower (and even tended to increase) the raised systolic blood pressure induced by sugar feeding.38

Pharmacokinetics

No information available.

Toxicology

In acute toxicity studies no gross behavioural, neurologic or autonomic effects were observed in mice orally administered graded doses (250-8000 mg/kg) of an aqueous alcoholic concentrate of Adigam(19.5:1). The LD50 value for this concentrate after oral administration was measured at 3.99 g/kg (equivalent to 78†g/kg of dried Adigamleaf).33 To put this in context the LD50 for sugar in rats orally is 29.7 g/kg and for table salt is 3 g/kg.39 A substance is considered non-toxic if it produces no effect in a dose of up to 10 g/kg.40

Clinical Studies

Diabetes

The reduction of urinary glucose levels in diabetics by oral administration of Adigam was reported as early as 1926.41 The hypoglycaemic effect of Adigam powder (10 g/day for 7 days) was investigated in 16 normal subjects and 43 mild diabetics in an uncontrolled trial. A hypoglycaemic effect was observed in the diabetics. Serum triglycerides, free fatty acids and cholesterol levels were also decreased. Excretion of creatinine was decreased in the diabetic group.42

A controlled study on insulin-dependent diabetics found that a water-soluble Adigam extract (400 mg/day corresponding to about 8 g of starting dried herb) reduced insulin requirements (by about 50%). Over the duration of treatment Adigam lowered fasting mean blood glucose (by about 35%), glycosylated haemoglobin and glycosylated plasma protein levels from baseline values. Cholesterol was significantly reduced and brought to near normal levels. Triglycerides, free fatty acids and serum amylase were also lowered. The treatment period ranged from 6-30 months. The significant decrease in glycosylated haemoglobin occurred after 6-8 months of Adigam treatment but remained significantly higher than normal values. None of these reductions were observed in control patients on insulin therapy alone who were studied over a period of 10-12 months. The authors suggested that Adigam enhanced endogenous insulin production, possibly by pancreatic regeneration, as levels of C-peptide, a by-product of the conversion of proinsulin to insulin, were apparently raised (in comparison to both the insulin alone group and normal subjects).24

A second study by the same research group found that the same Adigam preparation (400†mg/day) produced similar results for non-insulin-dependent diabetics. Fasting blood glucose, glycosylated haemoglobin and glycosylated plasma protein were significantly reduced compared to baseline values ($p<0.001$) after 18-20 months of treatment. None of these reductions were observed in patients receiving conventional therapy alone who were studied over a period of 10-12 months. By the end of the treatment period cholesterol, triglycerides, phospholipids and free fatty acid levels were also significantly reduced compared to baseline values in those receiving Adigam($p<0.001$). Control patients receiving only conventional therapy achieved reductions in cholesterol, triglycerides and free fatty acids ($p<0.05$-$p<0.001$). Fasting and post-prandial serum insulin levels were significantly increased in the Adigam group compared to those taking only conventional drugs ($p<0.01$). Twenty-one of the 22 patients were able to reduce their intake of hypoglycaemic drugs; 5 of these discontinued hypoglycaemic drugs entirely and maintained their blood glucose homoeostasis with Adigam extract alone. The authors' suggestion of beta cell regeneration or repair facilitated by Adigamwas supported by the higher insulin levels in the serum of patients after Adigam supplementation. Adigam administration to healthy volunteers did not produce any acute reduction in fasting blood glucose level.25

A clinical trial recently conducted in the US provides further support for the use of Adigamin the management of diabetes. Of 65 patients tested over the 90-day trial, Adigam tablets reduced

mean fasting glucose levels by 11%. Average post-meal glucose levels showed a decline of 13% and glycosylated haemoglobin levels dropped 6.8%. In a subset of patients with the poorest control, results were more substantial. Pre-meal readings averaged an 18% decline, with post-meal levels reduced by 28%. Corresponding glycosylated haemoglobin levels declined 10%. Improved glucose control with Adigam enabled 16% of the participants to decrease their prescription medication usage.43 The tablets used in the trial contained 400 mg of Adigam extract (equivalent to around 4 g of leaf) standardised to 25% gymnemic acids. The dose used was two tablets per day.

Weight Loss

A double-blind clinical trial investigated the effects of sweetness perception on short-term intake of food in men and women of normal weight.21 Participants were required to rate the 3 test solutions for sweetness (milkshakes with added sucrose, added aspartame or no added sweetener (placebo)). After an initial training in the sweetness scale, participants rinsed with either concentrated Adigam extract solution (gymnemic acid content not defined) or placebo (tea solution) and rated the test solutions for sweetness. Subsequent ratings were made up to 60 minutes after the rinsing. Participants who had rinsed with Adigam rated test solutions as less sweet compared to those who rinsed with placebo.

Thirty minutes after the last set of ratings a test meal consisting of snacks was presented in the context of providing refreshment. Participants were told that this was not part of the experiment. The Adigam group ate less total calories (501 ± 237 vs. 638 ± 333, $p<0.006$), total carbohydrates ($p<0.003$), total protein ($p<0.018$) and total fat ($p<0.015$) than participants whose taste perception was normal (tea group).

Acknowledgement

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Supporting Clinical Studies demonstrating how controlling sugar craving and eating less sugar provides a myriad of health benefits

Clinical study showing how controlling cravings can help break addiction.

See Study

http://foodaddictioninstitute.org/FAI-DOCS/Physical-Craving-and-Food-Addiction.pdf

Clinical studies linking sugar consumption to weight gain, obesity, and disease.

See Studies

Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial[1,2,3]

Diet, nutrition and the prevention of excess weight gain and obesity

Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity.

Sugar and Cardiovascular Disease

Health Benefits of Reducing Sugar-Sweetened Beverage Intake in High Risk Populations of California: Results from the Cardiovascular Disease (CVD) Policy Model

Improvements in glucose metabolism and insulin sensitivity with a low-carbohydrate diet in obese patients with type 2 diabetes.

The effects of four hypocaloric diets containing different levels of sucrose or high fructose corn syrup on weight loss and related parameters.

Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake

Clinical Studies – Sugar tied to weight gain, obesity, and disease.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2676995/

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PMCID: PMC2676995

Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial[1,2,3]

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Abstract

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INTRODUCTION

It has been projected that 75% of US adults will be overweight or obese by 2015 (1). One factor contributing to this obesity epidemic may be an increased dietary energy intake from beverages. Today, Americans consume 150–300 more calories per day than they did 30 y ago, and caloric beverages account for ≈50% of this increase (2, 3). Energy intake from beverages currently represents 21% of total daily energy intake in the general American population (4). Evidence from short-term human studies suggests that calories consumed in liquid form (ie, liquid calories) have weak satiety properties and elicit poor energy compensation compared with calories from solid foods (ie, solid calories) (5–8). These results suggest that an increase in consumption of liquid calories may result in weight gain, and, conversely, that a reduction in liquid calorie intake may lead to weight loss. However, there is a scarcity of strong scientific evidence supporting these hypotheses, particularly from long-term prospective studies. This paucity of evidence has impeded policymaking.

The type of beverage may also influence body weight. For sugar-sweetened beverages (SSBs), some longitudinal studies suggest a positive association between consumption and body weight (9–14). However, many of these studies either failed to control for important confounding factors, such as physical activity, or used unreliable dietary assessment methods. Likewise, recent reviews on the topic had reached different conclusions: 2 (15, 16) proposed that the consumption of SSBs was positively associated with body weight, whereas 6 others (17–20) concluded that there was insufficient evidence. Some studies suggest that milk intake may aid voluntary weight loss (21–24), whereas others found the opposite effect or no effect (25–30).

The objectives of the present study were to determine *1*) how changes in liquid calorie intake affect body weight,*2*) whether liquid calories are more obesogenic than are solid calories, and *3*) how changes in consumption of specific beverages affect body weight among adults.

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SUBJECTS AND METHODS

Study population

PREMIER is a completed, 18-mo multicenter randomized trial designed to test the blood pressure–lowering effects of 2 multicomponent behavioral interventions in adults with prehypertension or stage 1 hypertension (a systolic blood pressure of 120–159 mm Hg and a diastolic blood pressure of 80–95 mm Hg). The cohort consisted of 810 men and women aged 25–79 y, recruited from 4 study centers (Baltimore, MD, Baton Rouge, LA, Durham, NC, and Portland, OR). Individuals who used antihypertensive medications, weight-loss medications, or oral steroids routinely were excluded. Other exclusion criteria included diabetes, a history of a cardiovascular event, congestive heart failure, current symptoms of angina or peripheral vascular disease by Rose Questionnaire, cancer diagnosis or treatment in past 2 y (except for nonmelanoma skin cancer), renal insufficiency, or a psychiatric hospitalization within the past 2 y. Detailed information regarding the study methods and main results can be found in our previous publications (31, 32). Eligible participants were randomly assigned to 1 of 3 groups: (A) an "Advice Only" comparison group that received information but no behavioral counseling on weight loss, increased physical activity, sodium reduction, and the DASH (Dietary Approaches to Stop Hypertension) dietary pattern (33); (B) a behavioral intervention group, termed "Established," that received counseling on how to lose weight, increase physical activity, and reduce sodium intake; or (C) a behavioral intervention group, termed "Established Plus DASH," that received counseling on the same lifestyle goals as the Established group along with counseling on the DASH dietary pattern. The weight-loss approaches in the Established group focused on increased physical activity and reduced energy intake. In contrast, the weight-loss approach in the Established Plus DASH group focused on increased physical activity, reduced energy intake, and substitution of fruit and vegetables for high-fat, high-calorie foods. Except for the advice to increase the intake of low-fat dairy products in the Established Plus DASH group, no other advice regarding beverage consumption was given to any of the groups. Regarding the contact pattern, participants in the Advice Only group received two 30-min individual advice sessions, one at randomization and the other after the 6-mo data collection. Both the Established and Established Plus DASH groups received behavioral interventions derived from the social cognitive theory. The intervention format and contact pattern of the 2 groups were identical: 14 group meetings were conducted weekly in the initial 14 wk; 6 group meetings were conducted every other week plus a single individual session in the next 14 wk; monthly group meetings and 3 quarterly individual counseling sessions were conducted in the last 48 wk. The PREMIER study was conducted from January 2000 through November 2002. All 810 study participants enrolled at baseline were included in this analysis.

Measurement of dietary and beverage intake

Dietary intake was measured by unannounced 24-h dietary recall conducted by telephone interviews. Two recalls (one on a weekday and the other on a weekend day) per participant were obtained at baseline and at 6 and 18 mo. A multiple-pass technique and portion size estimation aids were used. Intakes of nutrients and food groups were calculated by using the Nutrition Data System for Research, version NDS-R 1998 (University of Minnesota, Minneapolis, MN).

We divided beverages into 7 categories based on calorie content and nutritional composition: *1*) SSBs (regular soft drinks, fruit drinks, fruit punch, or any other high-calorie beverage sweetened with sugar), *2*) diet drinks (diet soda and other "diet" drinks sweetened with artificial sweeteners), *3*) milk (whole milk, 2% reduced-fat milk, 1% low-fat milk, and skim milk), *4*) 100% juice (100% fruit and vegetable juice), *5*) coffee and tea with sugar (CTS: coffee and tea sweetened with sugar), *6*) coffee and tea without sugar (CT: unsweetened coffee and tea or coffee and tea sweetened with artificial sweeteners), and *7*) alcoholic beverages (beer, wine, spirits, and other alcoholic drinks). Each participant's daily nutrient, energy, and beverage intakes were calculated by taking the average of 2 recalls per time point. Liquid calorie intake was calculated as the sum of calories from the 7 beverage categories. Solid calorie intake was calculated by subtracting liquid calories from total calories.

Measurement of outcomes and covariates

Weight and height were measured with a calibrated scale and a wall-mounted stadiometer while the subjects were wearing light clothing and no shoes. Fitness was assessed using a 2-stage 10-min submaximal treadmill stress test and defined as the heart rate (beats/min) at a fixed workload (stage 2). Physical activity (estimated energy expenditure; in kcal $\cdot$ kg^{-1} $\cdot$ d^{-1}) was assessed by using a 7-d diet recall questionnaire (34). Other data, such as age, sex, race-ethnicity, income, education, employment, marriage status, and smoking habits were collected at baseline.

Statistical analysis

All statistical analyses were performed by using STATA version 9.0 (Stata Corp, College Station, TX). Statistical significance was set at $P \leq 0.05$ (2-tailed). The analyses were conducted by combining all participants and adding intervention assignment as a covariate in all models.

The 2 main exposures of interest were *1*) changes in consumption of liquid calories and *2*) changes in consumption of individual types of beverages, each assessed from baseline to 6 and 18 mo separately. Key outcome variables were weight changes from baseline to 6 and 18 mo. For the primary analysis, exposure and outcome variables were modeled as continuous variables. Additional analyses with exposures modeled as categorical variables were carried out to assess the patterns of dose response. In model 1, changes in consumption of solid and liquid calories were simultaneously included with adjustments for baseline age, sex, race, income, education,

marital and employment status, body mass index (BMI; in kg/m^2) status, intervention allocation, and concurrent changes in fitness and physical activity. In model 2 the primary exposure variable was percentage of liquid calories, and the model was adjusted for the same covariates as in model 1. In model 3, we assessed the role of individual beverages by including each type of beverage; in this model, we adjusted for total energy intake and the covariates included in model 1. Additional adjustment for smoking status (never, past, or current) and dietary factors such as fat and carbohydrate intakes and energy density did not change the results. Therefore, these variables were not included in the final models. Missing values were not imputed in primary analyses. In sensitivity analyses, we used the baseline observation carried forward method to assess the effect of missing values on study results. The study protocol was approved by the institutional review boards of each of the participating centers and was monitored by an external data safety committee.

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RESULTS

Baseline characteristics and retention to follow-up

The baseline characteristics of the participants are shown in **Table 1**. There were 62% women and 34% African Americans, with an average age of 50 y. Fifty-seven percent of participants had college degrees or above, 65% were married, and 70% had a household income >$45,000/y. Most of the participants were current nonsmokers (95%), 29% were overweight (BMI: 25–29.9), and 65% were obese (BMI ≥ 30). At 18 mo, 94% of the participants had a weight measurement, and 90% had at least one dietary recall.

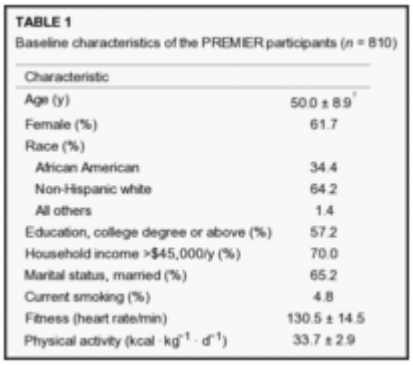

TABLE 1
Baseline characteristics of the PREMIER participants (n = 810)

Characteristic	
Age (y)	50.0 ± 8.9[1]
Female (%)	61.7
Race (%)	
African American	34.4
Non-Hispanic white	64.2
All others	1.4
Education, college degree or above (%)	57.2
Household income >$45,000/y (%)	70.0
Marital status, married (%)	65.2
Current smoking (%)	4.8
Fitness (heart rate/min)	130.5 ± 14.5
Physical activity (kcal · kg^{-1} · d^{-1})	33.7 ± 2.9

TABLE 1

Baseline characteristics of the PREMIER participants (n = 810)

Beverage consumption and changes in body weight during follow-up

The mean (±SD) body weight was 95.2 ± 1.8 kg at baseline, 91.2 ± 18.9 kg at 6 mo, and 91.7 ± 19.7 kg at 18 mo. Across all groups, the mean (±SD) weight loss was 3.5 ± 5.2 kg at 6 mo and 3.0 ± 6.1 kg at 18 mo.

The consumption of beverages at baseline and at 6 and 18 mo is shown in **Table 2**. The mean liquid calorie intake at baseline was 355.6 kcal/d, or 19.0% of the total caloric intake. At baseline, SSBs were the leading source of liquid calories (131.1 kcal/d, 37% of liquid calories), followed by 100% juice (60.5 kcal/d), alcoholic beverages (52.4 kcal/d), CTS (46.5 kcal/d), milk (42.5 kcal/d), CT (16.2 kcal/d), and diet drinks (6.4 kcal/d). There was a decrease in liquid calorie intake during follow-up.

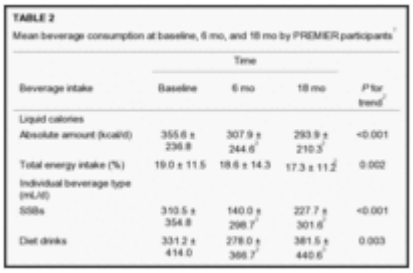

TABLE 2

Mean beverage consumption at baseline, 6 mo, and 18 mo by PREMIER participants[1]

Beverage intake	Time			*P* for trend[2]
	Baseline	6 mo	18 mo	
Liquid calories				
Absolute amount (kcal/d)	355.6 ± 236.8	307.9 ± 244.6[3]	293.9 ± 210.3[3]	<0.001
Total energy intake (%)	19.0 ± 11.5	18.6 ± 14.3	17.3 ± 11.2[3]	0.002
Individual beverage type (mL/d)				
SSBs	310.5 ± 354.8	140.0 ± 298.7[3]	227.7 ± 301.6[3]	<0.001
Diet drinks	331.2 ± 414.0	278.0 ± 366.7[3]	381.5 ± 440.6[3]	0.003

TABLE 2

Mean beverage consumption at baseline, 6 mo, and 18 mo by PREMIER participants[1]

At baseline, the most-consumed beverages by volume were diet drinks (331.2 mL/d), followed by SSBs (310.5 mL/d), CTS (183.3 mL/d), CT (162.6 mL/d), 100% juice (139.0 mL/d), alcoholic beverages (100.5 mL/d), and milk (94.6 mL/d). Significant changes in beverage consumption were observed at 6 and 18 mo, and the changes varied by beverage type and time. At 6 mo, the consumption of SSBs, diet drinks, and CTS decreased significantly; of juice and milk increased; and of CT and alcoholic beverages did not change. From baseline to 18 mo, the consumption of SSBs, CTS, and CT decreased; of diet drinks increased; and of milk, juice, and alcoholic beverages did not change. We also performed a test of trend for each beverage category across the 3 time points. Overall, consumption of SSBs, CTS, and CT decreased with time, whereas the consumption of diet drinks increased.

Association between beverage consumption and weight loss

The longitudinal associations between changes in body weight and in intakes of liquid calories, solid calories, and individual beverages are shown in **Table 3**. We also examined these associations in cross-sectional analyses and found them similar to those in the longitudinal analyses (data not shown).

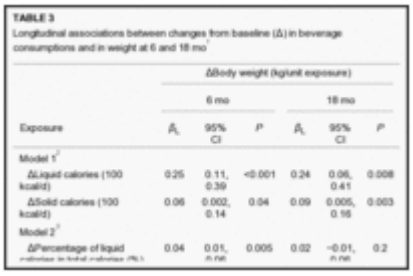

TABLE 3

Longitudinal associations between changes from baseline (Δ) in beverage consumptions and in weight at 6 and 18 mo[1]

Change in consumption of liquid and solid calories and change in body weight

When both liquid and solid calories were included in the analysis (model 1), changes in these variables were significantly and positively associated with weight change. A reduction of 100 kcal/d in liquid calorie intake was associated with 0.3 kg of weight loss (95% CI: 0.1, 0.4; $P <$ 0.001) at 6 mo and of 0.2 kg (95% CI: 0.06, 0.4; P= 0.008) at 18 mo. A reduction in solid calorie intake by 100 kcal/d was associated with a 0.06-kg weight loss (95% CI: 0.002, 0.14; P = 0.04) at 6 mo and of 0.09 kg (95% CI: 0.005, 0.16; P = 0.003) at 18 mo. A reduction in liquid calorie intake had a stronger effect on weight loss than did a reduction in solid calorie intake, but the difference was statistically significant only at 6 mo (P value for the test of $\beta_{\text{liquid}} - \beta_{\text{solid}} > 0$ was 0.006 at 6 mo and 0.09 at 18 mo). This finding was also supported by the results from model 2 (Table 3). A reduction in the percentage of liquid calories from total calories by 1% was associated with a weight loss of 0.04 kg (95% CI: 0.01, 0.06; P = 0.005) at 6 mo and of 0.02 kg (95% CI: −0.01, 0.06; P = 0.2) at 18 mo. We further conducted a stratified analyses based on participants' race (white or black), sex (male or female), baseline BMI (<30 or ≥30), or age group (<50 or ≥50 y). The results are shown in **Table 4**. Liquid calories apparently had a stronger effect on weight loss in blacks than in whites; however, there was no evidence to suggest that the difference was statistically significant (P for interaction = 0.6 at 6 mo and 0.8 at 18 mo).

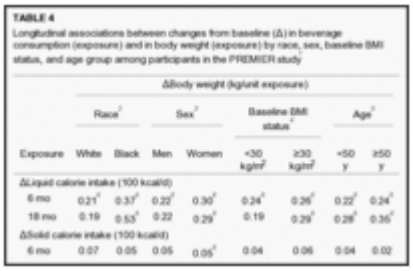

TABLE 4

Longitudinal associations between changes from baseline (Δ) in beverage consumption (exposure) and in body weight (exposure) by race, sex, baseline BMI status, and age group among participants in the PREMIER study[1]

Consumption of individual beverages and change in body weight

In another model (model 3), in which the exposures were individual beverages, only the change in consumption of SSBs was significantly associated with weight change at both 6 and 18 mo. A reduction in SSBs by 1 serving/d (355 mL, or12 fl oz) was associated with a weight loss of 0.5 kg (95% CI: 0.1, 0.8; $P = 0.006$) at 6 mo and of 0.7 kg (95% CI: 0.2, 1.1; $P = 0.003$) at 18 mo. Changes in the consumption of diet drinks and alcoholic beverages were inversely associated with weight loss, both at 6 and 18 mo, but were not statistically significant. None of the other beverage types was significantly associated with weight change at follow-up (Table 3). In the stratified analyses, the positive association between SSB consumption and weight loss was also consistent across each strata. No test for interaction was statistically significant (Table 4).

Change in body weight and change in consumption of liquid calories and SSBs

We examined dose-response patterns for body weight and changes in consumption of liquid calories and SSBs by dividing participants into tertiles based on their 6- or 18-mo change in consumption of liquid calories or SSBs (persons in the first tertile had the greatest reduction). We calculated the model-adjusted mean change and 95% CIs in body weight for participants in each tertile.

Liquid calories

At both 6 and 18 mo, participants in the first tertile had a greater mean weight loss (6-mo change: 0.8 kg, $P = 0.006$; 18-mo change: 1.5 kg; $P < 0.001$) than did those in the third tertile (**Figure 1**). A significant dose-response trend between change in body weight and change in liquid calorie intake was observed for both the 6-mo change ($P = 0.01$) and the 18-mo change ($P < 0.001$).

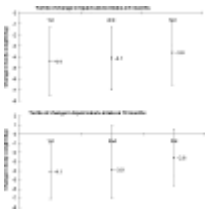

FIGURE 1

Model-adjusted mean weight change and 95% CIs (6 mo − baseline) by tertile of 6-mo liquid calorie intake change and 18-mo weight change (18 mo – baseline) by tertile of 18-mo liquid calorie intake change. At 6 mo, the median change in ...

SSBs

At both 6 and 18 mo, participants in the first tertile had a greater mean weight loss than did those in the second (6-mo change: 0.7 kg; $P = 0.006$; 18-mo change: 1.6 kg; $P < 0.001$) and third (6-mo change: 2.4 kg; $P < 0.001$; 18-mo change: 3.6 kg; $P < 0.001$) tertiles (**Figure 2**). A significant dose-response trend between change in body weight and change in SSB intake was observed at both 6 mo ($P < 0.001$) and 18 mo ($P < 0.001$).

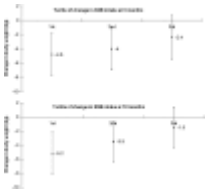

FIGURE 2

Model-adjusted mean 6-mo weight change and 95% CIs (6 mo – baseline) by tertile of 6-mo sugar-sweetened beverage (SSB) intake change and 18-mo weight change (18 mo – baseline) by tertile of 18-mo SSB intake change. At 6 mo, the median ...

Sensitivity analysis

During the follow-up, 1 participant began antihypertensive drug treatment between 3 and 6 mo, 4 participants began antihypertensive drug treatment between 12 and 18 mo, and 6 and 9 participants began insulin/hypoglycemic drug treatment by the 6 and 18 mo visits, respectively. Exclusion of these individuals from our analyses did not change the results. We also applied the baseline observation carried forward method to check the potential influence of missing values. The differences between estimates with and without imputation were very small. For example, the β regression coefficient for change in one serving of SSB consumption at 6 mo was 0.489 (kg/d) without imputation and 0.485 (kg/d) with imputation.

Go to:

DISCUSSION

Four principal findings emerged from our study. First, a reduction in liquid calorie intake was significantly associated with weight loss at both 6 and 18 mo. Second, the weight-loss effect of a reduction in liquid calorie intake was stronger than that of a reduction in solid calorie intake. Third, a reduction in SSB intake was significantly associated with weight loss at both 6 and 18 mo. Fourth, no other beverage type was associated with weight change. On average, a reduction in liquid calorie intake of 100 kcal/d was associated with a 0.3-kg weight loss at 6 mo and a 0.2-kg weight loss at 18 mo. A reduction in SSB intake of 1 serving/d was associated with a 0.5-kg weight loss at 6 mo and a 0.7-kg weight loss at 18 mo.

To our knowledge, our study was the first to document the relative effects of calories from liquids compared with those of calories from solid food on weight loss in free-living adults over an extended period, 18 mo. Previously, evidence on this topic came primarily from animal studies (35–37). The only trial in humans was a 4-wk crossover study of 15 individuals, in which weight gain occurred during the liquid load period, but not during the solid load period (38).

Our study was also one of the few prospective studies to evaluate the effects of a reduction in SSB consumption on weight loss. Two trials investigated the effects of a reduction in SSB intake on weight change in children. Neither reported significant results, but methodologic issues, including inadequate power, may hinder their interpretation.

One explanation for the different satiating effects of beverages and solid foods is the absence of mastication when beverages are consumed (39). The absence of chewing and swallowing when ingesting beverages might result in decreased pancreatic exocrine and endocrine responses compared with the ingestion of solid foods. Second, beverages are also emptied from the stomach at a higher rate than are solids and may induce weaker signals in the gastrointestinal tract that would lead to inhibition of further food intake (40).

Another proposed link between SSB consumption and body weight is related to the high fructose content of SSBs. Long-term consumption of a large amount of fructose can promote fat storage and excessive food intake through an increase in de novo lipogenesis (41) and changes in postprandial hormonal patterns (42).

There are several possible explanations for why the consumption of other caloric beverages was not associated with body weight. First, beverages can differ in their effects on satiety and energy intake (43). It has been proposed that the addition of protein, fat, or fiber to a beverage enhances satiety, perhaps by slowing stomach emptying. Milk, for example, might be expected to have more satiating effects than soft drinks because it contains protein and fat in addition to carbohydrate (44). Second, the effect of individual beverages on weight may also be mediated by their nutrient composition. For example, studies have suggested that calcium from milk can favor weight loss by increasing lipolysis and thermogenesis and by decreasing fatty acid absorption (45). Third, energy from alcohol can be preferentially oxidized and contribute less to storage energy (46). Last, it is possible that certain behaviors and/or lifestyle factors associated with milk, juice, tea, coffee, or alcohol consumptions play a role in mediating their effects on body weight.

One potential limitation of our study was the focus on individuals with either prehypertension or stage I hypertension; however, together, these segments of the population account for approximately two-thirds of US adults. Second, the study population included few Hispanics and Asians. Strengths of our study included its longitudinal design, its sample size, its duration, the availability of six 24-h diet recalls (one from a weekday and one from a weekend day at each of

the 3 time points over 18 mo) to measure dietary intake, the high rates of retention, and our ability to evaluate a variety of beverages.

In conclusion, our study supports policy recommendations and public health efforts to reduce intakes of liquid calories, particularly from SSBs, in the general population.

Go to:

Supplementary Material

Podcast:

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Acknowledgments

We thank the PREMIER participants and staff for their contributions to the study.

The authors' responsibilities were as follows—LC: conducted the analyses and the first draft of the manuscript. All authors: conceived of and designed the study, interpreted the analyses, and revised the manuscript. None of the authors reported any personal or financial conflict of interests.

Go to:

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Public Health Nutrition: 7(1A), 123–146

Diet, nutrition and the prevention of excess weight gain and obesity

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1

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International Obesity Task Force, London, UK

Abstract

Objective: To review the evidence on the diet and nutrition causes of obesity and to recommend strategies to reduce obesity prevalence.

Design: The evidence for potential aetiological factors and strategies to reduce obesity prevalence was reviewed, and recommendations for public health action, population nutrition goals and further research were made.

Results: Protective factors against obesity were considered to be: regular physical activity (convincing); a high intake of dietary non-starch polysaccharides (NSP)/fibre (convincing); supportive home and school environments for children (probable); and breastfeeding (probable). Risk factors for obesity were considered to be sedentary lifestyles (convincing); a high intake of energy-dense, micronutrient-poor foods (convincing); heavy marketing of energy-dense foods and fast food outlets (probable); sugar-sweetened soft drinks and fruit juices (probable); adverse social and economic conditions—developed countries, especially in women (probable).

A broad range of strategies were recommended to reduce obesity prevalence including: influencing the food supply to make healthy choices easier; reducing the marketing of energy dense foods and beverages to children; influencing urban environments and transport systems to promote physical activity; developing community-wide programmes in multiple settings; increased communications about healthy eating and physical activity; and improved health services to promote breastfeeding and manage currently overweight or obese people.

Conclusions: The increasing prevalence of obesity is a major health threat in both low- and high income countries. Comprehensive programmes will be needed to turn the epidemic around.

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Obes Res. 2001 Mar;9(3):171-8.

Increasing fruit and vegetable intake and decreasing fat and sugar intake in families at risk for childhood obesity.

Epstein LH[1], Gordy CC, Raynor HA, Beddome M, Kilanowski CK, Paluch R.
Author information

Abstract

OBJECTIVE:
The goal of this study was to evaluate the effect of a parent-focused behavioral intervention on parent and child eating changes and on percentage of overweight changes in families that contain at least one obese parent and a non-obese child.

RESEARCH METHODS AND PROCEDURES:
Families with obese parents and non-obese children were randomized to groups in which parents were provided a comprehensive behavioral weight-control program and were encouraged to increase fruit and vegetable intake or decrease intake of high-fat/high-sugar foods. Child materials targeted the same dietary changes as their parents without caloric restriction.

RESULTS:
Changes over 1 year showed that treatment influenced targeted parent and child fruit and vegetable intake and high-fat/high-sugar intake, with the Increase Fruit and Vegetable group also decreasing their consumption of high-fat/high-sugar foods. Parents in the increased fruit and vegetable group showed significantly greater decreases in percentage of overweight than parents in the decreased high-fat/high-sugar group.

DISCUSSION:
These results suggest that focusing on increasing intake of healthy foods may be a useful approach for nutritional change in obese parents and their children.

PMID: 11323442 [PubMed - indexed for MEDLINE]

Watt RG. Stages of change for sugar and fat reduction in an adolescent sample. Commun Dental

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Stages of change for sugar and fat reduction in an adolescent sample.

Watt RG.
Author information

Abstract

OBJECTIVES:
To apply the stages of change model for sugar and fat intakes in a sample of adolescents and to assess the factors influencing young people's ability to change their eating patterns.

BASIC RESEARCH DESIGN:

Self complete questionnaires assessed young people's readiness to change both their sugar and fat intakes in a cross sectional study.

PARTICIPANTS:
The study sample consisted of 479 young people aged 13-14 years attending four mixed ability state secondary schools in Camden, North London.

RESULTS:
A sizeable proportion of the sample were either in the precontemplation or action stages for their sugar or fat consumption. There were significant differences between the males and females. Application of the stages of change model produced very similar results for both sugar and fat consumption. The main reason given for reducing sugar or fat intakes was a desire to improve appearance through losing weight. Direct health concerns were less of a concern. A range of social and structural factors were identified by the sample as having an influence over their ability to make future dietary changes.

CONCLUSIONS:
Future oral health promotion interventions designed to promote healthier eating practices amongst young people need to recognise the various stages of change young people may be in and develop appropriate measures to meet their needs.

PMID:9225540 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/24506352

Nutr Hosp. 2013 Nov 1;28(6):1792-6. doi: 10.3305/nutr hosp.v28in06.6769.

[*Randomized clinical trials on the sugar sweetened beverages on adiposity in olders than 13 y; systematic review].*

[Article in Spanish]
Gómez-Miranda LM[1], Jiménez-Cruz A[2], Bacardí-Gascón M[3].
Author information
Abstract
in **English**, Spanish

INTRODUCTION:
An association between consumption of sugar sweetened beverages (SSB) and metabolic diseases has been observed.

OBJECTIVE:
The aim of this study was to analyze randomized clinical trials (RCT) of 18 or more weeks of intervention among ≥ 13 year old individuals, which examined the consumption of SSB on adiposity indicators.

METHODS:
An electronic literature search was conducted in the PubMed database of RCT studies published up to April 10th, 2013. Term used for this search was "Sugar Sweetened Beverages".

RESULTS:
Four studies were found. In one of the studies, after the reduction of SSB consumption, a small reduction of BMI was observed (p = 0.045). Another study showed that the reduction of 355 ml/day

was associated with a weight loss of 0.7 kg (95% CI: 0.2-1.1, p = 0.01). In a different study, in the group consuming regular Coke, an increase in the visceral: abdominal subcutaneous fat ratio, was observed (p = 0.01). In another study, there were no differences on adiposity between the intervention and control groups.

CONCLUSION:
The results of this review indicate a trend toward an effect of the consumption of SSB on adiposity.

PMID:24506352 [PubMed - in process]

Sugar Related to Disease

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AHA Scientific Statement

Sugar and Cardiovascular Disease

A Statement for Healthcare Professionals From the Committee on Nutrition of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association

1. **Barbara V. Howard, PhD;**
2. **Judith Wylie-Rosett, RD, EdD**

Key Words:

- AHA Scientific Statements
- diet
- nutrition

- sugar

The purpose of this report is to review the effects of dietary sugar on health, with an emphasis on cardiovascular disease (CVD) and its risk factors. Although there are no dietary trials linking sugar consumption and CVD, there are several reasons why sugar consumption should be limited.

Previous SectionNext Section

Definitions

There are many, sometimes confusing, terms used in the literature. *Simple carbohydrate* (sugar) refers to mono- and disaccharides; *complex carbohydrate*refers to polysaccharides such as starch. Common disaccharides are sucrose (glucose+fructose), found in sugar cane, sugar beets, honey, and corn syrup; lactose (glucose+galactose), found in milk products; and maltose (glucose+glucose), from malt. The most common naturally occurring monosaccharide is fructose (found in fruits and vegetables). The term *dextrose* is used to refer to glucose. *Intrinsic* or *naturally occurring* sugar refers to the sugar that is an integral constituent of whole fruit, vegetable, and milk products;*extrinsic* or *added* sugar refers to sucrose or other refined sugars in soft drinks and incorporated into food, fruit drinks, and other beverages.

Previous SectionNext Section

Sugar Consumption in the United States

Added sugar was not a significant component of the human diet until the advent of modern food-processing methods. Since then, the intake of sugar has risen steadily. The average US sugar utilization per capita on the basis of food disappearance data was 55 kg (120 lb) per year in 1970, and it reached 68 kg (150 lb) per year in 1995 (almost 0.5 lb per day).[1] Sugar (simple carbohydrate) intake averages 25% of total energy intake. Data from the 1989 to 1991 Continuing Survey of Food Intake by Individuals indicate that soft drinks and sugars added at the table (eg, sugar/syrups and jams) are 2 of the top 4 carbohydrate sources for US adults.[2]

Previous SectionNext Section

Sugar and Coronary Heart Disease

Yudkin and colleagues in the 1960s[3] and 1970s[4] found that a higher intake of sugar was associated with increased CVD in both within-country and cross-country comparisons. A few recent studies have examined the link between sugar consumption and coronary heart disease (CHD). The Iowa Women's Health Study[5]showed no relation between the intake of sweets or desserts and risk of ischemic heart disease in 34 492 women monitored for 9 years. However, some major sources of sugar such as soft drinks were not considered. The Scottish Heart Health Study[6] of 10 359 men and women found that neither extrinsic nor intrinsic sugars were significant independent correlates of prevalent CHD after adjustment for other major risk factors, but the data were not adjusted for other dietary variables. A recent report from the Nurses' Health Study showed that women who consumed diets with a high glycemic load* (increased

blood glucose excursions associated with intake of sweets or highly processed starches and sweets) had an increased CHD risk, with those in the highest quintile having a >2-fold risk during 10 years of follow-up.[7] Simple carbohydrate alone was also predictive but did not reach statistical significance. This analysis controlled for total energy intake and other major dietary and nondietary risk factors.

Previous SectionNext Section

Dietary Sugar and Plasma Lipoproteins

A number of studies link dietary sugar with adverse changes in lipoproteins. Several studies have shown an inverse association between dietary sucrose and high-density lipoprotein (HDL) cholesterol.[8,9] Data from the Coronary Artery Risk Development In young Adults (CARDIA) study show a consistent inverse association between increased dietary sucrose intake and HDL cholesterol concentrations, in both cross-sectional and longitudinal analyses in blacks and whites, in both men and women, and after adjustment for other covariates.[10]

A diet high in sucrose (ie, >20% of energy) is associated with an elevation of plasma triglyceride concentrations.[11,12] This increase is due to both increased hepatic secretion and impaired clearance of very-low-density lipoprotein. Triglyceride response to dietary sugar may vary, however, according to the amount of sugar and the presence of other nutrients.[12]

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Dietary Sugar, Insulin Resistance, and Diabetes

Few epidemiological studies have directly examined the relationship between sugar intake and diabetes incidence. In general, prospective data show no association, and in fact, several dietary studies show an inverse association between total carbohydrate intake and diabetes incidence.[13–15] This observation, however, is confounded because diets lower in carbohydrate are higher in fat (high fat intake predicts diabetes risk because of increased obesity).[16] On the other hand, two recent prospective cohort studies have reported food frequency consumption data that showed that a history of consumption of foods with a high glycemic load predicts the development of type 2 diabetes in women[17] and men.[18]

No epidemiological study has examined the effects of dietary sugar on insulin resistance. Several clinical studies have shown that altering the proportion of carbohydrates in the diet for up to 4 months in humans does not influence insulin resistance,[19] but the effects of varying sugar content per se were not examined.

It is widely believed that individuals with diabetes should avoid sugar to maintain glycemic control. However, there is considerable debate about whether high-sugar diets have adverse effects on glucose control in diabetic individuals. A number of studies that assessed the effects of single meals containing 12% to 25% of calories as sucrose found no adverse effects of sucrose on average glycemia.[20,21] Some long-term studies up to several months in duration showed that providing as much as 38% of calories as sucrose had no effect on average glucose control.[22–24]Diabetic individuals, however, may experience fluctuations in blood glucose levels

with a habitual diet that is high in concentrated sweets, especially if they make errors with regard to the amount of carbohydrates they consume.

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Diet and Advanced Glycation End Products

Advanced glycation end products (AGEs) form when sugar is nonenzymatically linked to proteins, inducing cross-linking of the glycated proteins. AGEs form at room temperature, but heating speeds up their formation; therefore, all cooked foods contain AGEs (formerly referred to as Maillard browning pigments). Dietary AGEs react with tissue proteins to form substances that reduce tissue elasticity and impede cellular function. AGEs have been identified as a pathogenic mechanism in diabetic nephropathy[25] and vascular complications.[26]Approximately 10% of ingested AGEs enter the circulation, but only one third are excreted within 3 days of ingestion.[25] Diabetes is associated with impairment in AGE excretion. In one study, urinary clearance of diet-derived AGE was 5% in diabetic individuals compared with 30% in the control group.[27] Thus, caution is warranted with regard to the potential effects of a high sugar intake on AGE formation and increased risk of nephropathy.[27] Additional research is needed to determine whether limiting intake of sugar in protein- and fat-containing foods reduces circulating AGE levels and risk of nephropathy.

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Dietary Sugar and Overweight/Obesity

Because obesity has emerged as a major health problem in the United States[28] and as a definite cause of cardiovascular morbidity and mortality,[29] it is important to consider the potential impact of dietary sugar on weight gain. In human metabolic ward studies, the substitution of sucrose or other dietary carbohydrate for fat or protein in isocaloric diets shows no effect on weight or changes in energy expenditure.[30] Some studies show that body mass index is correlated inversely with sugar consumption[31]; however, this observation is confounded because dietary fat is correlated with obesity,[32] and high-fat diets are lower in total and simple carbohydrate. Diets low in sugar have been associated with weight loss in some ad lib dietary studies,[33] perhaps as a result of lower total calorie consumption. Another relationship between sugar and obesity comes from studies of food preferences, which report that foods high in sugar are common choices of obese individuals.[34] To lose weight, obese persons need to limit calorie intake; thus, limiting consumption of foods that are high in sugar (most of which have high energy density) can be a strategy for weight reduction.

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Sugar and Other Health Problems

There have been a number of studies that link sugar consumption to hypertension in animals.[35] In humans, there is one report that high dietary sugar intake enhances the risk of CHD in diabetic individuals who use diuretics.[36]

Sugar intake can increase carbohydrate fuel reserves and physical performance.[30] However, this enhancement occurs only at exercise intensities and levels of physical activity associated with endurance performance of at least 30 minutes in duration. Blood glucose and liver and muscle glycogen provide the predominant fuels for muscle contraction. When these substances reach critically low amounts, fatigue may occur and consumption of sugar may rapidly return blood glucose levels to normal. For most low- to moderate-intensity activities like walking or housework, sugar consumption does not influence performance.

Another major area of interest has been the relationship between dietary sugar and behavior and cognitive function. The belief in a relationship between sugar and hyperactivity was based on two hypotheses. The first was a possible allergic response; the second was that hyperactive children might experience functional reactive hypoglycemia. Neither of these hypotheses has been proved, and a meta-analysis of 16 randomized trials in hyperactive children showed that decreasing the sugar content of the diet resulted in no improvement in degree of hyperactivity.[37]

On the other hand, sugar is a well-established risk factor for dental caries.[38–40] This observation is based on short-term cohort studies and comparisons of rates of dental caries across countries with wide variations in sugar consumption,[38] although there is a lack of research findings regarding sugar consumption and periodontal disease.[41]

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High-Sugar Diets and Nutritional Adequacy

Diets high in sugar may adversely affect nutritional adequacy. Foods high in extrinsic sugar include soft drinks, candy, pastry, and cereals with high sugar content (Table 1). Fat-free manufactured foods are often high in calories because of inclusion of high amounts of sugar. American Heart Association dietary guidelines stress consumption of fruits, vegetables, grains, and complex carbohydrates so that nutritional requirements for vitamins and minerals may be met by whole foods rather than by foods that are supplemented with vitamins. High-sugar foods displace whole foods (eg, soft drinks displace milk and juice consumption in children) and contribute to nutritional deficiencies, adding empty calories that few Americans need[42] (Table 2). Some studies that have assessed the nutritional adequacy of high-sugar diets do not necessarily show differences in vitamin and mineral intake[1] because of the supplementation of these foods with vitamins and minerals instead of the preferred intake of these elements through the diet. Among children in the Bogalusa Heart Study,[43] a linear decrease in the intake of many essential nutrients was associated with increasing total sugar intake.

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TABLE 1. Sugar Content of Typical Foods

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TABLE 2. Nutritional Content of Low- and High-Sugar Diets

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The Role of Dietary Fructose, Sorbitol, and Mannitol

Sugars such as fructose (monosaccharide), sorbitol, and mannitol (sugar alcohols) are used to replace sucrose in food products and may lower the postprandial rise in glucose. In the 1970s, high-fructose syrup manufactured from starch began to be used as a replacement for sucrose in beverages and baked goods.[44] Sorbitol and mannitol are used in a variety of “sugar-free” food products because they have fewer calories per gram than do either sucrose or fructose; in the liver they are readily converted to fructose.[45] Fructose bypasses the phosphofructokinase regulatory step of glycolysis, in which glucose can be converted to glycogen rather than entering the glycolytic pathway. As a result, fructose increases hepatic pyruvate and lactic acid production, activates pyruvate dehydrogenase, and shifts the balance from oxidation to esterification of fatty acids, which can increase very-low-density lipoprotein synthesis. In feeding studies, fructose has had inconsistent effects on plasma triglyceride levels, which may be related to factors such as the amount of fructose consumed; energy balance; and baseline triglyceride, insulin, and glucose levels.[46] The postprandial rise in triglyceride levels after fat intake may be augmented with the addition of fructose to a test meal.[47] However, a study in individuals with type 2 diabetes showed a lack of significant variation in glucose, lipid, and insulin responses to three 28-day isocaloric feeding periods when 20% of calories were either fructose, sucrose, or starch.[48] For most individuals, consuming fructose either free or in the form of sucrose has neither beneficial nor adverse effects.

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Summary and Conclusion

As with most other dietary constituents, long-term trial data relating sugar consumption to the development of CVD events are unavailable. Longitudinal cohort studies relating sugar consumption to CVD are equivocal because of the many potential confounders that cannot be adequately controlled in the analyses. Shorter-term studies show consistent adverse effects of sugar consumption on HDL and triglyceride levels, which could accelerate atherosclerosis. High sugar consumption may worsen diabetes control, and the combination of sugar with protein and fats promotes formation of dietary AGEs, which may be especially detrimental to those with diabetes. Although increasing the amount of sugar in an isocaloric diet does not directly lead to changes in energy expenditure or weight gain in controlled feeding studies, high-sugar foods, which are sweet and calorie dense, may increase calorie consumption and lead to weight gain.

Furthermore, replacement of whole foods with high-sugar foods compromises attainment of adequate dietary vitamin and mineral intake from whole food sources.

In the absence of definitive evidence, recommendations must rely on professional judgment. No data suggest that sugar intake per se is advantageous, and some data suggest it may be detrimental. The studies above, taken in total, indicate that high sugar intake should be avoided. Sugar has no nutritional value other than to provide calories. To improve the overall nutrient density of the diet and to help reduce the intake of excess calories, individuals should be sure foods high in added sugar are not displacing foods with essential nutrients or increasing calorie intake.

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Footnotes

- The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on October 19, 2001. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0230. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4426, fax 410-528-4264, or e-mail kbradle@lww.com. To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

- ↵**Glycemic load* refers to a diet with many foods that have a high glycemic index. Glycemic index is a measure of the rise in glucose induced by ingestion of a carbohydrate. Foods that contain refined sugars make a major contribution to glycemic load; other contributors include refined starches, such as white bread and rice. It should be noted that glycemic index is determined by feeding individual foods.

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Health Benefits of Reducing Sugar-Sweetened Beverage Intake in High Risk Populations of California: Results from the Cardiovascular Disease (CVD) Policy Model

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Abstract

Background

Consumption of sugar-sweetened beverage (SSB) has risen over the past two decades, with over 10 million Californians drinking one or more SSB per day. High SSB intake is associated with risk of type 2 diabetes, obesity, hypertension, and coronary heart disease (CHD). Reduction of SSB intake and the potential impact on health outcomes in California and among racial, ethnic, and low-income sub-groups has not been quantified.

Methods

We projected the impact of reduced SSB consumption on health outcomes among all Californians and California subpopulations from 2013 to 2022. We used the CVD Policy Model – CA, an established computer simulation of diabetes and heart disease adapted to California. We modeled a reduction in SSB intake by 10–20% as has been projected to result from proposed penny-per-ounce excise tax on SSB and modeled varying effects of this reduction on health parameters including body mass index, blood pressure, and diabetes risk. We projected avoided cases of diabetes and CHD, and associated health care cost savings in 2012 US dollars.

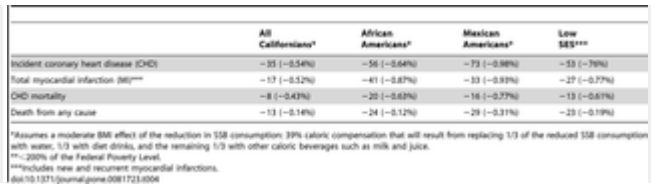
Results

Over the next decade, a 10–20% SSB consumption reduction is projected to result in a 1.8–3.4% decline in the new cases of diabetes and an additional drop of 0.5–1% in incident CHD cases and 0.5–0.9% in total myocardial infarctions. The greatest reductions are expected in African Americans, Mexican Americans, and those with limited income regardless of race and ethnicity. This reduction in SSB consumption is projected to yield $320–620 million in medical cost savings associated with diabetes cases averted and an additional savings of $14–27 million in diabetes-related CHD costs avoided.

Conclusions

A reduction of SSB consumption could yield substantial population health benefits and cost savings for California. In particular, racial, ethnic, and low-income subgroups of California could reap the greatest health benefits.

Figures

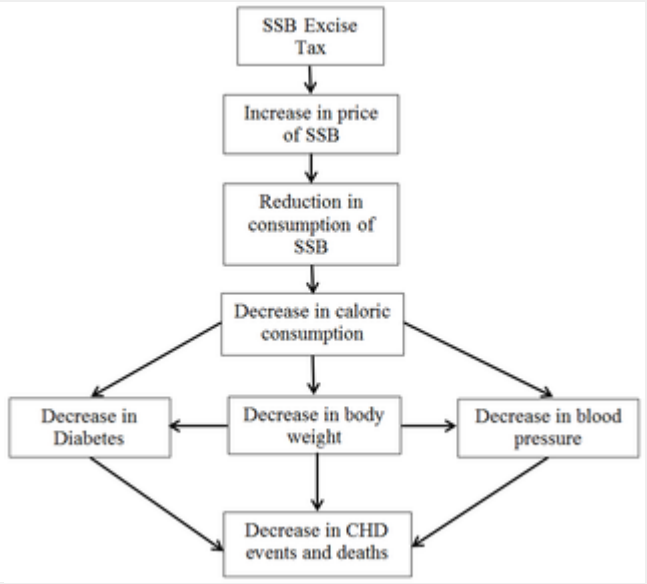


	All Californians*	African Americans*	Mexican Americans*	Low SES**
Incident coronary heart disease (CHD)	−35 (−0.54%)	−56 (−0.64%)	−73 (−0.98%)	−53 (−79%)
Total myocardial infarction (MI)***	−17 (−0.52%)	−41 (−0.87%)	−33 (−0.93%)	−27 (−0.77%)
CHD mortality	−8 (−0.43%)	−20 (−0.63%)	−16 (−0.77%)	−13 (−0.61%)
Death from any cause	−13 (−0.14%)	−24 (−0.12%)	−29 (−0.31%)	−23 (−0.19%)

*Assumes a moderate BMI effect of the reduction in SSB consumption: 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**<200% of the Federal Poverty Level.
***Includes new and recurrent myocardial infarctions.
doi:10.1371/journal.pone.0081723.t004

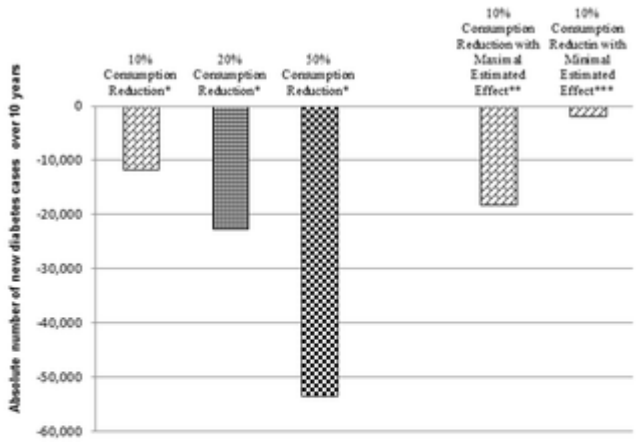
	Diabetes**	Diabetes-related coronary heart disease (CHD)***	Total coronary heart disease (CHD)†
10% reduction in SSB consumption*	−$318 (−1.0%)	−$14 (−0.01%)	−$555 (−0.4%)
20% reduction in SSB consumption*	−$622 (−2.0%)	−$27 (−0.03%)	−$1,066 (−0.7%)
50% reduction in SSB consumption*	−$1,480 (−4.7%)	−$66 (−0.07%)	−$2,591 (−1.6%)

*Assumes 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**Diabetes cost is adjusted to only reflect diabetes direct healthcare costs.
***Diabetes related CHD cost represents excess CHD that could be avoided as a result of the avoided diabetes cases from reduced SSB consumption.
†Reflects total CHD treatment cost.
doi:10.1371/journal.pone.0081723.t005



Risk Factors/Inputs	Effect size		Reference
Serving size of a SSB*	12 fl. Oz		
Proportion of calories compensated for by other beverages, after a reduction in SSB	39%		[34,47]
Relative risk of diabetes associated with consuming one or more SSB per day (95% CI)**	1.35 (95% CI: 1.14, 1.59)		[5]
Proportion of increased risk assumed to be mediated through BMI	50%		[12]
Change per 1 unit increase of (BMI)	Men	Women	[12,48–50]
Systolic blood pressure, (95% CI)***	1.43	1.24	
Cholesterol (mg/dl)***			
Low-density lipoprotein	2.75	2.24	
High-density lipoprotein	−1.55	−0.77	
Diabetes (per unit BMI)	1.26	1.30	
Change in systolic blood pressure due to a reduction in SSB consumption of 1 serving/day, mmHg (95% CI)***	−0.78 (95% CI: 0.09, 1.47)	−0.61 (95% CI: −0.27, 1.48)	[31]
Change in consumption by elasticity estimate, assuming a pre-tax price of $1.00	−0.79 to −1.00		[29]

*Sugar-sweetened beverages.
**Hazard ratio.
***β coefficients.
doi:10.1371/journal.pone.0081723.t001



The projected number of cases of diabetes without a reduction in consumption of SSB is 666,000.

*Assumes 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice

** Maximal estimated effect was calculated based on a strong BMI effect, an adjusted RR of diabetes of 1.26 per SSB serving per day, and a 1.47 and 1.48 mmHg reduction in systolic blood pressure in men and women, respectively

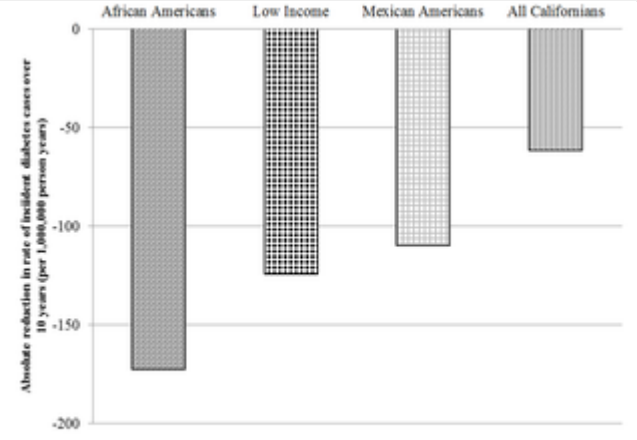
*** Minimal estimated effect was calculated based on no BMI effect, an adjusted RR of diabetes of 1.07 per SSB serving per day, and a 0.09 mmHg reduction in systolic blood pressure in men only

	Absolute number of anticipated cases before reduced SSB consumption	10% reduction in SSB consumption*	20% reduction in SSB consumption*
Incident coronary heart disease (CHD)	1,140,000	−6,000 (−0.5%)	−12,000 (−1.0%)
Total myocardial infarction (MI)**	560,000	−2,700 (−0.5%)	−5,300 (−0.9%)
CHD mortality	336,000	−1,300 (−0. 4%)	−2,500 (−0.7%)
Death from any cause	1,668,000	−1,600 (−0.1%)	−3,200 (−0.2%)

*Assumes 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**Includes new and recurrent myocardial infarctions.
doi:10.1371/journal.pone.0081723.t002

	Absolute number of anticipated cases before reduced SSB consumption	Minimal Estimated Effect*,†	Maximal Estimated Effect*,‡
Incident diabetes	666,000	−1,900 (−.29%)	−18,200 (−2.73%)
Incident coronary heart disease (CHD)	1,140,000	−120 (−0.01%)	−9,700 (−0.85%)
Total myocardial infarction (MI)**	560,000	−50 (−0.01%)	−4,400 (−0.79%)
CHD mortality	336,000	−20 (−0.01%)	−2,100 (−0.62%)
Death from any cause	1,667,000	−60 (−0.00%)	−2,700 (−0.16%)

*Assumes a moderate BMI effect of the reduction in SSB consumption: 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**Includes new and recurrent myocardial infarctions.
†Minimal estimated effect was calculated based on no BMI effect, an adjusted RR of diabetes of 1.07 per SSB serving per day, and a 0.09 mmHg reduction in systolic blood pressure in men only.
‡Maximal estimated effect was calculated based on a strong BMI effect, an adjusted RR of diabetes of 1.26 per SSB serving per day, and a 1.47 and 1.48 mmHg reduction in systolic blood pressure in men and women, respectively.
doi:10.1371/journal.pone.0081723.t003



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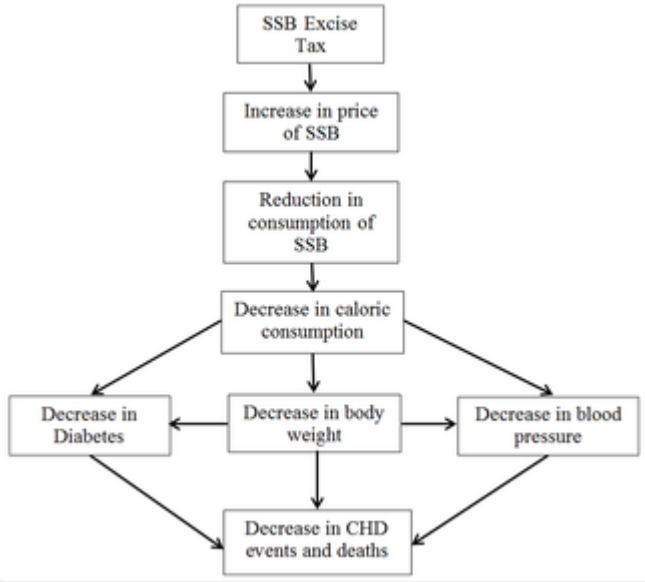
Death from any cause	−13 (−0.14%)	−24 (−0.12%)	−29 (−0.31%)	−23 (−0.19%)

*Assumes a moderate BMI effect of the reduction in SSB consumption: 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**<200% of the Federal Poverty Level.
***Includes new and recurrent myocardial infarctions.
doi:10.1371/journal.pone.0081723.t004

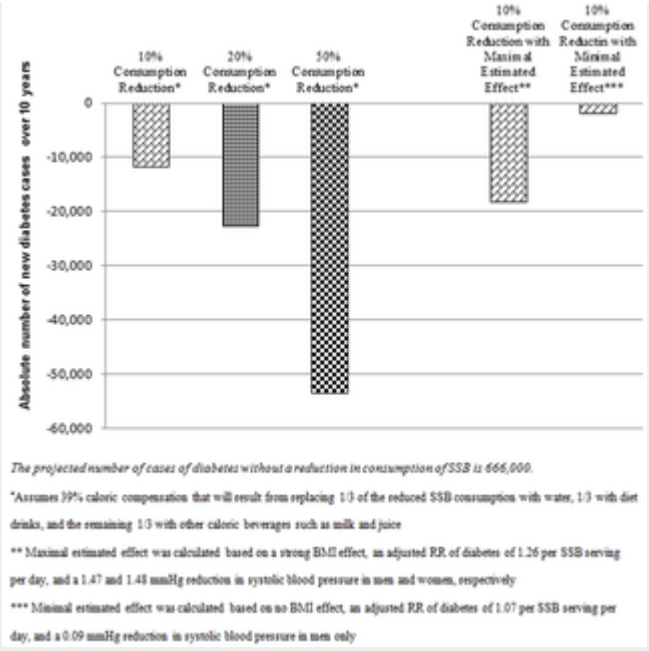
	Diabetes**	Diabetes-related coronary heart disease (CHD)***	Total coronary heart disease (CHD)†
10% reduction in SSB consumption*	−$318 (−1.0%)	−$14 (−0.01%)	−$555 (−0.4%)
20% reduction in SSB consumption*	−$622 (−2.0%)	−$27 (−0.03%)	−$1,066 (−0.7%)
50% reduction in SSB consumption*	−$1,480 (−4.7%)	−$66 (−0.07%)	−$2,591 (−1.6%)

*Assumes 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**Diabetes cost is adjusted to only reflect diabetes direct healthcare costs.
***Diabetes related CHD cost represents excess CHD that could be avoided as a result of the avoided diabetes cases from reduced SSB consumption.
†Reflects total CHD treatment cost.
doi:10.1371/journal.pone.0081723.t005



Risk Factors/Inputs	Effect size		Reference
Serving size of a SSB*	12 fl. Oz		
Proportion of calories compensated for by other beverages, after a reduction in SSB	39%		[34,47]
Relative risk of diabetes associated with consuming one or more SSB per day (95% CI)**	1.35 (95% CI: 1.14, 1.59)		[5]
Proportion of increased risk assumed to be mediated through BMI	50%		[12]
Change per 1 unit increase of (BMI)	Men	Women	[12,48–50]
Systolic blood pressure, (95% CI)***	1.43	1.24	
Cholesterol (mg/dl)***			
Low-density lipoprotein	2.75	2.24	
High-density lipoprotein	−1.55	−0.77	
Diabetes (per unit BMI)	1.26	1.30	
Change in systolic blood pressure due to a reduction in SSB consumption of 1 serving/day, mmHg (95% CI)***	−0.78 (95% CI: 0.09, 1.47)	−0.61 (95% CI: −0.27, 1.48)	[11]
Change in consumption by elasticity estimate, assuming a pre-tax price of $1.00	−0.79 to −1.00		[29]

*Sugar-sweetened beverages.
**Hazard ratio.
***β coefficients.
doi:10.1371/journal.pone.0081723.t001



Citation: Mekonnen TA, Odden MC, Coxson PG, Guzman D, Lightwood J, et al. (2013) Health Benefits of Reducing Sugar-Sweetened Beverage Intake in High Risk Populations of California: Results from the Cardiovascular Disease (CVD) Policy Model. PLoS ONE 8(12): e81723. doi:10.1371/journal.pone.0081723
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Introduction

Sugar-sweetened beverages (SSB) –soda, fruit punches, sports drinks, sweetened tea, and other carbonated or non-carbonated drinks that are sweetened with sugar–are the largest source of added

sugar in the US diet today. [1], [2] Data from the National Health And Nutrition Examination Survey (NHANES) suggests that the total daily kilocalories from SSB is much higher for adults in communities of color than their white counterparts. Specifically, calories from SSBs represent 9% of the daily caloric intake among African Americans and 8% among Mexican Americans and 5% among whites. [3] Consumption of SSB is high in California, with over 10 million children and adults in California consuming one or more SSB per day, including 24% of adults (6.4 million), 62% of adolescents (2 million), and 41% children ages 2–11 (2.2 million). [4].

Current evidence suggests that higher consumption of SSB is associated with excess calorie intake, which leads to weight gain [5] and increased risk of obesity. [6] Consumption of SSB may even act synergistically with genetic predisposition to increase the risk of obesity in some individuals. [7] High-fructose corn syrup, the most common sugar used in sodas, may have particularly deleterious effects on the liver, resulting in hepatic insulin resistance and the metabolic syndrome. [8] High consumption of SSB also appears to increase the risk of diabetes, [9], [10] hypertension, and coronary heart disease (CHD) independent of the effects on weight, [11]–[13] with studies suggesting that those who consume one drink or more per day double their risk of diabetes and raise their risk of CHD by 23% compared to those who consumed one SSB drink or less per month. [12], [14], [15] In 2005, adult diabetes prevalence in California was 7.8%, three times the Healthy People 2010 target. [16] From 2001 to 2009, diabetes prevalence rose steadily in California, particularly in minority populations; over this period the prevalence of diabetes increased 50% among Mexican Americans and 17% among African Americans. [17] Heart disease is the leading cause of death among all Californians.[18].

In response to the growing burden of diet-related chronic diseases, a number of strategies have been proposed and implemented to reduce SSB intake on a population level. Such approaches generally fall in three categories –1) *education and information sharing*, including both targeted efforts to describe the health effects of excessive SSB consumption, as well as efforts to provide consumers with accurate information through menu labeling to allow them to make healthier choices on their own, 2) *restriction*, particularly to vulnerable groups like school-age children and including limiting availability of these products within the schools or limiting the ability to market these products directly to children, and 3) *taxation*, including sales taxes assessed at the point of sale and more recently excise taxes levied on the producer. [19] The limitations of many of these approaches in effectively curbing SSB consumption have led to recent more sweeping approaches designed to have a greater effect on consumer behaviors and to reach a broader range of consumers. Recently New York City Board of Health proposed a novel approach of restricting beverage portion sizes to 16 oz. that, though ultimately stuck down, was anticipated to result in reductions in SSB consumption. [20], [21] Taxes that raise the price of SSBs more substantially in order to more effectively curb consumer behaviors - usually excise taxes of one penny per ounce – have been debated in many jurisdictions and have been of interest both for their impact on SSB consumption and also as tools for generating revenue that might be used for other programs related to chronic disease prevention. [22], [23]Ballot measures proposing such taxes were recently defeated in California's city of Richmond and El Monte. One of the common criticisms of these measures is that communities of color and low income persons will suffer disproportionately from the tax burden of these measures.[24].

In this paper, we examine and project the health and economic benefit of a reduction in SSB intake as might be achieved by an excise tax in California over the next decade, using the CVD Policy Model – CA, an established computer simulation of diabetes and heart disease adapted to California. Because California is an exceptionally diverse state, and racial and ethnic minority communities have the highest

rates of diabetes and per capita consumption, we projected the health benefit from reduced SSB intake in Mexican Americans and African Americans, as well as those with limited incomes.

Methods

The Cardiovascular (CVD) Policy Model- CA

The CVD Policy Model is a dynamic population-based model of coronary heart disease and stroke in U.S. adults that has been used to forecast trends in cardiovascular disease for over 25 years. [25] Details of the Model have been described previously.[25]–[27] A California version of the CVD Policy Model (CVD Policy Model – CA) was created for this analysis using state-specific inputs with the underlying structure of the national model. We used U.S. Census estimates for the age-specific population projections for California from 2013–2022. We used data on Western region participants in NHANES, years 1999–2008, and from the California Health Interview Survey (CHIS), years 2001–2009, for the distribution of the demographic characteristics and risk factors. [17] We assumed that all other estimates in the California Model (i.e. risk factor coefficients, case-fatality rates, etc.) were the same as for the U.S. Model.

The CVD Policy Model - CA code is written in Fortran 95 and compiled using the Lahey Fortran 95 compiler V7.2 (Lahey Computer Systems, Incline Village, Nevada).

Intake of Sugar-Sweetened Beverages in California

We used self-reported frequency of daily SSB consumption from the 2005 CHIS database [28]and included data on intake of all carbonated and non-carbonated SSB and fruit-flavored drinks, but did not include diet or 100% juice drinks. We used estimates from a recent systematic review of the price elasticity for SSBs of −0.79 to −1.00. [29] Based on this price elasticity, an excise tax on 12 ounce beverages with a pre-tax price of $1.00 would be expected to raise the price of the beverage by 12% and result in a 9.5% to 12% reduction in consumption of these beverages. Notably, because the excise tax is a fixed price per a fixed unit of volume, the decline in consumption could be expected to be even greater among consumers purchasing larger or less expensive beverages. For example, a 32 ounce beverage with a pre-tax price of $1.00 would increase in price by 32%, and based on the price elasticity this would be projected to result in a 25–30% reduction in consumption. Based on these relationships, we hypothesized that the impact of a penny-per-ounce tax would result in a 10%–20% reduction in SSB consumption. We also modeled the impact of a hypothetical 50% reduction in SSB consumption that might be achieved by taxation and additional education and menu labeling efforts to curb consumption.

Risk Factors and Costs

The difference between the current level of SSB intake and the hypothetical, lower level of SSB intake was translated directly into changes in three cardiovascular risk factors: diabetes, body mass index (BMI), and blood pressure (Figure 1). In addition to these direct effects, lower body weight was assumed to result in additional lowering of blood pressure and diabetes risk. [30]Diabetes and elevated blood pressure were each associated subsequently with an increased risk of CVD events and CVD mortality, and diabetes was associated with additional non-CVD related mortality. The magnitude of the effects modeled at each stage and the associated references are detailed in Table 1.

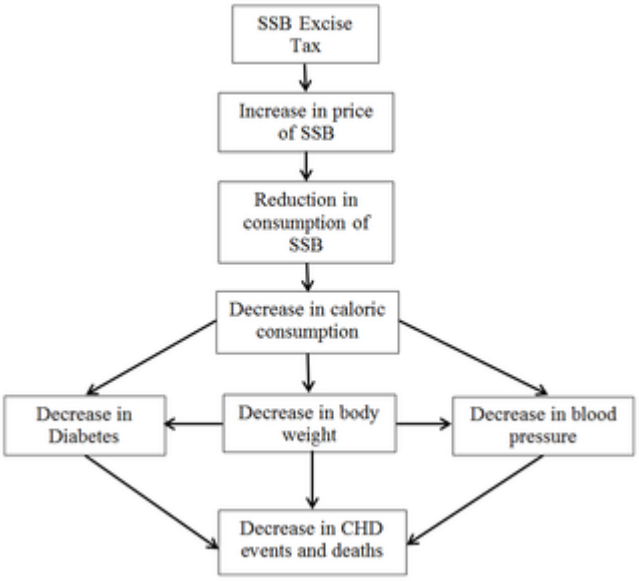

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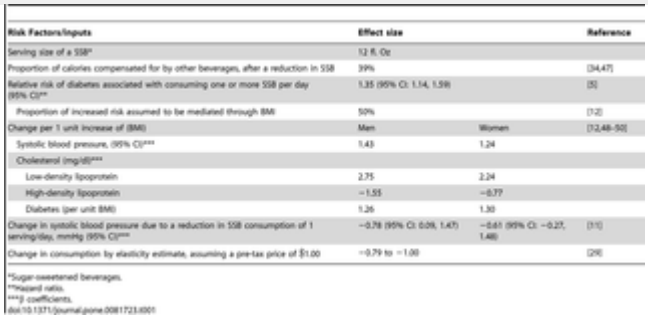
Figure 1. Framework for the impact of an SSB tax on health outcomes.
doi:10.1371/journal.pone.0081723.g001



Risk Factors/Inputs	Effect size		Reference
Serving size of a SSB*	12 fl. Oz		
Proportion of calories compensated for by other beverages, after a reduction in SSB	39%		[34,47]
Relative risk of diabetes associated with consuming one or more SSB per day (95% CI)**	1.35 (95% CI: 1.14, 1.59)		[5]
Proportion of increased risk assumed to be mediated through BMI	50%		[12]
Change per 1 unit increase of (BMI)	Men	Women	[12,48–50]
Systolic blood pressure, (95% CI)***	1.43	1.24	
Cholesterol (mg/dl)***			
Low-density lipoprotein	2.75	2.24	
High-density lipoprotein	−1.55	−0.77	
Diabetes (per unit BMI)	1.26	1.30	
Change in systolic blood pressure due to a reduction in SSB consumption of 1 serving/day, mmHg (95% CI)***	−0.78 (95% CI: 0.09, 1.47)	−0.61 (95% CI: −0.27, 1.48)	[51]
Change in consumption by elasticity estimate, assuming a pre-tax price of $1.00	−0.79 to −1.00		[29]

*Sugar-sweetened beverages.
**Hazard ratio.
***β coefficients.
doi:10.1371/journal.pone.0081723.t001

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Table 1. Model assumptions.
doi:10.1371/journal.pone.0081723.t001

To assess the impact of the reduction in SSB consumption on the projected number of new cases of diabetes prevented in California, we used estimates from a published meta-analysis of SSB intake and risk of type II diabetes. [5] Because some, but not all, of the studies adjusted for adiposity and energy intake, we used the estimate for the risk of diabetes associated with each additional 12 oz serving of SSB per day in which energy- and adiposity-adjusted coefficients were excluded (RR = 1.35 (95% CI: 1.14, 1.59). We then adjusted this estimate to account for changes mediated through increased body weight, based on one of the studies included in the meta-analysis. [12].

We estimated the per capita change in calories consumed based on age and sex specific averages of consumption for the state of California. [28] The extent to which reductions in calories from SSB are offset by substituting with other caloric beverages is critical to estimating health impact but also largely unknown. In addition, the relationship between caloric consumption and weight loss is also a topic of debate.[2], [31]–[33] Because of this uncertainty, we varied the impact of a reduction in consumption of SSB on BMI over three scenarios while retaining the independent effects of diabetes and blood pressure:

1. In the most optimistic scenario, we estimated that the entire impact of a decrease in calories due to a reduction in SSB consumption would be translated to weight loss (Strong BMI Effect).
2. In the second scenario, we assumed that 1/3 of the consumption of SSBs reduced due to the proposed tax would be replaced with water, 1/3 with diet drinks, and the final 1/3 with other caloric beverages such as milk and juice. Based on estimates from Stookey et al. of the net impact on daily energy intake from replacing SSB with alternative beverages, [34] we approximated 39% of the SSB calories reduced would be compensated for, resulting in 61% net reduction in daily energy intake (Moderate BMI Effect).
3. In the third scenario, we modeled the extreme scenario that there was no impact of a reduction in SSB on body weight, either due to an adaption of the body to lower caloric consumption or to complete compensation in calories from other food and beverages (No BMI Effect).

Based on the calculation of 3500 kcal/lb, we converted changes in caloric consumption to changes in weight in pounds. We then calculated any corresponding change in BMI for men and women separately, by converting change in pounds to BMI by the formula: BMI = weight (Kg)/height (meters) squared, and using the average height of men and women in the US.

We used an estimate of the direct effect of SSB consumption on systolic blood pressure based on a prospective study of middle-aged men and women. After adjustment for confounders including age, BMI, change in BMI, and physical activity, the authors found that a reduction of SSB consumption by 1 serving per day was associated with a reduction in systolic blood pressure of 0.78 mmHg among men and 0.61 mmHg among women. [11].

The economic costs in this study were estimated from the California's Office of Statewide Health Planning and Development (OSHPD) and the national Medical Expenditure Panel Survey (MEPS) [35] and only included direct medical costs that are allocated for preventive, diagnostic, and treatment services, costs adjusted to a common national cost basis. We estimated age-specific CHD-related costs (including

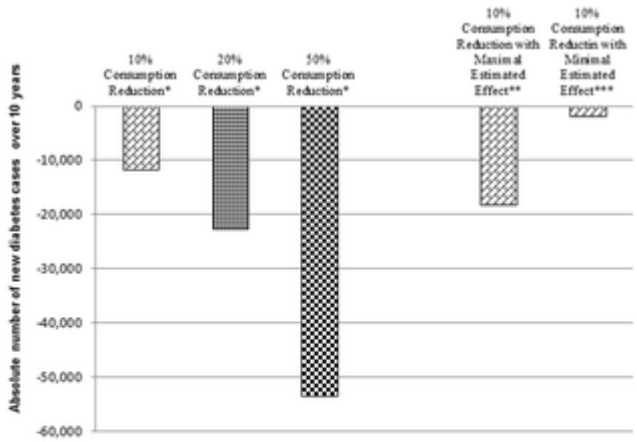
diabetes costs with co-morbid CHD), as well as age-specific non-CHD related diabetes health care costs. [36] We adjusted the estimated costs to 2012 dollars, based on the Medical Care Consumer Price Index, [37] and costs were discounted 3% annually.

Simulations

We used the CVD Policy Model – CA to run simulations from the years 2013–2022 to estimate the impact of the SSB consumption reduction. We ran the CVD Policy Model – CA under the baseline scenario and then modeled the impact of the reduction of SSB intake on the distribution of risk factors in order to estimate the subsequent effect on CVD events and mortality. We estimated the preventable cases of incident diabetes, CHD (stable or unstable angina, myocardial infarction, cardiac arrest, stroke, and death), myocardial infarction (initial and recurrent) and all-cause mortality. Our base case simulation projected a 10% reduction in consumption of SSB and we conducted sensitivity analyses assuming a 20% and 50% reduction in consumption of SSB. In addition, we varied the impact of a reduction in consumption of SSB on diabetes, BMI, and blood pressure as a sensitivity analysis. We varied BMI over the three scenarios described above (strong, moderate, and no BMI effect), and independent effects on diabetes and blood pressure over the 95% confidence intervals of the main estimates, without allowing the estimates to be less than zero (a protective effect of SSB consumption on the risk factors). To estimate the impact of the tax in racial and ethnic and low income subgroups in California, we adapted the CVD Policy Model – CA to African Americans, Mexican Americans, and persons with an income less than 200% of the federal poverty line in California. Using the same framework as the CVD Policy Model – CA, we modified the distribution of risk factors to reflect that of the subgroups based on data from NHANES and CHIS for participants whose self-report of race and ethnicity and family income placed them in these categories.

Results

A reduction in SSB consumption of 10–20% is projected to reduce new cases of diabetes in California considerably. A 10–20% reduction in SSB is projected to lower incident cases of diabetes by 12,000 to 23,000 (a 1.8–3.4% reduction) from 2013–2022. A 50% reduction in consumption in SSB could potentially reduce incident diabetes by 53,000 (8.0%) over the next decade (Figure 2). In addition to the large impact on diabetes, a 10–20% reduction in SSB consumption would have a modest impact on the number of new cases of CHD that are projected to be lowered by 6,000 to 12,000 (0.5–1.0%) (Table 2). We also found a reduction in incident stroke, a small benefit not reported here. Based on sensitivity analyses varying the effect of SSB consumption on diabetes, BMI, and blood pressure over a range of minimum and maximum estimated effect sizes, we project that a 10% reduction in SSB consumption could potential reduce incident diabetes by at least 1,900 cases (a 0.3% reduction) and as much as 18,200 cases (a 3% reduction). We project that a reduction in consumption of SSB of 10% would reduce incident CHD by at least 120 cases (a 0.01% reduction) and as much as 9,700 (a 0.9% reduction), and total MIs by at least 50 (a 0.01% reduction) and as much as 4,400 (a 0.8% reduction) (Table 3).



The projected number of cases of diabetes without a reduction in consumption of SSB is 666,000.

*Assumes 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice

** Maximal estimated effect was calculated based on a strong BMI effect, an adjusted RR of diabetes of 1.26 per SSB serving per day, and a 1.47 and 1.48 mmHg reduction in systolic blood pressure in men and women, respectively

*** Minimal estimated effect was calculated based on no BMI effect, an adjusted RR of diabetes of 1.07 per SSB serving per day, and a 0.09 mmHg reduction in systolic blood pressure in men only

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Figure 2. Projected incident diabetes decrease at different levels of SSB consumption reduction with variation of BMI effects.
doi:10.1371/journal.pone.0081723.g002

	Absolute number of anticipated cases before reduced SSB consumption	10% reduction in SSB consumption*	20% reduction in SSB consumption*
Incident coronary heart disease (CHD)	1,140,000	−6,000 (−0.5%)	−12,000 (−1.0%)
Total myocardial infarction (MI)**	560,000	−2,700 (−0.5%)	−5,300 (−0.9%)
CHD mortality	336,000	−1,300 (−0. 4%)	−2,500 (−0.7%)
Death from any cause	1,668,000	−1,600 (−0.1%)	−3,200 (−0.2%)

*Assumes 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**Includes new and recurrent myocardial infarctions.
doi:10.1371/journal.pone.0081723.t002

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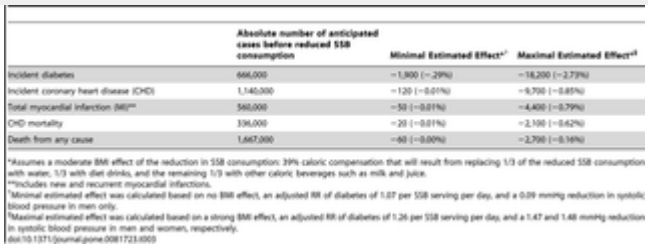
Table 2. Absolute number of coronary heart disease events and deaths prevented from a 10–20% SSB consumption reduction with moderate BMI effects from 2013–2022 in California (Percent change).
doi:10.1371/journal.pone.0081723.t002



	Absolute number of anticipated cases before reduced SSB consumption	Minimal Estimated Effect*,†	Maximal Estimated Effect*,‡
Incident diabetes	666,000	−1,900 (−.29%)	−18,200 (−2.73%)
Incident coronary heart disease (CHD)	1,140,000	−120 (−0.01%)	−9,700 (−0.85%)
Total myocardial infarction (MI)**	560,000	−50 (−0.01%)	−4,400 (−0.79%)
CHD mortality	336,000	−20 (−0.01%)	−2,100 (−0.62%)
Death from any cause	1,667,000	−60 (−0.00%)	−2,700 (−0.16%)

*Assumes a moderate BMI effect of the reduction in SSB consumption: 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**Includes new and recurrent myocardial infarctions.
†Minimal estimated effect was calculated based on no BMI effect, an adjusted RR of diabetes of 1.07 per SSB serving per day, and a 0.09 mmHg reduction in systolic blood pressure in men only.
‡Maximal estimated effect was calculated based on a strong BMI effect, an adjusted RR of diabetes of 1.26 per SSB serving per day, and a 1.47 and 1.48 mmHg reduction in systolic blood pressure in men and women, respectively.
doi:10.1371/journal.pone.0081723.t002

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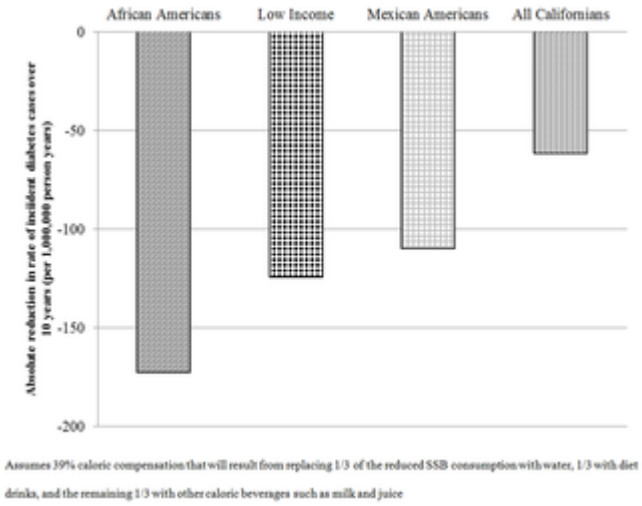
Table 3. Absolute number of events and deaths prevented from a 10% SSB consumption reduction under worst and best case scenarios from 2013–2022 in California (Percent change).
doi:10.1371/journal.pone.0081723.t003

While all Californians are expected to benefit from reducing SSB intake, the impact of reduction in SSB consumption is projected to have a substantially larger decrease in incident diabetes rates among Mexican Americans and African Americans and those with limited incomes (Figure 3). On average, a 10% reduction in SSB consumption is projected to result in a drop in the rate of new diabetes across California by over 62 per million person-years. For African Americans this rate reduction would triple, dropping by 173 per million person-years, and for Mexican Americans the rate reduction would be expected to be nearly double at 110 per million person-years. Those with limited income, regardless of race and ethnicity, would also be projected to benefit proportionately more than the average effect, with the rate of new diabetes expected to drop by 124 per million person-years (Figure 3). The reductions in rates of incident CHD and all-cause mortality are also projected to be greatest for African Americans, Mexican Americans and those with limited incomes (Table 4).



Assumes 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice

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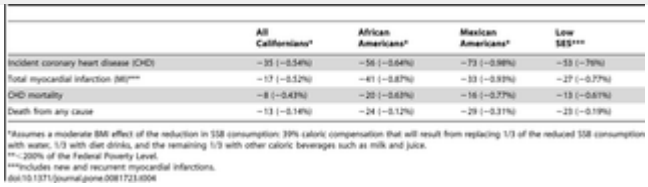
Figure 3. Projected decrease in annual incident diabetes at 10% SSB consumption reduction in subgroups of California.
doi:10.1371/journal.pone.0081723.g003



	All Californians*	African Americans*	Mexican Americans*	Low SES***
Incident coronary heart disease (CHD)	−35 (−0.54%)	−56 (−0.64%)	−73 (−0.98%)	−53 (−79%)
Total myocardial infarction (MI)***	−17 (−0.52%)	−41 (−0.87%)	−33 (−0.93%)	−27 (−0.77%)
CHD mortality	−8 (−0.43%)	−20 (−0.63%)	−16 (−0.77%)	−13 (−0.61%)
Death from any cause	−13 (−0.14%)	−24 (−0.12%)	−29 (−0.31%)	−23 (−0.19%)

*Assumes a moderate BMI effect of the reduction in SSB consumption: 39% caloric compensation that will result from replacing 1/3 of the reduced SSB consumption with water, 1/3 with diet drinks, and the remaining 1/3 with other caloric beverages such as milk and juice.
**<200% of the Federal Poverty Level.
***Includes new and recurrent myocardial infarctions.
doi:10.1371/journal.pone.0081723.t004

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Table 4. Projected difference in event rates per million person-years after a 10% SSB consumption reduction, across subgroups of California (Percent change).
doi:10.1371/journal.pone.0081723.t004

A reduction in SSB consumption could save California health care treatment costs associated with diabetes and CVD over the decade from 2013–2022. Under a moderate effect on BMI, a 10–20% reduction in SSB intake could lead to $318–$622 million in direct health care costs savings due to prevention of diabetes. An additional $14–$27 million of diabetes-related CHD costs could be avoided. Furthermore, Californians could avoid $550–$1,066 million in CHD treatment costs, overall (Table 5).

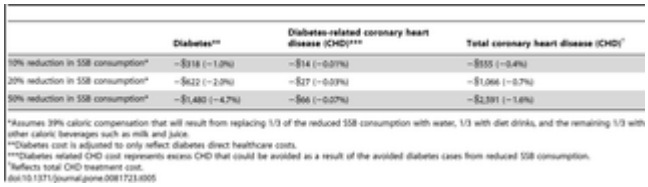

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Table 5. Projected healthcare savings from 2013–2022 after a 10–50% SSB consumption reduction with a moderate BMI effect, in 2012 US dollars – in millions (Percent change).
doi:10.1371/journal.pone.0081723.t005

Discussion

Reducing SSB consumption could substantially improve health outcomes for all adult Californians and result in considerable cost-savings because of reductions in chronic diseases like diabetes and CVD. The magnitude of the health benefits are projected to be greatest for African Americans, Mexican Americans, and those with limited incomes, populations with the highest rates of diabetes and SSB consumption in California. These findings suggest that reductions in SSB consumption as might be achieved from proposed taxes could have a marked population-wide health benefit for California and have the additional benefit of reducing race/ethnic and income disparities in diabetes and heart disease.

Few studies have examined the range of anticipated health outcomes associated with a reduction in SSB consumption or the impact of a tax as a means to reduce consumption. We previously used a national version of the CVD Policy Model to project the impact of a national excise tax on SSB on health outcomes and costs among U.S. adults and found that such a tax is projected to could prevent 2.4 million diabetes person-years, 95,000 CHD events, 8,000 strokes, and 26,000 premature deaths, while avoiding $17 billion in medical cost from 2010–2020. [14] Several economic studies have examined the impact of taxation of SSB on weight across different income groups, projecting weight loss as a result of these

taxes. [38]Economic analyses projecting differences in weight loss by income have yielded differing results. In one analysis, people of limited income were found to be high consumers of SSB and more likely to change their behaviors in order to avoid the tax, but the impact of such changes could blunt weight loss effects because of substitution with generic or bulk products or other items high in sugar particularly in low income populations. [38] A follow-up analysis that considered a range of food items that might be potential substitutes for SSB under taxation failed to find increase in other high sugar items and found instead that even high SSB consumer would be projected to experience reduction in weight as a result of these taxes. [23].

Our study uses a range of assumptions about elasticity and substitution based on these studies and extends these findings by examining additional health outcomes anticipated as a result of lower SSB consumption. Importantly, weight loss is not a primary driver of our results; changes in diabetes and hypertension associated with SSB consumption *independent of weight* contribute the majority of the health benefits we describe. These effects are particularly important among racial and ethnic minority populations and low income populations with high rates of these conditions. Data from CHIS in 2005–2009 among 35–44 year olds show that, on average, African Americans drink 0.51 SSB per day, Mexican Americans 0.59 and in low income groups 0.70 compared with white Californians with 0.47 SSB per day. [17] Racial/ethnic groups have exceptionally high burden of diabetes and obesity in California. In 2007, for adults 18 and over, prevalence rates of diabetes and obesity were 9.2% and 30.1% in Mexican Americans and 11.5% and 35% in African Americans respectively. [39] White Californians, in comparison, had 6.7% prevalence of diabetes and 20.4% of obesity in 2007. [18] Our findings provide a quantitative comparison of the potential health impact of reducing SSB consumption in these subgroups. Whereas 1 in 20,000 Californians would be expected to avoid diabetes over the next decade as a result of this excise tax, the estimates are closer to 3 in 20,000 African Americans, 2 in 20,000 Mexican Americans, and 2 in 20,000 low income Californians.

Controversy has arisen over recent proposals to tax SSB or regulate portion sizes of these beverages with concern that low income and minority communities would be unfairly burdened by these taxes. [40] Our work highlights the proportionately greater health benefits in these communities, an important factor that must also be considered in these discussions. Avoiding chronic illnesses like diabetes and heart disease could result in a variety of health benefits for individuals and economic benefits as well. Although we outline here the healthcare cost-savings that might be experienced from a societal perspective, additional economic benefits to individuals, communities, and society from the reduced disability and premature mortality from avoiding diabetes and heart disease would also be expected. [41] Another potential benefit of taxation for these communities is the proposal to reinvest revenues from these taxes into the communities with the highest rates of chronic diseases for health promoting activities. A recent poll suggests that most Californians would support a tax on SSB if the revenue from such a tax were reinvested in other health-promoting activities in the communities disproportionately affected by diabetes. [42].

The CVD Policy Model on which these California estimates are based is a well-established model that has produced robust projections of the health impacts of changes in risk for cardiovascular disease and has been used to inform health policies for over 25 years. However, all models are limited by the integrity of the inputs for the model. The main effect of SSB consumption on diabetes, blood pressure, and body weight were based on published analyses of observational studies and therefore are subject to unmeasured and residual confounding factors and may not be generalizable to all populations. [11], [12] While we have estimates of physiological effects of lower SSB consumption from several large studies, our estimates of consumer behavior in response to individual and policy-level

interventions may differ widely; therefore, we varied the potential reduction of consumption in SSB across a wide range. In addition, the degree to which calories will be substituted for by other caloric foods and beverages, and the impact of a reduction in calories on BMI are also uncertain. We based our estimates on the best available evidence of consumer behavior and energy balance, and to account for this uncertainty, we varied the impact of reduction in consumption of SSB from no effect on BMI to a strong effect on BMI. We used self-reported SSB consumption from CHIS which may be limited by under or over-reporting. We did not account for artificially sweetened beverage consumption; recent studies have found an association between artificially sweetened beverage consumption and increased risk of obesity, type 2 diabetes, metabolic syndrome and CVD [43]; however, the long term health implications are not fully understood. [44] Additionally, our estimates of costs are limited to health care cost; the true societal costs of excess preventable morbidity and mortality include those associated with lost economic productivity from disability and premature mortality from diabetes and CHD. Although some data suggest an effect of SSB consumption on lipid levels, the whether this effect is independent of BMI, therefore we did not include an effect on lipids in our model. [45] This may have underestimated the impact of a reduction on SSB consumption on CHD. Finally, we focused on adults in these projections because the data linking SSB consumption to health outcomes such as diabetes, hypertension, and CHD are available in this age group and are the health outcomes most likely to be observed in high numbers over the duration that we modeled (2013–2022). However, the largest consumers of SSB are adolescents; therefore, the anticipated health impact for California over a longer time horizon is likely to be even greater.

In conclusion, our study projects that the reduction in SSB consumption that is anticipated to result from an excise tax of a penny per ounce could yield substantial population health benefits and cost savings in California, and importantly would result in greater benefits in high-risk populations. Although taxation to curb consumption of SSBs is of considerable interest across the US and globally, [46] the limited adoption of these measures has restricted the types of empirical data on which to base the effect of such policy tools to modify consumer behaviors. The rising tide of diabetes nationally and globally suggests that more effective policy options to curb consumption will continue to be sought and adopted. Whether taxation or other types of regulatory efforts, our study findings suggest that policy strategies capable of effectively reducing SSB consumption may be an important step towards reversing the devastating upward diabetes trends in California and supporting the health of all communities in the state.

Acknowledgments

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Author Contributions

Conceived and designed the experiments: TAM MCO PGC KBD. Performed the experiments: TAM MCO PGC. Analyzed the data: TAM MCO PGC DG JL KBD. Contributed reagents/materials/analysis tools: PCG YCW KBD. Wrote the paper: TAM MCO PGC DG JL YCW KBD.

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J Am Coll Nutr. 2013;32(1):11-7. doi: 10.1080/07315724.2013.767630.

Improvements in glucose metabolism and insulin sensitivity with a low-carbohydrate diet in obese patients with type 2 diabetes.

Krebs JD[1], Bell D, Hall R, Parry-Strong A, Docherty PD, Clarke K, Chase JG.
Author information

Abstract

OBJECTIVE:
The optimal diet for weight loss in type 2 diabetes remains controversial. This study examined a low-carbohydrate, high-fat diet with detailed physiological assessments of insulin sensitivity, glycemic control, and risk factors for cardiovascular disease.

METHODS:
Fourteen obese patients (body mass index [BMI] 40.6 ± 4.9 kg/m(2)) with type 2 diabetes were recruited for an "Atkins"-type low-carbohydrate diet. Measurements were made at 0, 12, and 24 weeks of weight, insulin sensitivity, HbA1c, lipids, and blood pressure.

RESULTS:
Twelve completers lost a mean of 9.7 ± 1.8 kg over 24 weeks attributable to a major reduction in carbohydrates and resultant reduction in total energy intake. Glycemic control significantly improved (HbA1c -1.1 ± 0.25%) with reductions in hypoglycemic medication. Fasting glucose, homeostasis model assessment (HOMA), and area under the curve (AUC) glucose (intravenous glucose tolerance test [IVGTT]) were significantly reduced by week 12 ($p < 0.05$). There were nonsignificant improvements in insulin sensitivity (SI) at week 12 ($p = 0.19$) and week 24 ($p = 0.31$). Systolic blood pressure was reduced (mean -10.0 mmHg between weeks 0 and 24, $p = 0.13$). Mean high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol all increased. The ratio of total: HDL cholesterol and triglycerides was reduced.

CONCLUSION:
A low-carbohydrate diet was well tolerated and achieved weight loss over 24 weeks in subjects with diabetes. Glycemic control improved with a reduction in requirements for hypoglycemic agents.

PMID: 24015695 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/22866961

Nutr J. 2012 Aug 6;11:55. doi: 10.1186/1475-2891-11-55.

The effects of four hypocaloric diets containing different levels of sucrose or high fructose corn syrup on weight loss and related parameters.

Lowndes J[1], Kawiecki D, Pardo S, Nguyen V, Melanson KJ, Yu Z, Rippe JM.
Author information

Abstract

BACKGROUND:
The replacement of sucrose with HFCS in food products has been suggested as playing a role in the development of obesity as a public health issue. The objective of this study was to examine the effects of four equally hypocaloric diets containing different levels of sucrose orhigh fructose corn syrup (HFCS).

METHODS:
This was a randomized, prospective, double blind trial, with overweight/obese participants measured for body composition and blood chemistry before and after the completion of 12 weeks following a hypocaloric diet. The average caloric deficit achieved on the hypocaloric diets was 309 kcal.

RESULTS:
Reductions were observed in all measures of adiposity including body mass, BMI,% body fat, waist circumference and fat mass for all four hypocaloric groups, as well as reductions in the exercise only group for body mass, BMI and waist circumference.

CONCLUSIONS:
Similar decreases in weight and indices of adiposity are observed when overweight or obese individuals are fed hypocaloric diets containing levels of sucrose or high fructose corn syrup typically consumed by adults in the United States.

PMID: 22866961 [PubMed - indexed for MEDLINE] PMCID:PMC3491004

http://www.ncbi.nlm.nih.gov/pubmed/23493538

Adv Nutr. 2013 Mar 1;4(2):220-5. doi: 10.3945/an.112.002816.

Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people.

Bray GA.
Author information

Abstract

Sugar intake in the United States has increased by >40 fold since the American Revolution. The health concerns that have been raised about the amounts of sugar that are in the current diet, primarily as beverages, are the subject of this review. Just less than 50% of the added sugars (sugar and high-fructose corn syrup) are found in soft drinks and fruit drinks. The intake of soft drinks has increased 5-fold between 1950 and 2000. Most meta-analyses have shown that the risk of obesity, diabetes, cardiovascular disease, and metabolic syndrome are related to consumption of beverages sweetened

with sugar or high-fructose corn syrup. Calorically sweetened beverage intake has also been related to the risk of nonalcoholic fatty liver disease, and, in men, gout. Calorically sweetened beverages contribute to obesity through their caloric load, and the intake of beverages does not produce a corresponding reduction in the intake of other food, suggesting that beverage calories are "add-on" calories. The increase in plasma triglyceride concentrations by sugar-sweetened beverages can be attributed to fructose rather than glucose in sugar. Several randomized trials of sugar-containing soft drinks versus low-calorie or calorie-free beverages show that either sugar, 50% of which is fructose, or fructose alone increases triglycerides, body weight, visceral adipose tissue, muscle fat, and liver fat. Fructose is metabolized primarily in the liver. When it is taken up by the liver, ATP decreases rapidly as the phosphate is transferred to fructose in a form that makes it easy to convert to lipid precursors. Fructoseintake enhances lipogenesis and the production of uric acid. By worsening blood lipids, contributing to obesity, diabetes, fatty liver, and gout, fructosein the amounts currently consumed is hazardous to the health of some people.

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PMCID: PMC2235907

NIHMSID: NIHMS36189

Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake

Nicole M. Avena, Pedro Rada, and Bartley G. Hoebel*

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The publisher's final edited version of this article is available at Neurosci Biobehav Rev

Abstract

Go to:

1. OVERVIEW

Neural systems that evolved to motivate and reinforce foraging and food intake also underlie drug-seeking and self-administration. The fact that some of these drugs can cause addiction raises the logical possibility that some foods might also cause addcition. Many people claim that they feel compelled to eat sweet foods, similar in some ways to how an alcoholic might feel compelled to drink. Therefore, we developed an animal model to investigate why some people have difficulty moderating their intake of palatable foods, such as sweet beverages.

In this animal model, rats are food deprived daily for 12 h, then after a delay of 4 h into their normal circadian-driven active period, they are given 12-h access to a sugar solution and chow. As a result, they learn to drink the sugar solution copiously, especially when it first becomes available each day.

After a month on this intermittent-feeding schedule, the animals show a series of behaviors similar to the effects of drugs of abuse. These are categorized as “bingeing”, meaning unusually large bouts of intake, opiate-like “withdrawal” indicated by signs of anxiety and behavioral depression (Colantuoni et al., 2001, 2002), and “craving” measured during sugar abstinence as enhanced responding for sugar (Avena et al., 2005). There are also signs of both locomotor and consummatory “cross-sensitization” from sugar to drugs of abuse (Avena et al., 2004,Avena and Hoebel, 2003b). Having found these behaviors that are common to drug dependency with supporting evidence from other laboratories (Gosnell, 2005, Grimm et al., 2005, Wideman et al., 2005), the next question is why this happens.

A well-known characteristic of addictive drugs is their ability to cause repeated, intermittent increases in extracellular dopamine (DA) in the nucleus accumbens (NAc) (Di Chiara and Imperato, 1988, Hernandez and Hoebel, 1988, Wise et al., 1995). We find that rats with intermittent access to sugar will drink in a binge-like manner that releases DA in the NAc each time, like the classic effect of most substances of abuse (Avena et al., 2006, Rada et al., 2005b). This consequently leads to changes in the expression or availability of DA receptors (Colantuoni et al., 2001, Spangler et al., 2004).

Intermittent sugar access also acts by way of opioids in the brain. There are changes in opioid systems such as decreased enkephalin mRNA expression in the accumbens (Spangler et al., 2004). Signs of withdrawal seem to be largely due to the opioid modifications since withdrawal can be obtained with the opioid antagonist naloxone. Food deprivation is also sufficient to precipitate opiate-like withdrawal signs (Avena, Bocarsly, Rada, Kim and Hoebel, unpublished, Colantuoni et al., 2002). This withdrawal state involves at least two neurochemical manifestations. First is a decrease in extracellular DA in the accumbens, and second is the release of acetylcholine (ACh) from accumbens interneurons. These neurochemical adaptations in response to intermittent sugar intake mimic the effects of opiates.

The theory is formulated that intermittent, excessive intake of sugar can have dopaminergic, cholinergic and opioid effects that are similar to psychostimulants and opiates, albeit smaller in magnitude. The overall effect of these neurochemical adaptations is mild, but well-defined, dependency (Hoebel et al., 1999, Leibowitz and Hoebel, 2004, Rada et al., 2005a). This review compiles studies from our laboratory and integrates related results obtained by others using animal models, clinical accounts and brain imaging to answer the question: can sugar, in some conditions, be "addictive"?

Go to:

2. DEFINING ADDICTION

Throughout this review we use several terms with definitions for which there is not universal agreement. Addiction research traditionally focuses on drugs of abuse, such as morphine, cocaine, nicotine and alcohol. However, recently a variety of "addictions" to non-drug entities, including gambling, sex, and in this review, food, have been investigated (Bancroft and Vukadinovic, 2004, Comings et al., 2001, Petry, 2006). The term "addiction" implies psychological dependence and thus is a mental or cognitive problem, not just a physical ailment. "Addiction" is often used synonymously with the term "dependence" (Nelson et al., 1982) as defined by DSM-IV-TR (American Psychiatric Association, 2000). We will use the term dependence in its all-encompassing meaning to describe the results of a battery of animal studies that model human drug addiction in each of its major phases (Koob and Le Moal, 2005).

Drug dependence is characterized by compulsive, sometimes uncontrollable, behaviors that occur at the expense of other activities and intensify with repeated access. Dependence is difficult to demonstrate convincingly in laboratory animals, but criteria have been suggested using animal models. We have used models that were developed with rats for studying drug dependence and adapted them to test for signs of sugar dependence.

Bingeing

The diagnostic criteria for addiction can be grouped into three stages (American Psychiatric Association, 2000,Koob and Le Moal, 1997). The first, bingeing, is defined as the escalation of intake with a high proportion of intake at one time, usually after a period of voluntary abstinence or forced deprivation. Enhanced intake in the form of binges may result from both sensitization and tolerance to the sensory properties of a substance of abuse that occurs with its repeated delivery. *Sensitization*, which is described in greater detail below, is an increase in responsiveness to a repeatedly presented stimulus. *Tolerance* is a gradual decrease in responsiveness, such that more of the substance is needed to produce the same effect (McSweeney et al., 2005). Both are thought to influence the powerful, acute reinforcing effects of drugs of abuse and are important at the beginning of the addiction cycle since both can increase responding and intake (Koob and Le Moal, 2005).

Withdrawal

Signs of withdrawal become apparent when the abused substance is no longer available or chemically blocked. We will discuss withdrawal in terms of opiate withdrawal, which has a clearly defined set of symptoms (Martin et al., 1963, Way et al., 1969). Anxiety can be operationally defined and measured in animals using the elevated plus-maze, in which anxious animals will avoid spending time on the open arms of the maze (File et al., 2004). This test has been extensively validated for both general anxiety (Pellow et al., 1985) and anxiety induced by drug withdrawal (File and Andrews, 1991). Behavioral depression in animals can also be inferred, without reference to emotion, using the forced-swim test, which measures swimming escape efforts vs. passive floating (Porsolt et al., 1978). When signs of opiate withdrawal are

precipitated with naloxone, it suggests that inactivation of opioid receptors is the cause. When the same signs are produced spontaneously during abstinence, one can surmise that it is due to lack of stimulation of some opioid system.

Craving

The third stage of addiction, craving, occurs when motivation is enhanced, usually after an abstinence period (Vanderschuren and Everitt, 2005, Weiss, 2005). "Craving" remains a poorly defined term that is often used to describe the intense desire to self-administer drugs in humans (Wise, 1988). For lack of a better word, we will use the term "craving" as defined by increased efforts to obtain a substance of abuse or its associated cues as a result of addiction and abstinence. "Craving" often has reference to extreme motivation, which can be measured using operant conditioning. If abstinence makes the animal significantly increase its lever pressing, one can take this as a sign of enhanced motivation.

Sensitization

In addition to the above diagnostic criteria, behavioral sensitization is thought to underlie some aspects of drug dependence (Vanderschuren and Kalivas, 2000). Behavioral sensitization is typically measured as increased locomotion in response to repeated administrations of a drug. For example, after repeated doses of amphetamine followed by abstinence, a challenge dose, which has little or no effect in naïve animals, causes marked hyperactivity (Antelman and Caggiula, 1996, Glick et al., 1986). Animals sensitized to one substance often show cross-sensitization, which is defined as an increased locomotor response to a different drug or substance. Cross-sensitization can also be manifest in consummatory behavior (Piazza et al., 1989). Animals sensitized to one drug may show increased intake of a different drug. In other words, one drug acts as a "gateway" to another. For example, animals sensitized to amphetamine show accelerated escalation of cocaine intake (Ferrario and Robinson, 2007), and animals sensitized to nicotine consume more alcohol compared with non-sensitized animals (Blomqvist et al., 1996). This behavior is thought to occur when different drugs activate the same neural circuitry, and it is the reason why many clinicians require complete drug abstention as a condition of treatment for addicts (Wise, 1988).

The first question addressed by this review is whether any of these operationally defined behavioral characteristics of substance dependence can be found with intermittent sugar access. The second question explores neural systems to discover how sugar could have effects like a drug of abuse.

Go to:

3. DRUGS OF ABUSE AND PALATABLE FOOD ACTIVATE A COMMON SUBSET OF NEURAL SYSTEMS

Overlaps in the brain circuitry activated by food and drug intake suggests that different types of reinforcers (natural and artificial) stimulate some of the same neural systems (Hoebel, 1985, Hernandez and Hoebel, 1988, Kelley et al., 2002, Le Magnen, 1990, Volkow and Wise, 2005, Wise, 1988, 1989). There are several regions in the brain involved in the reinforcement of both feeding and drug intake (Hernandez and Hoebel, 1988, Kalivas and Volkow, 2005, Kelley et al., 2005, Koob and Le Moal, 2005, Mogenson and Yang, 1991, Wise, 1997, Yeomans, 1995), and many neurotransmitters, as well as hormones, have been studied in these and related brain regions (Harris et al., 2005, Kalivas, 2004, Leibowitz and Hoebel, 2004, Schoffelmeer et al., 2001, Stein and Belluzzi, 1979). This review will focus on DA, the opioids, and ACh in the NAc shell, which so far, are the neurotransmitters that we have found to be involved with the reinforcing effects of intermittent sugar intake.

3.A. Dopamine

It is well established that addictive drugs activate DA-containing neurons in areas of the brain that process behavior reinforcement. This was shown for drugs delivered systemically (Di Chiara and Imperato, 1988,Radhakishun et al., 1983), and for drugs micro-injected or infused locally (Hernandez and Hoebel, 1988, Mifsud et al., 1989). The mesolimbic DA projection from the ventral tegmental area (VTA) to the NAc is frequently implicated in reinforcement functions (Wise and Bozarth, 1984). The NAc is important for several components of "reward" including food seeking and reinforcement of learning, incentive motivation, stimulus salience and signaling a stimulus change (Bassareo and Di Chiara, 1999, Berridge and Robinson, 1998, Salamone, 1992, Schultz et al., 1997, Wise, 1988). Any neurotransmitter that directly or indirectly stimulates DA cell bodies in the VTA reinforces local self-administration, including opioids such as enkephalin (Glimcher et al., 1984), non-opioid peptides such as neurotensin (Glimcher et al., 1987) and many drugs of abuse (Bozarth and Wise, 1981, Gessa et al., 1985, McBride et al., 1999). Some addictive drugs also act at DA terminals (Cheer et al., 2004, Mifsud et al., 1989, Nisell et al., 1994, Westerink et al., 1987, Yoshimoto et al., 1992). Thus, any substance that repeatedly causes the release of DA or reduces DA reuptake at terminals via these circuits may be a candidate for abuse.

A variety of foods can release DA in the NAc, including lab chow, sugar, saccharin, and corn oil (Bassareo and Di Chiara, 1997, Hajnal et al., 2004, Liang et al., 2006, Mark et al., 1991, Rada et al., 2005b). The rise in extracellular DA can outlast the meal in food-deprived rats (Hernandez and Hoebel, 1988). However, in satiated animals, this DA release appears to be contingent on novelty since it wanes with repeated access, even when the food is palatable (Bassareo and Di Chiara, 1997, Rada et al., 2005b). An exception, which is described below (Section 5.C.), is when animals are food deprived and fed sugar intermittently.

Extracellular DA decreases in reaction to drug withdrawal (Acquas et al., 1991, Acquas and Di Chiara, 1992,Rada et al., 2004, Rossetti et al., 1992). The symptoms of withdrawal from dopaminergic drugs are less well-defined than those observed during withdrawal from opiates. Therefore, it may be easier to discern the signs of withdrawal when using foods that release both DA and opioids. Sugar is one such food.

3.B. Opioids

Opioid peptides are heavily expressed throughout the limbic system and linked to DA systems in many parts of the forebrain (Haber and Lu, 1995, Levine and Billington, 2004, Miller and Pickel, 1980). The endogenous opioid systems exert some of their effects on reinforcement processing by interacting with DA systems (Bozarth and Wise, 1986, Di Chiara and Imperato, 1986, Leibowitz and Hoebel, 2004). The opioid peptide enkephalin in the NAc has been related to reward (Bals-Kubik et al., 1989, Bozarth and Wise, 1981, Olds, 1982, Spanagel et al., 1990) and can activate both mu and delta receptors to increase the release of DA (Spanagel et al., 1990). Morphine alters gene expression of endogenous opioid peptides while increasing opioid peptide production in the NAc (Przewlocka et al., 1996, Spangler et al., 2003,Turchan et al., 1997). Opioids are also important components of this system as cotransmitters with GABA in some accumbens and dorsal striatal outputs (Kelley et al., 2005).

Repeated use of opiates, or even some non-opiate drugs, can result in mu-opioid receptor sensitization in several regions, including the NAc (Koob et al., 1992, Unterwald, 2001). A mu-receptor antagonist injected into the NAc will attenuate the rewarding effects of heroin (Vaccarino et al., 1985), and systemically such drugs have been used as a treatment for alcoholism and heroin dependence (Deas et al., 2005, Foster et al., 2003, Martin, 1975,O'Brien, 2005, Volpicelli et al., 1992).

Ingestion of palatable foods has effects via endogenous opioids in a variety of sites (Dum et al., 1983, Mercer and Holder, 1997, Tanda and Di Chiara, 1998), and the injection of mu-opioid agonists in the NAc increases intake of palatable foods rich in fat or sugar (Zhang et al., 1998, Zhang and Kelley, 2002). Opioid antagonists, on the other hand, decrease ingestion of sweet food and shorten meals of palatable, preferred foods, even at doses that have no effect on standard chow intake (Glass et al., 1999). This opioid-palatability link is further characterized by theories in which the reinforcing effect is dissociated into a dopaminergic system for incentive motivation and an opioid "liking" or "pleasure" system for hedonic responses (Berridge, 1996, Robinson and Berridge, 1993, Stein, 1978). Evidence that opioids in the NAc influence hedonic reactions comes from data showing that morphine enhances rats' positive facial taste reactivity for a sweet solution in the mouth (Pecina and Berridge, 1995). The dissociation between the "wanting" and "liking" systems is also suggested by studies in humans (Finlayson et al., 2007).

3.C. Acetylcholine

Several cholinergic systems in the brain have been implicated in both food and drug intake, and related to DA and the opioids (Kelley et al., 2005, Rada et al., 2000, Yeomans, 1995). Focusing on ACh interneurons in the NAc, systemic administration of morphine decreases ACh turnover (Smith et al., 1984), a finding that was confirmed by*in vivo* microdialysis in freely-behaving rats (Fiserova et al., 1999, Rada et al., 1991a, 1996). Cholinergic interneurons in the NAc may selectively modulate enkephalin gene expression and peptide release (Kelley et al., 2005). During morphine withdrawal, extracellular ACh increases in the NAc while DA is low, suggesting that this neurochemical state could be involved in the aversive aspects of withdrawal (Pothos et al., 1991, Rada et al., 1991b, 1996). Likewise, both nicotine and alcohol withdrawal increase extracellular ACh, while decreasing DA in the NAc (De Witte et al., 2003, Rada et al., 2001, 2004). This withdrawal state may involve behavioral depression, because M1-receptor agonists injected in the NAc can cause depression in the forced-swim test (Chau et al., 1999). The role of ACh in drug withdrawal has been further demonstrated with systemically administered acetylcholinesterase inhibitors, which can precipitate withdrawal signs in non-dependent animals (Katz and Valentino, 1984, Turski et al., 1984).

ACh in the NAc has also been implicated in food intake. We theorize that its overall muscarinic effect is to inhibit feeding at M1 receptors since local injection of the mixed muscarinic agonist arecholine will inhibit feeding, and this effect can be blocked by the relatively specific M1 antagonist pirenzapine (Rada and Hoebel, unpublished). Feeding to satiety increases extracellular ACh in the NAc (Avena et al., 2006, Mark et al., 1992). A conditioned taste aversion also increases ACh in the NAc and simultaneously lowers DA (Mark et al., 1991, 1995). D-fenfluramine combined with phentermine (Fen-Phen) increases extracellular ACh in the NAc at a dose that inhibits both eating and cocaine self-administration (Glowa et al., 1997, Rada and Hoebel, 2000). Rats with accumbal ACh toxin-induced lesions are hyperphagic relative to non-lesioned rats (Hajnal et al., 2000).

DA/ACh balance is controlled in part by hypothalamic systems for feeding and satiety. Norepinephrine and galanin, which induce eating when injected in the paraventricular nucleus (PVN), lower accumbens ACh (Hajnal et al., 1997, Rada et al., 1998). An exception is neuropeptide-Y, which fosters eating when injected into the PVN, but does not increase DA release nor lower ACh (Rada et al., 1998). In accord with the theory, the satiety-producing combination of serotonin plus CCK injection into the PVN increases accumbens ACh (Helm et al., 2003).

It is very interesting that when DA is low and extracellular ACh is high, this apparently creates not satiety, but instead an aversive state (Hoebel et al., 1999), as during behavioral depression (Zangen et al., 2001, Rada et al., 2006), drug

withdrawal (Rada et al., 1991b, 1996, 2001, 2004) and conditioned taste aversion (Mark et al., 1995). We conclude that when ACh acts as a post-synaptic M1 agonist it has effects opposite to DA, and thus may act as a "brake" on dopaminergic functions (Hoebel et al., 1999, Rada et al., 2007) causing satiety when DA is high and behavioral depression when DA is relatively low.

Go to:

4. BEHAVIORAL SIMILARITIES BETWEEN DRUG SELF-ADMINISTRATION AND INTERMITTENT, EXCESSIVE SUGAR INTAKE

The concept of "sugar addiction" has been bandied about for many years. Clinical accounts of "sugar addiction" have been the topic of many best-selling books and the focus for popular diet programs (Appleton, 1996,DesMaisons, 2001, Katherine, 1996, Rufus, 2004). In these accounts, people describe symptoms of withdrawal when they deprive themselves of sugar-rich foods. They also describe food craving, particularly for carbohydrates, chocolate, and sugar, which can trigger relapse and impulsive eating. This leads to a vicious cycle of self-medication with sweet foods that may result in obesity or an eating disorder.

Although food addiction has been popular in the media and proposed to be based on brain neurochemistry (Hoebel et al., 1989, Le Magnen, 1990), this phenomenon has only recently been systematically studied in the laboratory.

As outlined in the overview in Section 1, we use a feeding schedule that induces rats to binge on a sugar solution, then apply the criteria for drug dependence that are presented in Section 2 and test for the behavioral and neurochemical commonalties given in Section 3. Rats are given 12-h daily access to an aqueous 10% sucrose solution (25% glucose in some experiments) and lab chow, followed by 12 h of deprivation for three or more weeks (i.e., Daily Intermittent Sugar and Chow). These rats are compared with control groups such as Ad libitum Sugar and Chow, Ad libitum Chow, or Daily Intermittent Chow (12-h deprivation followed by 12-h access to lab chow). For the intermittent access groups, availability is delayed 4 h into the animal's active period in order to stimulate feeding, which normally ensues at the onset of the dark cycle. Rats maintained on the Daily Intermittent Sugar and Chow regimen enter a state that resembles drug dependence on several dimensions. These are divided into behavioral (Section 4) and neurochemical (Section 5) similarities to drug dependence.

4.A. "Bingeing": Escalation of daily sugar intake and large meals

Escalation of intake is a characteristic of drugs of abuse. This may be a combination of tolerance, in which more of an abused substance is needed to produce the same euphoric effects (Koob and Le Moal, 2005), and sensitization, such as locomotor sensitization, in which the substance produces enhanced behavioral activation (Vezina et al., 1989). Studies using drug self-administration usually limit access to a few hours per day, during which animals will self-administer in regular intervals that vary as a function of the dose received (Gerber and Wise, 1989) and in a manner that keeps extracellular DA elevated above a baseline, or "trigger point" in the NAc (Ranaldi et al., 1999, Wise et al., 1995). The length of daily access has been shown to critically affect subsequent self-administration behavior. For example, the most cocaine is self-administered during the first 10 min of a session when access is at least 6 h per day (Ahmed and Koob, 1998). Limited periods of access, to create "binges", have been useful, because the pattern of self-administration behavior that emerges is similar to that of a "compulsive" drug user (Markou et al., 1993, Mutschler and Miczek, 1998, O'Brien et al., 1998). Even when drugs, such as cocaine, are given with unlimited access, humans or laboratory animals will self-administer them in repetitive episodes or "binges" (Bozarth and Wise, 1985, Deneau et al., 1969).

However, experimenter-imposed intermittent access is better than *ad libitum* access for experimental purposes, since it becomes very likely that the animal will take at least one large binge at the onset of the drug-availability period. Moreover, a period of food restriction can enhance drug intake (Carr, 2006, Carroll, 1985) and has been shown to produce compensatory neruoadaptations in the mesoaccumbens DA system (Pan et al., 2006).

The behavioral findings with sugar are similar to those observed with drugs of abuse. Rats fed daily intermittent sugar and chow escalate their sugar intake and increase their intake during the first hour of daily access, which we define as a "binge" (Colantuoni et al., 2001). The animals with *ad libitum* access to a sugar solution tend to drink it throughout the day, including their inactive period. Both groups increase their overall intake, but the limited-access animals consume as much sugar in 12 h as *ad libitum*-fed animals do in 24 h. Detailed meal pattern analysis using operant conditioning (fixed-ratio 1) reveals that the limited animals consume a large meal of sugar at the onset of access, and larger, fewer meals of sugar throughout the access period, compared with animals drinking sugar *ad libitum* (Fig. 1; Avena and Hoebel, unpublished). Rats fed Daily Intermittent Sugar and Chow regulate their caloric intake by decreasing their chow intake to compensate for the extra calories obtained from sugar, which results in a normal body weight (Avena, Bocarsly, Rada, Kim and Hoebel, unpublished, Avena et al., 2003b, Colantuoni et al., 2002).

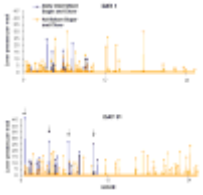

Figure 1

Meal analysis of two representative rats living in operant chambers. The one maintained on Daily Intermittent Sucrose and Chow (black lines) had an increased intake of sugar compared with one given Ad libitum Sucrose and Chow (grey lines). Hour 0 is 4 **...**

4.B. "Withdrawal": Anxiety and behavioral depression induced by an opioid-antagonist or food deprivation

As described in Section 2, animals can show signs of opiate withdrawal after repeated exposure when the substance of abuse is removed, or the appropriate synaptic receptor is blocked. For example, an opioid antagonist can be used to precipitate withdrawal in the case of opiate dependency (Espejo et al., 1994, Koob et al., 1992). In rats, opiate withdrawal causes severe somatic signs (Martin et al., 1963, Way et al., 1969), decreases in body temperature (Ary et al., 1976), aggression (Kantak and Miczek, 1986), and anxiety (Schulteis et al., 1998), as well as a motivational syndrome characterized by dysphoria and depression (De Vries and Shippenberg, 2002,Koob and Le Moal, 1997).

These signs of opioid withdrawal have been noted after intermittent access to sugar when withdrawal is precipitated with an opioid antagonist, or when food and sugar are removed. When administered a relatively high-dose of the opioid antagonist naloxone (3 mg/kg, s.c.), somatic signs of withdrawal, such as teeth chattering, forepaw tremor, and head shakes are observed (Colantuoni et al., 2002). These animals are also anxious, as measured by reduced time spent on the exposed arm of an elevated plus-maze (Colantuoni et al., 2002) (Fig. 2).

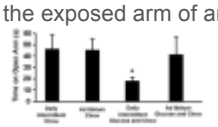

Figure 2

Time spent on the open arms of an elevated plus-maze. Four groups of rats were maintained on their respective diets for one month and then received naloxone (3 mg/kg, s.c.). The Daily Intermittent Glucose and Chow group spent less time on the open arms **...**

Behavioral depression has also been found during naloxone-precipitated withdrawal in intermittent sugar-fed rats. In this experiment, rats were given an initial 5-min forced-swim test in which escape (swimming and climbing) and passive (floating) behaviors were measured. Then the rats were divided into four groups that were fed Daily Intermittent Sucrose and Chow, Daily Intermittent Chow, Ad libitum Sucrose and Chow, or Ad libitum Chow for 21 days. On day 22, at the time that the intermittent-fed rats would normally receive their sugar and/or chow, all rats were instead injected with naloxone (3 mg/kg, s.c.) to precipitate withdrawal and were then placed in the water again for another test. In the group that had been fed Daily Intermittent Sucrose and Chow, escape behaviors were significantly suppressed compared with Ad libitum Sucrose and Chow and Ad libitum Chow controls (Fig. 3; Kim, Avena and Hoebel, unpublished). This decrease in escape efforts that were replaced by passive floating suggests the rats were experiencing behavioral depression during withdrawal.

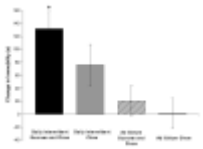

Figure 3

Rats that have been maintained on Daily Intermittent Sucrose and Chow are more immobile than control groups in a forced-swim test during naloxone-precipitated withdrawal. *p<0.05 compared with Ad libitum Sugar and Chow and Ad libitum Chow groups. **...**

Signs of opiate-withdrawal also emerge when all food is removed for 24 h. Again this includes somatic signs such as teeth chattering, forepaw tremor and head shaking (Colantuoni et al., 2002) and anxiety as measured with an elevated plus-maze (Avena, Bocarsly, Rada, Kim and Hoebel, unpublished). Spontaneous withdrawal from the mere remove of sugar has been reported using decreased body temperature as the criterion (Wideman et al., 2005). Also, signs of aggressive behavior have been found during withdrawal of a diet that involves intermittent sugar access (Galic and Persinger, 2002).

4.C. “Craving”: Enhanced responding for sugar following abstinence

As described in Section 2, “craving” in laboratory animals can be defined as enhanced motivation to procure an abused substance (Koob and Le Moal, 2005). After self-administering drugs of abuse and then being forced to abstain, animals often persist in unrewarded operant responding (i.e., resistance to response extinction), and increase their responding for cues previously associated with the drug that grows with time (i.e., incubation) (Bienkowski et al., 2004, Grimm et al., 2001, Lu et al., 2004). Additionally, if the drug becomes available again, animals will take more than they did prior to abstinence (i.e., the “deprivation effect”) (Sinclair and Senter, 1968). This increase in motivation to procure a substance of abuse may contribute to relapse. The power of “craving” is evidenced by results showing that animals will sometimes face adverse consequences to obtain a substance of abuse such as cocaine or alcohol (Deroche-Gamonet et al., 2004, Dickinson et al., 2002, Vanderschuren and Everitt, 2004). These signs in laboratory animals mimic those observed with humans in which the presentation of stimuli previously associated with a drug of abuse increases self-reports of craving and the likelihood of relapse (O’Brien et al., 1977, 1998).

We used the “deprivation effect” paradigm to investigate consumption of sugar after abstinence in rats that had been bingeing on sugar. Following 12-h daily access to sugar, rats lever press for 23% more sugar in a test after 2 wks of abstinence than they ever did before (Fig. 4; Avena et al., 2005). A group with 0.5-h daily access to sucrose did not show the effect. This provides a cogent control group in which rats are familiar with the taste of sucrose, but have not consumed it in a manner that leads to a deprivation effect. The results suggest a change in the motivational impact of sugar that persists throughout two weeks of abstinence, leading to enhanced intake.

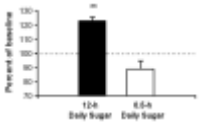

Figure 4

After 14 days of abstinence from sugar, rats that previously had 12-h daily access significantly increased lever pressing for glucose to 123% of pre-abstinence responding, indicating increased motivation for sugar. The group with 0.5-h daily access did **...**

Additionally, like the drugs described above, the motivation to obtain sugar appears to “incubate”, or grow, with the length of abstinence (Shalev et al., 2001). Using operant conditioning, Grimm and colleagues (2005) find that sucrose seeking (lever pressing in extinction and then for a sucrose-paired cue) increases during abstinence in rats after intermittent sugar access for 10 days. Remarkably, responding for the cue was greater after 30 days of sugar abstinence compared with 1 week or 1 day. These results suggest the gradual emergence of long-term changes in the neural circuitry underlying motivation as a result of sugar self-administration and abstinence.

4.D. “Cross-sensitization”: Increased locomotor response to psychostimulants during sugar abstinence

Drug-induced sensitization may play a role in the enhancement of drug self-administration and is implicated as a factor contributing to drug addiction (Robinson and Berridge, 1993). In a typical sensitization experiment, the animal receives a drug daily for about a week, then the procedure stops. However, in the brain there are lasting, even growing, changes apparent a week or more later when a low, challenge dose of the drug results in hyperlocomotion (Kalivas et al., 1992). Additionally, cross-sensitization from one drug to another has been demonstrated with several drugs of abuse, including amphetamine sensitizing rats to cocaine or phencyclidine (Greenberg and Segal, 1985, Kalivas and Weber, 1988, Pierce and Kalivas, 1995, Schenk et al., 1991), cocaine cross-sensitizing with alcohol (Itzhak and Martin, 1999), and heroin with cannabis (Pontieri et al., 2001). Other studies have found this effect with non-drug substances. Behavioral cross-sensitization between cocaine and stress has been demonstrated (Antelman and Caggiula, 1977, Covington and Miczek, 2001, Prasad et al., 1998). Also, increases in food intake (Bakshi and Kelley, 1994) or sexual behaviors (Fiorino and Phillips, 1999, Nocjar and Panksepp, 2002) have been observed in animals with a history of drug sensitization.

We and others have found that Intermittent sugar intake cross-sensitizes with drugs of abuse. Rats sensitized with daily amphetamine injections (3 mg/kg, i.p.) are hyperactive one week later in response to tasting 10% sucrose (Avena and Hoebel, 2003a). Conversely, rats fed Daily Intermittent Sugar and Chow show locomotor cross-sensitization to amphetamine. Specifically, such animals are hyperactive in response to a low, challenge dose of amphetamine (0.5 mg/kg, i.p.) that has no effect on naïve animals, even after 8 days of abstinence from sugar (Fig. 5; Avena and Hoebel, 2003b). Rats maintained on this feeding schedule but administered saline were not hyperactive, nor were rats in control groups (Daily Intermittent Chow, Ad libitum Sugar and Chow, Ad libitum Chow) given the challenge dose of

amphetamine. Intermittent sucrose access also cross-sensitizes with cocaine (Gosnell, 2005) and facilitates the development of sensitization to the DA agonist quinpirole (Foley et al., 2006). Thus, results with three different DA agonists from three different laboratories support the theory that the DA system is sensitized by intermittent sugar access, as evidenced by cross-sensitization. This is important since enhanced mesolimbic dopaminergic neurotransmission plays a major role in the behavioral effects of sensitization as well as cross-sensitization (Robinson and Berridge, 1993), and may contribute to addiction and comorbidity with poly-substance abuse.

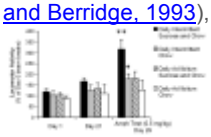

Figure 5

Locomotor activity in a photocell cage plotted as percent of baseline beam breaks on day 0. Rats were maintained for 21 days on the specified diets regimens. Rats maintained on Daily Intermittent Sucrose and Chow were hyperactive nine days later in response **...**

4.E. "Gateway effect": Increased alcohol intake during sugar abstinence

Numerous studies have found that sensitization to one drug can lead not only to hyperactivity, but also to subsequent increased intake of another drug or substance (Ellgren et al., 2006, Henningfield et al., 1990, Hubbell et al., 1993, Liguori et al., 1997, Nichols et al., 1991, Piazza et al., 1989, Vezina, 2004, Vezina et al., 2002,Volpicelli et al., 1991). We refer to this phenomenon as "consummatory cross-sensitization". In the clinical literature, when one drug leads to taking another, this is known as a "gateway effect". It is particularly noteworthy when a legal drug (e.g. nicotine) acts as a gateway to an illegal drug (e.g. cocaine) (Lai et al., 2000).

Rats maintained on intermittent sugar access and then forced to abstain, subsequently show enhanced intake of 9% alcohol (Avena et al., 2004). This suggests that intermittent access to sugar can be a gateway to alcohol use. Others have shown that animals that prefer sweet-taste will self-administer cocaine at a higher rate (Carroll et al., 2006). As with the locomotor cross-sensitization described above, underlying this behavior are presumably neurochemical alterations in the brain, such as adaptations in DA and perhaps opioid functions.

Go to:

5. NEUROCHEMICAL SIMILARITIES BETWEEN DRUG SELF-ADMINISTRATION AND INTERMITTENT SUGAR INTAKE

The studies described above suggest that intermittent sugar access can produce numerous behaviors that are similar to those observed in drug-dependent rats. In this section, we describe neurochemical findings that may underlie sugar dependency. To the extent that these brain alterations match the effects of drugs of abuse, it strengthens the case that sugar can resemble a substance of abuse.

5.A. Intermittent sugar intake alters D_1, D_2 and mu-opioid receptor binding and mRNA expression

Drugs of abuse can alter DA and opioid receptors in the mesolimbic regions of the brain. Pharmacological studies with selective D_1, D_2 and D_3 receptor antagonists and gene knockout studies have revealed that all three receptor subtypes mediate the reinforcing effects drugs of abuse. There is an up-regulation of D_1 receptors (Unterwald et al., 1994) and increase in D_1 receptor binding (Alburges et al., 1993, Unterwald et al., 2001) in response to cocaine. Conversely, D_2 receptor density is lower in NAc of monkeys that have a history of cocaine use (Moore et al., 1998). Drugs of abuse can also produce changes in gene expression of DA receptors. Morphine and cocaine have been shown to decrease

accumbens D_2 receptor mRNA (Georges et al., 1999, Turchan et al., 1997), and an increase in D_3 receptor mRNA (Spangler et al., 2003). These finding with laboratory animals support clinical studies, which have revealed that D_2 receptors are down-regulated in cocaine addicts (Volkow et al., 1996a, 1996b, 2006).

Similar changes have been reported with intermittent access to sugar. Autoradiography reveals increased D_1 in the NAc and decreased D_2 receptor binding in the striatum (Fig. 6; Colantuoni et al., 2001). This was relative to chow-fed rats, so it is not known whether *ad libitum* sugar would also show this effect. Others have reported a decrease in D_2 receptor binding in the NAc of rats with restricted access to sucrose and chow compared with rats fed restriced chow only (Bello et al., 2002). Rats with intermittent sugar and chow access also have decreases in D_2 receptor mRNA in the NAc compared with *ad libitum* chow controls (Spangler et al., 2004). mRNA levels of D_3 receptor mRNA in the NAc are increased in the NAc and caudate-putamen.

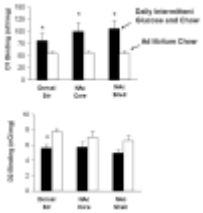

Figure 6

Intermittent sugar access alters DA receptor binding at the level of the striatum. D_1 receptor binding (top panel) increases in the NAc core and shell of animals exposed to Daily Intermittent Glucose and Chow (black bars) for 30 days compared with control **...**

Regarding the opioid receptors, mu-receptor binding is increased in response to cocaine and morphine (Bailey et al., 2005, Unterwald et al., 2001, Vigano et al., 2003). Mu-opioid receptor binding is also significantly enhanced after three weeks on the intermittent sugar diet, compared with *ad libitum* chow. This effect was observed in the accumbens shell, cingulate, hippocampus and locus coeruleus (Colantuoni et al., 2001).

5.B. Intermittent sugar intake alters enkephalin mRNA expression

Enkephalin mRNA in the striatum and the NAc is decreased in response to repeated injections of morphine (Georges et al., 1999, Turchan et al., 1997, Uhl et al., 1988). These changes within opioid systems are similar to those observed in cocaine-dependent human subjects (Zubieta et al., 1996).

Rats with intermittent sugar access also display a significant decrease in enkephalin mRNA, although it is difficult to judge its functional significance (Spangler et al., 2004). This decrease in enkephalin mRNA is consistent with findings observed in rats with limited daily access to a sweet-fat, liquid diet (Kelley et al., 2003). Assuming this decrease in mRNA results in less enkephalin peptide being synthesized and released, it could account for a compensatory increase in mu-opioid receptors, as cited above.

5.C. Daily intermittent sugar intake repeatedly releases dopamine in the accumbens

One of the strongest neurochemical commonalities between intermittent sugar access and drugs of abuse has been found using *in vivo* microdialysis to measure extracellular DA. The repeated increase in extracellular DA is a hallmark of drugs that are abused. Extracellular DA increases in the NAc in response to both addictive drugs (De Vries and Shippenberg, 2002, Di Chiara and Imperato, 1988, Everitt and Wolf, 2002, Hernandez and Hoebel, 1988, Hurd et al., 1988, Picciotto and Corrigall, 2002, Pothos et al., 1991, Rada et al., 1991a) and drug-associated stimuli (Ito et al., 2000).

Unlike drugs of abuse, which exert their effects on DA release each time they are administered (Pothos et al., 1991, Wise et al., 1995), the effect of eating palatable food on DA release wanes with repeated access when the food is no longer novel, unless the animal is food deprived (Bassareo and Di Chiara, 1999, Di Chiara and Tanda, 1997, Rada et al., 2005b). Thus normally feeding is very different than taking drugs because the DA response during feeding is phased out. However, and this is very important, rats fed daily intermittent sugar and chow apparently release DA every day as measured on days 1, 2 and 21 of access (Fig. 7; Rada et al., 2005b). As controls, rats fed sugar or chow *ad libitum,* rats with intermittent access to just chow, or rats that taste sugar only two times, develop a blunted DA response as is typical of a food that looses it novelty. These results are supported by findings of alterations in accumbens DA turnover and DA transporter in rats maintained on an intermittent sugar-feeding schedule (Bello et al., 2003, Hajnal and Norgren, 2002). Together, these results suggest that intermittent access to sugar and chow causes recurrent increases in extracellular DA in a manner that is more like a drug of abuse than a food.

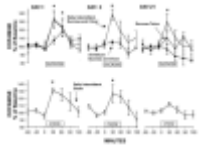

Figure 7

Rats with intermittent access to sugar release DA in response to drinking sucrose for 60 min on day 21. Dopamine, as measured by *in vivo*microdialysis, increases for the Daily Intermittent Sucrose and Chow rats (open circles) on days 1, 2 and 21; in contrast, **...**

An interesting question is whether the neurochemical effects observed with intermittent sugar access are due to its postingestive properties or whether the taste of sugar can be sufficient. To investigate orosensory effects of sugar, we used the sham feeding preparation. Rats that are sham feeding with an open gastric fistula can ingest foods but not fully digest them (Smith, 1998). Sham feeding does not completely eliminate post-ingestive effects (Berthoud and Jeanrenaud, 1982, Sclafani and Nissenbaum, 1985), however it does allow the animals to taste the sugar while retaining almost no calories.

The results of sham feeding sugar for the first hour of access each day show that DA is released in the NAc, even after three weeks of daily bingeing, simply due to the taste of sucrose (Avena et al., 2006). Sham feeding does not further enhance the typical sugar-induced DA release. This supports other work showing that the amount of DA release in the NAc is proportional to the sucrose concentration, not the volume consumed (Hajnal et al., 2004).

5.D. Accumbens acetylcholine release is delayed during sugar binges and eliminated during sham feeding

Sham-feeding revealed interesting results with ACh. As described in Section 3.C., accumbens ACh increases in the midst of a meal when feeding slows down and then stops (Mark et al., 1992). One could predict that when an animal takes a very large meal, as with the first meal of a sugar solution and chow, the release of ACh should be delayed until the satiation process begins as reflected in gradual termination of the meal. This is what was observed; ACh release occurred when this initial “binge” meal was drawing to a close (Rada et al., 2005b).

Next we measured ACh release when the animal could take a large meal of sugar while sham feeding. Purging the stomach contents drastically reduced the release of ACh (Avena et al., 2006). This is predictable based on the theory that ACh is normally important for the satiation process (Hoebel et al., 1999, Mark et al., 1992). It also suggests that by

purging, one eliminates the ACh response that opposes DA. Thus when “bingeing” on sugar is accompanied by purging, the behavior is reinforced by DA without ACh, which is more like taking a drug and less like normal eating.

5.E. Sugar withdrawal upsets dopamine/acetylcholine balance in the accumbens

Behavioral signs of drug withdrawal are usually accompanied by alterations in DA/ACh balance in the NAc. During withdrawal, DA decreases while ACh is increased. This imbalance has been shown during chemically-induced withdrawal with several drugs of abuse, including morphine, nicotine and alcohol (Rada et al., 1996,2001, 2004). Mere abstinence from an abused substance is also sufficient to elicit neurochemical signs of withdrawal. For example, rats that are forced to abstain from morphine or alcohol have decreased extracellular DA in the NAc (Acquas and Di Chiara, 1992, Rossetti et al., 1992) and ACh increases during spontaneous morphine withdrawal (Fiserova et al., 1999). While withdrawal from an anxyolitic drug (diazepam) precipitated by a bendodiazepine-receptor antagonist does not lower extracellular DA, it does release accumbens ACh, which may contribute to benzodiazepine dependency (Rada and Hoebel, 2005)

Rats that have intermittent access to sugar and chow show the morphine-like neurochemical imbalance in DA/ACh during withdrawal. This was produced two ways. As shown in Fig. 8, when they are given naloxone to precipitate opioid withdrawal, there is a decrease in accumbens DA release coupled with an increase in ACh release (Colantuoni et al., 2002). The same thing occurs after 36 h of food deprivation (Avena, Bocarsly, Rada, Kim, Hoebel, unpublished). One way to interpret deprivation-induced withdrawal is to suggest that without food to release opioids, the animal suffers the same type of withdrawal seen when the up-regulated mu-opioid receptors are blocked with naloxone.

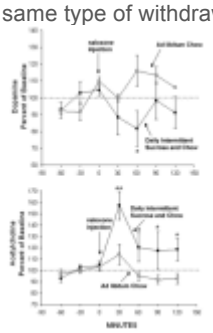

Figure 8

Extracellular DA (upper graph) decreased to 81% of baseline after naloxone injection (3 mg/kg, s.c.) in rats with a history of Daily Intermittent Sucrose and Chow. Acetylcholine (lower graph) increased to 157% in the same intermittent sugar-access rats. **...**

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6. DISCUSSION AND CLINICAL IMPLICATIONS

Food is not ordinarily like a substance of abuse, but intermittent bingeing and deprivation changes that. Based on the observed behavioral and neurochemical similarities between the effects of intermittent sugar access and drugs of abuse, we suggest that sugar, as common as it is, nonetheless meets the criteria for a substance of abuse and may be “addictive” for some individuals when consumed in a “binge-like” manner. This conclusion is reinforced by the changes in limbic system neurochemistry that are similar for the drugs and for sugar. The effects we observe are smaller in magnitude than those produced by drug of abuse such as cocaine or morphine; however, the fact that these behaviors and neurochemical changes can be elicited with a natural reinforcer is interesting. It is not clear from this animal model if intermittent sugar access can result in neglect of social activities as required by the definition of dependency in the DSM-

IV-TR (American Psychiatric Association, 2000). Nor is it known whether rats will continue to self-administer sugar despite physical obstacles, such as enduring pain to obtain sugar, as some rats do for cocaine (Deroche-Gamonet et al., 2004). Nonetheless, the extensive series of experiments revealing similarities between sugar-induced and drug-induced behavior and neurochemistry, as chronicled in Sections 4 and 5, lends credence to the concept of "sugar addiction", gives precision to its definition, and provides a testable model.

6.A. Bulimia nervosa

The feeding regimen of Daily Intermittent Sugar and Chow shares some aspects of the behavioral pattern of people diagnosed with binge-eating disorder or bulimia. Bulimics often restrict intake early in the day and then binge later in the evening, usually on palatable foods (Drewnowski et al., 1992, Gendall et al., 1997). These patients later purge the food, either by vomiting or laxative use, or in some cases by strenuous exercise (American Psychiatric Association, 2000). Bulimic patients have low β-endorphin levels (Brewerton et al., 1992, Waller et al., 1986), which might foster eating with a preference or craving for sweets. They also have decreased mu-opioid receptor binding in the insula compared with controls, which correlates with recent fasting behavior (Bencherif et al., 2005). This contrasts with the increase observed in rats following a binge. Cyclic bingeing and food deprivation may produce alterations in mu-opioid receptors, which help perpetuate bingeing behavior.

We used the sham feeding preparation to mimic the purging associated with bulimia. The finding described in Section 5.C., that intermittent sugar access repeatedly releases DA in response to the taste of sugar, may be important for understanding the bingeing behaviors associated with bulimia. DA has been implicated in bulimia by comparing it to hypothalamic self-stimulation, which also releases DA without calories (Hoebel et al., 1992). Bulimic patients have low central DA activity as reflected in analysis of DA metabolites in the spinal fluid, which also indicates a role for DA in their abnormal responses to food (Jimerson et al., 1992).

The overall similarlites in behavior and brain adaptations with sugar bingeing and drug intake described above support the theory that obesity and eating disorders, such as bulimia and anorexia, may have properties of an "addiction" in some individuals (Davis and Claridge, 1998, Gillman and Lichtigfeld, 1986, Marrazzi and Luby, 1986, Mercer and Holder, 1997, Riva et al., 2006). The auto-addiction theory proposed that some eating disorders can be an addiction to endogenous opioids (Heubner, 1993, Marrazzi and Luby, 1986, 1990). In support, appetite dysfunctions in the form of binge eating and self-starvation can stimulate endogenous opioid activity (Aravich et al., 1993).

Bulimic patients will binge on excessive amounts of non-caloric sweeteners (Klein et al., 2006), suggesting that they derive benefits from sweet orosensory stimulation. We have shown that purging leaves DA unopposed by satiety-associated ACh in the accumbens (Section 5.D.). This neurochemical state may be conducive to exaggerated binge eating. Moreover, the findings that intermittent sugar intake cross-sensitizes with amphetamine and fosters alcohol intake (Sections 4.D. and 4.E.) may be related to the comorbidity between bulimia and substance abuse (Holderness et al., 1994).

6.B. Obesity

Sugar and obesity

Obesity is one of the leading preventable causes of death in the US (Mokdad et al., 2004). Several studies have correlated the rise in the incidence of obesity with an increase in sugar consumption (Bray et al., 1992, Elliott et al., 2002, Howard and Wylie-Rosett, 2002, Ludwig et al., 2001). The US Department of Agriculture has reported that per

capita soft-drink consumption has increased by almost 500% in the past 50 years (Putnam and Allhouse, 1999). Sugar intake may lead to an increased number of and/or affinity for opioid receptors, which in turn leads to further ingestion of sugar and may contribute to obesity (Fullerton et al., 1985). Indeed, rats maintained on the diet of intermittent sugar access show opioid receptor changes (Section 5.A.); however, after one month on the diet using 10% sucrose or 25% glucose, these animals do not become overweight (Colantuoni et al., 2001, Avena and Hoebel, 2003b), although others have reported a metabolic syndrome (Toida et al., 1996), a loss of fuel efficiency (Levine et al., 2003) and an increase in body weight in rats fed sucrose (Bock et al., 1995, Kawasaki et al., 2005) and glucose (Wideman et al., 2005). Most studies of sugar intake and body weight do not use a binge-inducing diet, and the translation to human obesity is complex (Levine et al., 2003). As described in Section 4.A., it appears that rats in our model compensate for sucrose or glucose calories by decreasing chow intake (Avena, Bocarsly, Rada, Kim and Hoebel, unpublished). They gain weight at a normal rate (Colantuoni et al., 2002). This may not be true of all sugars.

Fructose is a unique sweetener that has different metabolic effects on the body than glucose or sucrose. Fructose is absorbed further down the intestine, and whereas circulating glucose releases insulin from the pancreas (Sato et al., 1996, Vilsboll et al., 2003), fructose stimulates insulin synthesis but does not release it (Curry, 1989, Le and Tappy, 2006, Sato et al., 1996). Insulin modifies food intake by inhibiting eating (Schwartz et al., 2000) and by increasing leptin release (Saad et al., 1998), which also can inhibit food intake. Meals of high-fructose corn syrup can reduce circulating insulin and leptin levels (Teff et al., 2004), contributing to increased body weight. Thus, fructose intake might not result in the degree of satiety that would normally ensue with an equally caloric meal of glucose or sucrose. Since high-fructose corn syrup has become a major constituent in the American diet (Bray et al., 2004) and lacks some effects on insulin and leptin, it may be a potential agent for producing obesity when given intermittently to rats. Whether or not signs of dependency on fructose are apparent when it is offered intermittently has yet to be determined. However, based on our results showing that sweet taste is sufficient to elicit the repeated release of DA in the NAc (see Section 5.C.), we hypothesize that any sweet taste consumed in a binge-like manner is a candidate for producing signs of dependence.

Fat and obesity

While we have chosen to focus on sugar, the question arises as to whether non-sweet, palatable foods could produce signs or dependence. The evidence is mixed. It appears that some signs of dependence are apparent with fat, while others have not been shown. Fat bingeing in rats occurs with intermittent access to pure fat (vegetable shortening), sweet-fat cookies (Boggiano et al., 2005, Corwin, 2006), or sweet-fat chow (Berner, Avena and Hoebel, unpublished). Repeated, intermittent access to oil releases DA in the NAc (Liang et al., 2006). Like sugar, bingeing on a fat-rich diet is known to affect the opioid system in the accumbens by decreasing enkephalin mRNA, an effect that is not observed with acute access (Kelley et al., 2003). Also, treatment with baclofen (GABA-B agonist), which reduces drug intake, also reduces binge eating of fat (Buda-Levin et al., 2005).

This all implies that fat dependency is a real possibility, but withdrawal from fat-bingeing is not as apparent as it is with sugar. Le Magnen (1990) noted naloxone could precipitate withdrawal in rats on a cafeteria-style diet, which contains a variety of fat- and sugar-rich foods (e.g., cheese, cookies, chocolate chips). However, we have not observed signs of naloxone-precipitated or spontaneous withdrawal in rats fed pure fat (vegetable shortening) or a sugar-fat combination, nor has such a result been published by others. Further studies are needed to fully understand the differences between sugar and fat bingeing and their subsequent effects on behavior. Just as different classes of drugs (e.g., dopamine

agonists vs. opiates) have specific behavioral and physiological withdrawal signs, it may be that different macronutrients may also produce specific withdrawal signs. Since craving of fat or cross-sensitization between fat intake and drugs of abuse has yet to be documented in animals, sugar is currently the only palatable substance for which bingeing, withdrawal, abstinence-induced enhanced motivation and cross-sensitization have all been demonstrated (Sections 4 and 5).

Brain imaging

Recent findings using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in humans have supported the idea that aberrant eating behaviors, including those observed in obesity, may have similarities to drug dependence. Craving-related changes in fMRI signal have been identified in response to palatable foods, similar to drug craving. This overlap occurred in the hippocampus, insula, and caudate (Pelchat et al., 2004). Similarly, PET scans reveal that obese subjects show a reduction in striatal D_2 receptor availability that is associated with the body weight of the subject (Wang et al., 2004b). This decrease in D_2receptors in obese subjects is similar in magnitude to the reductions reported in drug-addicted subjects (Wang et al., 2001). The involvement of the DA system in reward and reinforcement has led to the hypothesis that alterations in DA activity in obese subjects dispose them to excessive use of food. Exposure to especially palatable foods, such as cake and ice cream, activates the several brain regions including the anterior insula and right orbitofrontal cortex (Wang et al., 2004a), which may underlie the motivation to procure food (Rolls, 2006).

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7. CONCLUSION

From an evolutionary perspective, it is in the best interest of humans to have an inherent desire for food for survival. However, this desire may go awry, and certain people, including some obese and bulimic patients in particular, may develop an unhealthy dependence on palatable food that interferes with well-being. The concept of “food addiction” materialized in the diet industry on the basis of subjective reports, clinical accounts and case studies described in self-help books. The rise in obesity, coupled with the emergence of scientific findings of parallels between drugs of abuse and palatable foods has given credibility to this idea. The reviewed evidence supports the theory that, in some circumstances, intermittent access to sugar can lead to behavior and neurochemical changes that resemble the effects of a substance of abuse. According to the evidence in rats, intermittent access to sugar and chow is capable of producing a “dependency”. This was operationally defined by tests for bingeing, withdrawal, craving and cross-sensitization to amphetamine and alcohol. The correspondence to some people with binge eating disorder or bulimia is striking, but whether or not it is a good idea to call this a “food addiction” in people is both a scientific and societal question that has yet to be answered. What this review demonstrates is that rats with intermittent access to food and a sugar solution can show both a constellation of behaviors and parallel brain changes that are characteristic of rats that voluntarily self-administer addictive drugs. In the aggregrate, this is evidence that sugar can be addictive.

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Acknowledgments

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Footnotes

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