UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

THE AMERICAN BEVERAGE ASSOCIATION, CALIFORNIA RETAILERS ASSOCIATION, CALIFORNIA STATE OUTDOOR ADVERTISING ASSOCIATION, Plaintiffs, vs. THE CITY AND COUNTY OF SAN FRANCISCO, Defendant.	Case No. 3:15-cv-03415 EMC **EXPERT REPORT OF WALTER WILLETT** Hearing Date: April 7, 2016 Time: 1:30 p.m. Place: Crtrm. 5, 17th Fl. Trial Date: None set

I. QUALIFICATIONS

1. I am Professor of Epidemiology and Nutrition and Chairman of the Department of Nutrition at Harvard School of Public Health and Professor of Medicine at Harvard Medical School.

2. For the past 35 years, my work has focused on the development of methods, using both questionnaire and biochemical approaches, to study the effects of diet on the occurrence of major diseases, including obesity and diabetes. I have applied these methods since in 1980 in the Nurses' Health Studies I and II and the Health Professionals Follow-up Study. Together, these cohorts that include nearly 300,000 men and women with repeated dietary assessments are providing the most detailed information on the long-term health consequences of food choices.

3. I have published over 1,600 articles, including over 1,300 peer-reviewed articles, and have written the textbook *Nutritional Epidemiology*, published by Oxford University Press. I am the most cited nutritionist internationally, and am among the five most cited persons in all fields of clinical science. I am a member of the Institute of Medicine of the National Academy of Sciences and the recipient of many national and international awards for my research. My list of publications and further information about my background and experience are available in my current C.V., attached as Exhibit A.

4. A list of the documents I considered in formulating my opinion is attached as Exhibit B. I also considered my background, experience, and cumulative knowledge in the fields of nutrition and epidemiology.

5. I am not being compensated for my work in this matter. I was assisted in preparing this report by Dr. Vasanti Malik (ScD), a Research Scientist in the Department of Nutrition at the Harvard T,H. Chan School of Public Health. Dr. Malik was compensated $ 3,500 for her time and efforts. Her compensation was not contingent on the content or conclusions drawn in the report.

6. Neither I nor Dr. Malik have served as an expert witness or testified in any trials or depositions in the last four years.

II. SUMMARY OF OPINIONS

7. Obesity and diabetes are major public health challenges in the U.S., leading to enormous reductions in quality of life, reduced productivity and high health care expenditures. The total estimated cost of diagnosed diabetes in 2012 was $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity.[1] These figures underscore the need to identify and implement prevention strategies and policies to improve health and reduce the economic burden attributable to these conditions.

8. Sugar-sweetened beverages (SSBs), which include soda, sweetened fruit drinks, sports drinks, energy drinks, and sweetened teas and coffees, are the greatest contributor to intake of added sugar in the U.S. diet and the 3rd and 4th leading source of calories in the diets of children and adults respectively. It is estimated that half of the US population consumes soda on a daily basis, with one in four consuming more than one 12-oz serving per day. Consumption levels are higher among African–Americans, Hispanics and low-income individuals—the groups with disproportionally high prevalence of obesity and obesity related chronic diseases.

9. The U.S. Departments of Health and Human Services and Agriculture and the World Health Organization, based on a summary of the available evidence linking intake of added sugar and SSBs to adverse health outcomes including obesity and diabetes, have recommended that Americans consume no more than 10% of their daily calories in the form of added sugar. Yet standard single serving sizes of SSBs provide all (in a 20-ounce serving of many SSBs) or nearly all (in a 12-ounce serving) of the recommended maximum daily added sugar amount for most adults, and more in children. Numerous agencies, including the American Heart Association, American Diabetes Association, American Academy of Pediatrics, Institute of Medicine of the National Academies, American Medical Association, and the Centers for Disease Control, recommend limiting intake of added sugar and SSBs to improve population health.

10. In agreement with the recommendations of these organizations, I believe that the totality of the available evidence from prospective cohort studies and clinical trials is sufficient to conclude that consumption of SSBs causes excess weight gain and diabetes.

[1] Economic costs of diabetes in the U.S. in 2012. *Diabetes Care*. 2013;36:1033-1046.

11. SSBs contribute to weight by adding extra calories to the diet because of their limited induction of satiety (i.e. drinking SSBs does not lead to a feeling of fullness) and an incomplete compensatory reduction in solid calories at subsequent meals from intake of liquid calories. These beverages contribute to diabetes in part by increasing body weight but also independently through their glycemic effects and metabolic role of fructose. There is evidence supporting these biological mechanisms, but scientists continue to discuss the relative importance of the multiple pathways by which SSBs and added sugar contribute to weight and diabetes. This continuing discussion of mechanistic considerations, however, does not preclude the firm conclusion that SSBs contribute to obesity and diabetes in light of all of the evidence.

12. Obesity and diabetes are complex conditions. Prevention efforts need to include multiple strategies across different platforms to make a measurable impact. Because many individuals, including children and adolescents, consume multiple servings of SSBs daily, reducing consumption of SSBs is one important step in improving diet quality and reducing weight gain and diabetes. The warning required by the City and County of San Francisco is consistent with the strong evidence that consuming SSBs contributes to obesity and diabetes.

III. RATES OF CONSUMPTION OF SUGAR-SWEETENED BEVERAGES

13. The term "sugar-sweetened beverage" or SSB refers to any carbonated or noncarbonated soft drink that is sweetened with sugar or high fructose corn syrup (HFCS), including soda, juice drinks, fruit drinks, fruit ades, teas, coffees, sports drinks, and energy drinks. It does not include 100% fruit juice or milk.[2] SSBs are produced, sold and consumed in great quantities by adults and children. To estimate consumption levels, I reviewed available information from industry on

[2] Unlike 100% fruit juice and milk, SSBs typically have no nutritional value, although some SSBs are enriched with added vitamins. 100% fruit juice, on the other hand, contains a number of healthful vitamins and nutrients, and although such juices contain calories from natural sugar, these drinks are typically consumed in smaller amounts compared to SSBs. Milk also contains a number of important vitamins and minerals, including calcium, vitamin D and magnesium, as well as protein, which may have a satiating effect. Like juice, milk is consumed in smaller amounts than SSBs, and displacement of milk by SSBs (which lack nutritional value) in children is of great concern for nutritional adequacy. Harnack L, Stang J, Story M. Soft drink consumption among US children and adolescents: nutritional consequences. J Am Diet Assoc. 1999;99:436–441.

amounts of SSBs produced ("production figures") and from government surveys on amounts consumed by individuals ("consumption figures"). Production figures provide an estimate of the maximum volume of beverage available for consumption by the population. These values are assumed to be equal to sales figures, and they are often used as a proxy for consumption. But they tend to overestimate intake because not all SSBs that are produced are sold, and those that are sold may not be completely consumed. In contrast, dietary surveys depend on self-reports. These tend to underestimate SSB intake since individuals may not be able to precisely recall their intake levels. For these reasons, production data are useful for estimating SSB availability and for following intake trends, while dietary intake data are better suited to examine differences in intakes across various populations and time trends. True intake levels are likely to fall somewhere between the production and consumption estimates.

A. Production Data

14. For this section, I primarily consider production data from sugar-sweetened carbonated beverages or soda, as they represent the greatest contributor to overall SSB intake.[3] Because production data from industry is proprietary, has not been not shared with government agencies since 2003, and is not readily available to the public, I rely on a recently published book whose author, Marion Nestle, obtained proprietary industry data from the Beverage Marketing Corporation.[4] These data show that soda production increased rapidly from the early 1980's to the early 2000's, after which time it plateaued and then declined. Despite the decline, Nestle estimated that in 2012, more than 9 billion gallons of soda—equivalent to more than 95 billion 12 ounce servings—were available for consumption by the U.S. population. Translating soda production into amounts available per capita, and looking at longer-term trends, Nestle showed that per capita production increased from 11.5 gallons in 1952 (equivalent to 4 ounces of soda per person per day) to a peak in 1998 of 40.7 gallons produced (equivalent to 14 ounces per person per day) and then decreased to 29.6 gallons in 2012

[3] What we eat in America (WWEIA) food category analyses for the 2015 Dietary Guidelines Advisory Committee, Estimates based on day 1 dietary recalls from WWEIA, NHANES 2009-2010.

[4] Nestle M. *Soda politics: Taking on big soda (and winning)*. Oxford University Press, New York, NY; 2015.

(equivalent to 10 ounces per capita per day). Although per capita production decreased by about 20% from the peak year to 2012, the amount of soda produced in 2012 was still sufficient to provide every person in the U.S. with about one serving of soda per day. This estimate is for the entire U.S. population and includes those who never drink soda. For people who do drink soda, this average production estimate seriously underestimates actual intake.

15. While data on the number of individual sizes of soda produced is not readily available, in the past several decades, the portion size of sodas has increased substantially, from a 6.5-oz standard soft drink bottle in the 1950s to a typical 20-oz bottle today.[5] The Coca-Cola company reports on its website that 12-ounce cans, 2-liter bottles, and 20-ounce single serving bottles represent more than 70 percent of the volume of bottles and cans of Coca-Cola sold in North America.[6] The 20-ounce single serving bottle provides 65 grams of sugar (equivalent to 16 teaspoons) and 240 calories. For most people, this amount of soda alone exceeds the recommendations of the World Health Organization (WHO) [7] 7 and US 2015 dietary guidelines[8] to limit all added sugar to no more than 10 % of total daily energy (caloric) intake.[9]

B. Consumption Data

16. Consumption data for dietary intake are generated from self-reported surveys, typically asking an individual to recall all foods and beverages consumed within a 24-hour period. Because people tend to overreport consumption of foods perceived to be healthy and underreport intake of foods perceived to be less healthy, this dietary assessment method typically underreports consumption

[5] Piernas C, Popkin BM. Food portion patterns and trends among U.S. children and the relationship to total eating occasion size, 1977–2006. J Nutr 2011;141:1159–1164.

[6] Less is more: For coca-cola, small packs mean big business. http://www.Coca-colacompany.Com/stories/less-is-more-for-coca-cola-small-packs-mean-big-business/. Accessed 02/11/16.

[7] Guideline: Sugar intake for adults and children. Geneva: World Health Organization; 2015.

[8] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th edition. December 2015. Available at http://health.gov/dietaryguidelines/2015/guidelines/.

[9] Ten per cent of total energy (calories) from added sugar in a 2,000-calorie-a-day diet is equivalent to about 48 grams or about 12 teaspoons of sugar.

of foods perceived to be unhealthy by a factor of 30% to 40%.[10] In the US, national self-reported dietary intake data comes from the ongoing National Health and Nutrition Examination Surveys (NHANES) conducted by the Centers for Disease Control (CDC).

17. Data from the NHANES (2005–2008) show that half the US population (aged 2 years and over) consumes soda on a given day; one in four obtains at least 200 calories from such beverages, and 5% obtain at least 567 calories – equivalent to four cans of soda.[11] On average, adults who consume soda consume 155 calories per day from that source, equivalent to 13 ounces. Consumption is particularly high among African-Americans, Hispanics and low-income individuals—the groups with disproportionately high prevalence of obesity and obesity-related chronic diseases. These findings are confirmed by industry data which report that the soda-drinking half of the population are more likely to be male, young, single, poorly educated, low-income, blue-collar, Hispanic, African American, and living in the South or Midwest.[12] US children and youth obtain 224 calories per day from SSBs on average, which is nearly 11% of their daily total caloric intake.[13] Consumption is higher among boys than girls; 70% of boys aged 2–19 years consume SSBs daily. Calories from SSB's tend to increase with age in childhood, with survey data showing that children ages 2-5, 6-11, and 12-19 years consume 2, 5, and 12 ounces per day respectively.[14] Based on another analysis, 5 percent of young children, 16 percent of adolescents, and 20 percent of young adults consume more than 500 calories per day from soda (equivalent to 40 ounces).[15]

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[10] Davy BM, Jahren AH, Hedrick VE, Comber DL. Association of delta(1)(3)c in fingerstick blood with added-sugar and sugar-sweetened beverage intake. Journal of the American Dietetic Association. 2011;111:874-878.

[11] Ogden CL, Kit BK, Carroll MD, Park S. Consumption of sugar drinks in the united states, 2005-2008. *NCHS Data Brief*. 2011:1-8

[12] Nestle M. *Soda politics: Taking on big soda (and winning)*. Oxford University Press, New York, NY; 2015.

[13] Wang YC, Bleich SN, Gortmaker SL. Increasing caloric contribution from sugar-sweetened beverages and 100% fruit juices among us children and adolescents, 1988-2004. Pediatrics. 2008;121:e1604-1614

[14] Ogden CL, Kit BK, Carroll MD, Park S. Consumption of sugar drinks in the united states, 2005-2008. *NCHS Data Brief*. 2011:1-8

[15] Han E, Powell LM. Consumption patterns of sugar-sweetened beverages in the united states. Journal of the Academy of Nutrition and Dietetics. 2013;113:43-53.

18. Despite the decline in SSB consumption since the 1990s, the average amount of added sugar that Americans consume from soda alone still exceeds the recommended level of no more than 10% total energy from added sugar, without accounting for the many other sources of added sugar in U.S. diets; collectively SSBs remain the single largest source of added sugar.[16] Based on NHANES (2009-2010) data, added sugar accounts for about 13% of calories per day in the US population. Higher proportions are observed among children, adolescents and young adults, and 10% of the population consumes 25% or more of their energy from added sugar.[17] SSBs (not including sweetened coffees, teas, and milks) account for 39% of all added sugar intake, with 25% from soda.[18] The combined category of soda, energy drinks, and sports drinks remains the 4th leading source of total calories in the diets of adults and the third leading source of calories in children.[19] It is worth noting that these drinks are typically nutritionally valueless and do not provide macro- or micro-nutrients.

IV. DRINKING BEVERAGES WITH ADDED SUGARS UNEQUIVOCALLY CONTRIBUTES TO OBESITY AND DIABETES

19. Findings from observational studies and randomized controlled trials (RCTs) provide strong and consistent evidence that SSBs contribute to weight gain or risk of obesity and related chronic diseases, especially diabetes. Based on the totality of the scientific evidence, the warning's claim is true and evidence-based.

A. Time-Trend Data Concerning SSB Consumption and Obesity

20. Contrary to Kahn's interpretation (¶¶ 28), a comparison of data from recent decades concerning added sugar consumption and the epidemics of obesity and diabetes show a parallel between these trends. But because obesity and diabetes are complex multifactorial conditions, it is not

[16] WWEIA food category analyses for the 2015 dietary guidelines advisory committee. Estimates based on day 1 dietary recalls from WWEIA, NHANES 2009-2010.

[17] Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. *JAMA Internal Medicine*. 2014

[18] WWEIA food category analyses for the 2015 dietary guidelines advisory committee. Estimates based on day 1 dietary recalls from WWEIA, NHANES 2009-2010.

[19] U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary Guidelines for Americans, 2010. http://health.gov/dietaryguidelines/2010/.

possible to infer cause and effect from time-trend data alone. This section briefly discusses time-trend data before moving to the observational and experimental data that demonstrate the accuracy of the warning.

21. Time-trend data over the past 3-4 decades have shown a close parallel between intake of added sugars, largely from SSBs, and the obesity and diabetes epidemics in the US.[20, 21] Recent U.S. data suggest that rates of obesity have plateaued in children and nearly plateaued in adults, and that incidence of diabetes has decreased by approximately 20% over the last several years.[22] This is likely due in part to the decline in intake of added sugar and SSBs from 2003.[23]

22. Kahn interprets the time-trend data differently and notes that obesity rates have not declined despite the decline in added sugar and SSB consumption during this time (Kahn ¶ 30). Given that weight and prevalence of obesity had been rapidly increasing in the U.S. in both children and adults, and that weight change is a gradual process, however, one would not expect to see concurrent declines of added sugar consumption and obesity on the population level. Diabetes rates had also been rapidly increasing, and the reduction in incidence is a remarkable change. The bending of these epidemic curves closely following the decline in soda consumption is completely consistent with the anticipated benefits of soda reduction and is of great public health importance. Moreover, Kahn exaggerates the disparity he sees between the drop in added sugar consumption and the plateau in obesity rates by citing production data to establish a relative increase in calories consumed from sources other than sugar-sweetened beverages (Kahn ¶ 29) but citing survey-based consumption data to establish a reduction in consumption of added sugar and soft drinks (Kahn ¶ 30). As noted in ¶ 9,

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[20] Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: An ecologic assessment. *The American Journal of Clinical Nutrition*. 2004;79:774-779.

[21] Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *The American Journal of Clinical Nutrition*. 2004;79:537-543.

[22] Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey. Data computed by personnel in the Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, CDC. http://www.cdc.gov/diabetes/statistics/incidence/fig1.htm.

[23] Welsh JA, Sharma AJ, Grellinger L, Vos MB. Consumption of added sugars is decreasing in the united states. *The American Journal of Clinical Nutrition*. 2011;94:726-734.

supra, survey-based consumption data tend to underestimate consumption of foods perceived as unhealthy.

B. SSBs and Obesity

1. Observational Evidence

23. A great many epidemiologic studies have evaluated the relationship between consumption of SSBs and the development of obesity. Among the various study designs, ecologic studies (which make cross-population comparisons) are most susceptible to confounding and other biases. Cross-sectional studies, which evaluate the exposure and outcome at the same point in time, are also highly prone to confounding and reverse causation bias. Because these designs are not able to establish a temporal sequence and infer causality, they have limited utility in nutritional epidemiology outside of hypothesis generation, and I do not discuss evidence from these types of studies. Instead, I consider carefully conducted and analyzed prospective cohort studies, which study a group of people over time, and are considered the strongest non-randomized study design, able to capture long-term diet and disease relationships.[24] I also focus on evidence from meta-analyses and systematic reviews that provide overall summaries of the evidence. These studies are especially helpful in understanding a vast evidence base and informing policy.

24. The majority[25, 26, 27, 28, 29] but not all[30] of systematic reviews of prospective cohort studies have reported positive associations between SSB consumption and weight gain or risk of

[24] RCTs are often limited in their ability to capture long-term relationships between diet and disease. *See infra* ¶¶ 36, 55, 72.

[25] Hu FB, Malik VS. Sugar-sweetened beverages and risk of obesity and type 2 diabetes: Epidemiologic evidence. *Physiology & Behavior*. 2010;100:47-54

[26] Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. 2010;121:1356-1364

[27] Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: A systematic review. *The American Journal of Clinical Nutrition*. 2006;84:274-288

[28] Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition*. 2013;98:1084-1102

[29] Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: A systematic review and meta-analysis. *American Journal of Public Health*. 2007;97:667-675

overweight or obesity in children and in adults. (The outlier systematic review is addressed in more detail in ¶ 26, *infra*.) This association is most consistent among large prospective cohort studies with long durations of follow-up and without statistical adjustment for total energy intake.[31]

25. Studies that statistically adjust for total energy intake are less likely to show a positive association between SSBs and weight gain. This makes sense: Because SSBs add extra calories to the diet, total energy intake largely mediates the association between SSB intake and weight gain. Thus, statistically adjusting for total energy intake would be equivalent to assessing whatever effects of SSB intake on body weight that do not occur through a change in total energy intake. Such an analysis would artificially underestimate the overall association between SSBs and body weight. Kahn points to studies that statistically adjust for total energy intake to refute the evidence linking SSB intake with weight from cohort studies; he claims that when researchers adjust for total caloric intake, the results tend to show no relationship between added sugar consumption and body weight. (Kahn ¶ 61). However, one would only adjust for total energy to answer the question whether SSBs contribute to weight independent of the calories they contribute. That is a very different question from whether SSB's contribute to weight. Because the warning states only that SSBs contribute to obesity and does not state whether SSBs contribute to obesity independent of calories, the relevant studies are those that do not statistically adjust for total energy intake.

26. There is one meta-analysis that found no relationship between SSB intake and BMI among children and adolescents, as noted in ¶ 24, *supra*. This meta-analysis reviewed 10 prospective cohort studies and two RCTs.[32] However, this meta-analysis should be discounted because it was analytically flawed; it failed to appropriately scale the estimates and standard errors from two studies,

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[30] Forshee RA, Anderson PA, Storey ML. Sugar-sweetened beverages and body mass index in children and adolescents: a meta-analysis. *The American Journal of Clinical Nutrition*. 2008 Jun;87(6):1662-71. Erratum in: Am J Clin Nutr. 2009 Jan;89(1):441-2

[31] Hu FB, Malik VS. Sugar-sweetened beverages and risk of obesity and type 2 diabetes: Epidemiologic evidence. *Physiology & Behavior*. 2010;100:47-54

[32] Forshee RA, Anderson PA, Storey ML. Sugar-sweetened beverages and body mass index in children and adolescents: a meta-analysis. *The American Journal of Clinical Nutrition*. 2008 Jun;87(6):1662-71. Erratum in: Am J Clin Nutr. 2009 Jan;89(1):441-2

as I and co-authors demonstrated in a response to the meta-analysis.[33] The flawed meta-analysis expressed overall results as the change in BMI units per 12-oz serving change in SSBs. However, two studies that it relied on expressed their estimates as change per 1-oz serving in SSBs in their original publications, and these were not scaled correctly in the meta-analysis. After correcting for these errors and analyzing only the available estimates that were not adjusted for total energy intake, our updated meta-analysis found a significant positive association between SSB intake and BMI among children.[34]

27. It is notable that the flawed meta-analysis just discussed was funded by the American Beverage Association. Beverage industry-funded studies have been found to be four to eight times more likely to show a finding favorable to the industry's marketing interests compared to independently-funded studies.[35]

28. In 2013, I and several co-authors conducted a comprehensive systematic review and meta-analysis of cohort studies of SSB and weight gain in children and adults. This review and meta-analysis found consistent positive associations between SSB consumption and weight gain.[36] For this analysis we included estimates that were not adjusted for total energy intake, since as described above SSBs contribute to weight through calories. Based on 7 cohort studies in adults, a single 12-oz serving per day increase in SSB was associated with an additional weight gain of 0.12 kg over 1 year. Although this estimate seems modest, adult weight gain in the general population is a gradual process, occurring over decades and averaging about 1 pound per year[37] Thus, eliminating SSBs from the diet could be an effective way to reduce age-related weight gain. All of the studies included in the meta-analysis had repeated measurements of diet and weight and utilized a "change-on-change" analysis

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[33] Malik VS, Willett WC, Hu FB. Sugar-sweetened beverages and BMI in children and adolescents: Reanalyses of a meta-analysis. *The American Journal of Clinical Nutrition*. 2009;89:438-439; author reply 439-440

[34] *Id*.

[35] Lesser LI, Ebbeling CB, Goozner M, Wypij D, Ludwig DS. Relationship between funding source and conclusion among nutrition-related scientific articles. *PLoS Medicine*. 2007;4:e5

[36] Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition*. 2013;98:1084-1102.

[37] Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *The New England Journal of Medicine*.2011;364(25):2392-2404

strategy. This type of analysis has some of the features of a quasi-experimental design, although it lacks the element of randomization in a clinical trial. An advantage of this design is the generalizability to a real-world setting, relative to a controlled laboratory setting, because participants are able to change their diet and lifestyle without investigator-driven intervention.

29. Of the studies we reviewed in the 2013 meta-analysis just discussed, the largest and most influential was conducted among men and women in the three Harvard longitudinal cohorts (the Nurses' Health Study (NHS), Nurses' Health Study II (NHS II) and Health Professional's Follow-up study (HPFS)).[38] This study examined the relationships between changes in diet and lifestyle factors with weight change using repeated measurements every four years and found that SSB consumption was the variable most strongly associated with 4-year weight change after potato chips and potatoes. Each daily increase in one 12-oz. serving of SSB was associated with approximately 0.5 kg greater weight gain every 4 years (or 0.13 kg per year) in the multivariable adjusted model, which is similar to the results from our meta-analysis. Other obesogenic foods identified in this study included red and processed meat, refined grains and desserts. In contrast, greater consumption of fruit, vegetables, whole grains, nuts and yogurt was associated with less weight gain. These results suggest that obesity prevention should focus on improving overall diet quality by consuming more healthful foods and beverages and limiting unhealthy ones. Since many people, including children and adolescents, consume many servings of SSBs daily (which is rare for potato chips or potatoes), and SSBs thus contribute a large proportion of total caloric intake for many people, reducing consumption of SSBs is an important step in improving diet quality and reducing long-term weight gain, particularly in segments of the population with higher intake levels who are already at elevated risk for developing obesity and diabetes. In keeping with this evidence, the warning identifies reducing SSB consumption as an important point of intervention to reduce weight gain.

30. The contribution SSBs make to obesity is further demonstrated by a recent analysis of gene-SSB interactions, which examined whether consumption of SSBs can modify the genetic risk of obesity, using a genetic predisposition score based on 32 obesity genes identified from genome-wide

[38] *Id.*

association studies.[39] Based on data from 3 large cohorts (NHS, HPFS and the Women's Genome Health Study), this study found that greater consumption of SSBs was associated with a more pronounced genetic effect on elevated BMI and an increased risk of obesity. Individuals who consumed one or more servings of SSBs per day had genetic effects on BMI and obesity risk that were approximately twice as large as those who consumed less than one serving per month. These data suggest that regular consumers of SSBs may be more susceptible to genetic influences on obesity, implying that a genetic predisposition to obesity can be partly offset by healthier beverage choices. Alternatively, persons with a greater genetic predisposition to obesity may be more susceptible to the deleterious effects of SSBs on BMI.

31. Kahn dismisses the evidence from prospective cohort studies on the grounds that such studies cannot eliminate the possibility that a confounding variable, unaccounted for in the study, is responsible for whatever association between SSBs and obesity is seen. (Kahn ¶ 59.) Kahn further notes that the results of prospective cohort studies can be manipulated by researchers who have not pre-specified the scope of their analyses. (Kahn ¶ 60.) In the following paragraphs, I discuss why these hypothetical concerns should not discount prospective studies of SSB's.

32. It is true that there are certain limitations inherent in cohort studies. As Kahn notes, a major challenge when working with any kind of observational data is confounding. A confounder is a variable that is associated with both the exposure and outcome, and when unaccounted for, introduces bias into the exposure-disease relationship. The main reason why randomized trials are considered superior in inferring causality is that, so long as the sample size is large enough, randomly assigning participants to treatment groups nullifies all sources of measured and unmeasured confounding. To account for this type of bias in a prospective cohort study, researchers must identify and adjust for all relevant confounders.[40]

[39] Qi Q, Chu AY, Kang JH, Jensen MK, Curhan GC, Pasquale LR, Ridker PM, Hunter DJ, Willett WC, Rimm EB, Chasman DI, Hu FB, Qi L. Sugar-sweetened beverages and genetic risk of obesity. *The New England Journal of Medicine*. 2012;367:1387-1396

[40] Satija A, Yu E, Willett WC, Hu FB. Understanding nutritional epidemiology and its role in policy. *Advances in Nutrition*. 2015;6:5-18

33. Despite the inherent limitations of cohort studies, a well-conducted cohort study can simulate a randomized trial when the most relevant confounders are accounted for.[41] The prospective cohort studies discussed in this report all adjusted their analyses for potential confounding by various diet and lifestyle factors, and for the majority, a positive association persisted, suggesting an independent effect of SSBs.

34. It is true that residual confounding by unmeasured or imperfectly measured factors may still exist, and incomplete adjustment for various lifestyle factors could lead to an overestimation of the association. Because the finding of an association between SSBs and weight gain is consistent across different cohorts, however, it is unlikely that residual confounding is responsible for the findings.

35. Kahn's critique of cohort studies does not differentiate between studies of varying quality or acknowledge that many of the limitations of cohort studies can be overcome by appropriate design and analysis strategies. This is an important fact, since for many diet-disease relationships, it is not feasible to do a randomized clinical trial. Regulators therefore frequently rely on properly conducted cohort studies to formulate policy. For instance, the associations between cigarette smoking and risks of lung cancer, cardiovascular disease, and premature death were not substantiated by a randomized clinical trial; indeed the randomized trials conducted generally came to the misleading conclusion that smoking cessation has no benefit.[42] Nonetheless it is appropriate for regulators to inform consumers of the associations between cigarette smoking and lung cancer on the basis of cohort studies. Further, virtually all of our information on occupational exposures, air quality, ionizing radiation and other environmental exposures, and long term side effects of drugs and medical devices is based on observational cohort studies, which have been used as the basis for regulations, recommendations, and warnings that have greatly enhanced public health.

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[41] Hernan MA, Robins JM. Estimating causal effects from epidemiological data. *Journal of Epidemiology and Community Health*. 2006;60:578-586

[42] U.S. Department of Health and Human Services. Smoking cessation and overall mortality and morbidity. In: The Health Benefits of Smoking Cessation. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Center for Disease Control, Centers for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health; 1990:86-87. DHHS publication no. [CDC] 90-8416

2. Randomized Clinical Trials

36. Compared to observational studies, evidence of the association between SSBs and obesity from RCTs is limited, largely because of the difficulties of maintaining adherence to assigned beverages, and the majority of trials were designed to evaluate short-term effects of specific interventions on weight change rather than longer term effects.. Nonetheless, review of these experimental studies reinforces my conclusion that consumption of SSBs contributes to obesity.

37. I first consider studies that add SSBs to the diet of test subjects, or hypercaloric trials in Kahn's parlance. In my and my co-authors' recent meta-analysis of five hypercaloric trials in adults, we found that adding SSBs to the diet significantly increased body weight.[43] All of the studies in the analysis observed significantly greater weight gain or trends towards greater weight gain in intervention compared with control regimens, and there was no evidence of between-study heterogeneity. Similarly, another meta-analysis of seven hypercaloric RCTs found a significant dose-dependent increase in body weight when SSBs were added to participants' diets[44] as did the meta-analysis of 10 added sugar RCT's discussed in section III.[45] These studies demonstrate the calories from SSBs are not spontaneously compensated for by reduction in other sources of calories.

38. Kahn evaluates these two meta-analyses of hypercaloric RCTs in paragraph 48 of his report. He claims that "results from hypercaloric trials, which were only done in adults, were mixed" and that "some trials show that individuals fed a hypercaloric diet gained weight but this outcome was not seen in all trials." These claims are incorrect; instead both studies consistently showed that adding SSBs to the diet increased body weight. Kahn also interprets my and my co-authors' meta-analysis incorrectly, stating that "it was not possible in all trials, particularly those in which the subjects gained

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[43] Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition*. 2013;98:1084-1102

[44] Kaiser KA, Shikany JM, Keating KD, Allison DB. Will reducing sugar-sweetened beverage consumption reduce obesity? Evidence supporting conjecture is strong, but evidence when testing effect is weak. *Obesity Reviews*. 2013;14:620-633

[45] Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ*. 2013;346:e7492

weight when fed a hypercaloric diet, to separate out the effects of the increase in total calories versus the source of the increase in total calories." (Kahn ¶ 48.) That comment misrepresents the relevance of our research. As I discussed above in ¶ 20, *supra*, SSBs add extra calories to the diet, and the association between SSB intake and weight gain is largely mediated by the expected effect of these additional calories on body weight. Thus, a trial that evaluates whether individuals gain weight when their total caloric intake is not adjusted but their SSB consumption is adjusted—an isocaloric trial, in Kahn's terminology—is designed to evaluate whether SSBs contribute to weight gain independent of their caloric contribution, which is an unrealistic expectation. Notably, the warning does not make claims about whether SSBs contribute to obesity independent of calories. Thus, a hypercaloric RCT where study subjects receive added calories from SSBs, and then exhibit weight gain, demonstrates that consuming SSBs contributes to weight gain, which is the proposition advanced by the warning. There is no further need to "separate out" the effects of the increase in total calories, as Kahn proposes.

39. Hypocaloric trials, or trials where intervention subjects reduce their SSB consumption, also support the warning's claim. In a 2013 meta-analysis of 8 trials aiming to reduce SSB consumption for prevention of weight gain, there was no overall effect on subjects' body mass index, but a significant benefit was observed among individuals who were initially overweight.[46] Many of the trials in this meta-analysis had methodological limitations (including small sample sizes, short duration, poor compliance, lack of randomization at the individual level, lack of blinding and the overstating of subgroup findings). It should also be noted that these trials are "effectiveness" trials of behavioral modification. Such trials test methods of intervention more than they test causal relationships because their findings are greatly affected by intervention intensity and are limited by subjects' compliance. Thus, a lack of benefit does not mean that the relation between SSBs and weight gain is not causal but rather that the given modality might not be effective at changing behaviors.

[46] Kaiser KA, Shikany JM, Keating KD, Allison DB. Will reducing sugar-sweetened beverage consumption reduce obesity? Evidence supporting conjecture is strong, but evidence when testing effect is weak. *Obesity Reviews*. 2013;14:620-633.

40. In addition, the 2013 meta-analysis just discussed has significant limitations in my view. One limitation is its inclusion of a trial comparing soda consumption isocalorically with sweetened milk. Not surprisingly, this trial revealed no difference in weight change between the intervention and control groups since both the intervention and control beverages provided the same number of calories.[47] In my opinion this isocaloric trial should not have been included in the meta-analysis. Kahn cites this trial to contend that "this comparison illustrates how manipulating caloric intake may affect weight, while merely manipulating the source of calories does not." (Kahn ¶ 52.) But an isocaloric trial is relevant only to test whether SSBs contribute to weight gain independent of their caloric contribution, which is not the question we are asking when considering the warning. Even with the limitations of this meta-analysis, it did show that reduction SSBs did decrease body weight among children who were initially overweight, exactly the group of greatest concern.

41. Two large and rigorously conducted hypocaloric RCTs have recently overcome many of the limitations of previous trials, and provide strong evidence that decreasing consumption of SSBs significantly reduces weight gain and obesity in children and adolescents. Ebbeling et al.[48] randomly assigned 224 overweight and obese adolescents who regularly consumed SSBs to multi-component intervention and control groups. The intervention group received home delivery of water or diet drinks to replace SSBs, motivational phone calls with parents, and check-in visits and written motivational messages for one year. At one year, these participants had significant and beneficial changes in BMI compared with the control group. After an additional year of follow-up without active intervention (the pre-specified primary outcome), the intervention group still had less weight gain than the control group, although the between-group difference was not statistically significant. The intervention effects were significantly more pronounced among Hispanic than non-Hispanic participants. Interestingly, the consumption in the control group also declined substantially, which would have led to the

[47] Albala C, Ebbeling CB, Cifuentes M, Lera L, Bustos N, Ludwig DS. Effects of replacing the habitual consumption of sugar-sweetened beverages with milk in chilean children. *The American Journal of Clinical Nutrition*. 2008;88:605-611

[48] Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, Ludwig DS. A randomized trial of sugar-sweetened beverages and adolescent body weight. *The New England Journal of Medicine*. 2012;367:1407-1416

underestimation of the true magnitude of the intervention effect. The consumption of SSBs in both groups rebounded somewhat after the intervention ceased.

42. Kahn criticizes this study, suggesting that the analysis at year 1 was motivated by the investigators looking for data to support their desired position. (Kahn ¶ 50.) This claim is unfounded. Although the primary outcome was BMI change at two years, the authors clearly indicated in the methods section of the paper that the study included a 1-year intervention and a 1-year follow-up, with assessment of study outcomes at the end of each period. The fact that the differences in weight between the groups decreased after the intervention stopped at one year actually adds to evidence that consumption of SSBs affects body weight. Kahn also suggests that the sub-group findings of greater intervention effect among Hispanics compared to non-Hispanics at year 1 calls into question the generalizability of the findings to all children. (Kahn ¶ 50.) Because this was a sub-group analysis, it does not impact generalizability of the overall results. Kahn further criticizes the study by asserting that "it was impossible to determine whether the children in the intervention arm lost weight because of a reduction in the consumption of added sugar, a reduction in total energy consumed, or because they received much more attention and encouragement than the children in the control arm" (¶ 50). Kahn's criticism is misplaced. The study examined a multicomponent intervention that aimed to reduce intake of SSBs by emphasizing substituting noncaloric beverages for SSBs as a strategy to decrease consumption. Thus, the intention of the study was to evaluate the effect of the intervention as a package, not the individual components of the intervention. It is irrelevant to the study's aims that the study does not specify the magnitude of change attributable to each component.

43. A second recent hypercaloric RCT also supports the warning's claim. In a double-blinded placebo-controlled trial, de Ruyter et al.[49] randomized 641 normal-weight Dutch children to receive 250 mL (8 oz) per day of an artificially sweetened beverage (sugar-free group) or a similar sugar containing beverage that provided 104 kcal per serving (sugar group). After 18 months of the intervention, compared with the sugar group, the sugar-free group had significant reductions in BMI z-score, weight gain and body fat change. A major advantage of this study was the double-blind design,

[49] de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. *The New England Journal of Medicine*. 2012;367:1397-1406

which avoids potential biases because of psychological cues and social desirability. In addition, an objective biomarker (urinary sucralose) indicated a high degree of compliance. One limitation is that 26% of the participants did not complete the study, which may have led to underestimation of the true effects of the intervention.

44. Kahn criticizes this study because the investigators did not collect data on total energy intake and claims that it is not possible to know whether the findings are related to a reduction in calories from added sugar or a reduction in total caloric consumption (¶ 51). Again, this issue is not relevant to the question whether SSBs contribute to weight gain but rather to the altogether different question whether SSB's or added sugar have an effect independent of calories. And although blinding was imperfect, as Kahn mentions, it was more successful than in most randomized, double-blind trials.[50] The results from this study, together with the findings from Ebbeling et al.,[51] provide strong evidence that replacing SSBs with non-caloric beverages will significantly reduce childhood obesity, which is entirely consistent with the many prospective observational studies described above.

45. Among trials of SSB and body weight, it is important to distinguish between those that evaluate weight gain and weight loss. From a public health point of view, if the aim is to reduce obesity prevalence in the population, then identifying dietary determinants of weight gain is more important than short-term weight loss. This is because once an individual becomes obese, it is difficult to achieve and maintain weight loss.[52]

46. Kahn's report also discusses isocaloric trials, in which all subjects receive the same number of total calories but different levels of added sugar, and he concludes that these studies show that added sugar has no "unique" effect on weight. (¶ 47.) Isocaloric trials are not relevant to the

[50] Fergusson D, Glass KC, Waring D, Shapiro S. Turning a blind eye: The success of blinding reported in a random sample of randomised, placebo controlled trials. *BMJ*. 2004;328:432

[51] Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, Ludwig DS. A randomized trial of sugar-sweetened beverages and adolescent body weight. *The New England Journal of Medicine*. 2012;367:1407-1416

[52] Hu FB. Resolved: There is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obesity Reviews*. 2013;14:606-619

warning label under consideration because they are not designed to evaluate whether SSBs contribute to weight gain but rather whether they may impact weight independent of calories.

3. Meta-Analysis of Added Sugar

47. Studies that evaluate added sugar do not differentiate between liquid and solid added sugar. These studies are not as relevant to the question whether SSBs contribute to weight gain as studies that focus on SSBs rather than all added sugars, since there are likely mechanisms by which liquid sugar contributes independently to weight gain and diabetes, as I discuss in Section V, *infra*. Nonetheless I review a significant recent meta-analysis of the effects of added sugar here.

48. The World Health Organization commissioned a systematic review and meta-analysis to address the effects of added sugars on body weight and to determine whether the existing evidence supports its current recommendation to limit added sugar intake to less than 10 % of total energy.[53] WHO's study included 30 RCTs and 38 prospective cohort studies in children and adults that reported the intake of total sugars, a component of total sugars, or sugar-containing foods and beverages and at least one measure of body fatness. The meta-analysis found that in trials of adults with ad libitum (i.e. uncontrolled) diets, decreased intake of added sugars significantly reduced body weight by 0.80 kg, whereas increased consumption led to a comparable weight increase of 0.75 kg.

49. A meta-analysis of RCTs conducted among children did not show a significant effect of reducing added sugar consumption on body weight. However, the analysis did not include the two recently published large RCTs described in ¶¶ 36-39, *supra*. A meta-analysis of prospective cohort studies conducted in children revealed that higher consumption of SSBs was associated with a 55% higher risk of becoming overweight and obese compared with those with the lowest intake. The authors concluded that, "[a]mong free living people involving ad libitum diets, intake of free sugars or sugar sweetened beverages is a determinant of body weight." Furthermore, the authors noted, "[w]hen considering the rapid weight gain that occurs after an increased intake of sugars, it seems reasonable to conclude that advice relating to sugars intake is a relevant component of a strategy to reduce the high

[53] Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: Systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ*. 2013;346:e7492

risk of overweight and obesity in most countries." Kahn also reported findings from this paper but presented those pertaining to isocaloric replacement of sugars with other carbohydrates, which as expected did not result in any change in body weight (paragraph 47). In a subsequent point related to hypercaloric trials (paragraph 48), Kahn misinterprets the explanation from this paper that "the change in body fatness that occurs with modifying intakes seems to be mediated via changes in energy intakes," to refute the evidence linking SSB's to weight. This does not make sense since SSBs contribute to weight through their contribution to total energy intake.

C. SSBs and Diabetes

50. A large body of evidence indicates that SSB consumption is associated with increased risk of diabetes both through effects on body weight (since obesity is the greatest risk factor for developing diabetes) and independently through other metabolic effects.

51. Findings from well-designed prospective cohort studies have shown a strong and consistent association between SSB consumption and diabetes. In a meta-analysis of 8 prospective cohort studies evaluating SSB intake and risk of diabetes conducted by me and co-authors, we found that individuals in the highest category of SSB intake (usually 1-2 servings per day) had a 26% greater risk of developing diabetes compared to those in the lowest category (none or less than one per month).[54] A one-serving-per-day increase in SSB consumption was associated with about 15% increased risk for diabetes. This association was consistent across ethnic groups (Caucasians, African-Americans and Asians), age groups, and sex. As with our meta-analysis on weight gain, we did not adjust for variation in the total calories people consumed or in their weight, because these are at least part of the pathway connecting SSBs and risk of diabetes.

52. A similar association was recently seen in participants from eight cohorts participating in the very large European Prospective Investigation into Cancer and Nutrition (EPIC) study,[55] which

[54] Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: A meta-analysis. *Diabetes Care*. 2010;33:2477-2483

[55] The InterAct consortium. Consumption of sweet beverages and type 2 diabetes incidence in european adults: Results from epic-interact. *Diabetologia*. 2013;56:1520-1530

found that a one serving per day increase in SSBs was associated with a 22% greater risk of diabetes. As expected, the association was attenuated after further adjustment for total energy intake and BMI to an 18% increased risk. This suggests that some but not all of the association between SSB and diabetes is attributable to total energy intake and BMI, in contrast to Kahn's claim that excess total energy consumption seems far more likely to be the cause of diabetes (¶ 65). However, even if most or all of the effect of SSBs on the risk of diabetes was mediated by excessive energy intake, this would still be strong reason reduce SSB consumption.

53. These studies show an increased risk of diabetes with commonly consumed levels of intake—i.e. a one serving per day increase or 1-2 servings per day compared to none or less than one per month. As discussed in the Section I, *supra*, one quarter of soda drinkers consume at least one soda per day. Thus the warning's claim is well-founded in light of the evidence and common patterns of consumption.

54. Kahn's interpretation of the prospective cohort evidence is not well-founded in my opinion. Kahn's statement that associations with diabetes are most often absent at moderate levels of sugar consumption does not appear to be based on the evidence (¶ 69). In the same paragraph, Kahn reports that other prospective cohort studies have not found associations between SSB consumption and diabetes, but he bases this conclusion on a non-peer-reviewed book chapter on fructose alone or fructose-containing sugars (sucrose or HFCS) in relation to diabetes and not on data specific to SSBs. Interestingly, Kahn did not consider results from the two meta-analyses discussed above, both of which provide consistent evidence of a positive association between SSBs in amounts widely consumed and risk of diabetes, thus supporting the warning's claim.

55. Kahn also notes that there is limited experimental evidence concerning the link between SSB consumption and diabetes. It is true that there is limited experimental evidence from RCTs. This is because of the high cost, ethical considerations, and feasibility considerations which would make implementation of RCTs concerning clinical diabetes extremely challenging and potentially misleading. As Kahn points out, diabetes takes many years to develop and requires a substantial defect in both insulin action and insulin secretion (¶ 68). A diabetes trial would take many years of follow up, probably with thousands of persons, which would also compromise participant adherence to

soda consumption or the comparison beverage; whether this is feasible at all is dubious in light of other failed large RCTs. In contrast, prospective cohort studies are able to follow large groups of people for many years without investigator intervention. Such studies are able to evaluate long-term associations between diet and clinical outcomes. As discussed above, *supra* ¶¶ 32-35, a well-designed and analyzed cohort study can simulate a randomized trial when the most relevant confounders are accounted for.[56] Again, Kahn dismisses much of the evidence from cohort studies simply based on study design without differentiating between studies of varying quality and without acknowledging that many of the limitations can be overcome by design and analysis techniques.

56. Kahn also provides evidence of associations between other foods and behaviors with diabetes (from our cohorts) and concludes that there is no evidence that SSBs play a unique role in the development of diabetes (¶ 69). The fact that other diet and lifestyle factors are associated with diabetes does not refute the evidence that SSBs are also associated with diabetes. Like we know for heart disease and stroke, no single factor explains these diseases, but by acting on multiple risk factors simultaneously we have made great strides in reducing incidence and mortality from these major causes of death.

57. Kahn points out that some popular fruits, such as apples and pears, can have the same or more amounts of sugar than SSBs (¶ 27), albeit from natural sources. However, this is not a meaningful comparison. Some studies have shown a lower risk of diabetes with higher fruit consumption.[57] Unlike whole fruits, which are rich in fiber and a myriad of beneficial vitamins and nutrients, SSBs tend to have little nutritional value and are devoid of fiber, and the sugar in SSBs is absorbed more quickly (i.e., it has a higher glycemic index), which would contribute to their positive association with diabetes risk in contrast to whole fruit. Also, it is very difficult to consume the same amount of carbohydrate from whole fruits as from SSBs; for example a 20 oz. soda would be equivalent to about 6-8 whole oranges, which are rarely consumed at one time.

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[56] Hernan MA, Robins JM. Estimating causal effects from epidemiological data. *Journal of Epidemiology and Community Health*. 2006;60:578-586

[57] Muraki I, Imamura F, Manson JE, Hu FB, Willett WC, van Dam RM, Sun Q. Fruit consumption and risk of type 2 diabetes: Results from three prospective longitudinal cohort studies. *BMJ*. 2013;347:f5001

58. Although experimental data on SSBs and diabetes are limited, short-term mechanistic trials have established a biologic rationale and causal relationships with biomarkers of diabetes risk. These studies support the associations observed in prospective cohort studies. A recent review paper by my research group at Harvard summarized the evidence from trials linking intake of sugar-containing beverages to adverse glycemic, insulin, and lipid parameters; elevated markers of inflammation; and development of visceral adiposity, all of which are risk factors for diabetes.[58] Kahn mentions in paragraphs 67 and 68 that some of these studies provided participants with unrealistically high doses of sugar, and adverse effects were not observed at levels normally consumed in the population. However, this is incorrect since other trials have observed adverse effects with doses that are equivalent to frequently consumed intake levels of SSBs. One trial found that after 3 weeks, SSBs consumed in small to moderate quantities (600 mL or 20 oz. SSB/day containing 40–80 grams of sugar) significantly impaired glucose and lipid metabolism and promoted inflammation.[59] Recent data have also shown that consuming HFCS sweetened beverages containing 10% - 25% of energy produced significant linear increases in postprandial triglycerides (i.e. triglycerides in the blood, a key biomarker for diabetes).[60] Since added sugar intake in the US constitutes over 13% of caloric intake, with 10% of the population consuming 25% or more of their calories from added sugar,[61] the dose amounts in these experimental studies are equivalent to real-world added sugar intake, and thus their results are relevant as well. These short-term mechanistic studies, in combination with findings from prospective cohort studies with clinical diabetes as an outcome, make a strong case for a causal

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[58] Malik VS, Hu FB. Fructose and cardiometabolic health: What the evidence from sugar-sweetened beverages tells us. *Journal of the American College of Cardiology*. 2015;66:1615-1624

[59] Aeberli I, Gerber PA, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. *The American Journal of Clinical Nutrition*. 2011;94(2):479-85

[60] Stanhope KL, Medici V, Bremer AA, Lee V, Lam HD, Nunez MV, Chen GX, Keim NL, Havel PJ. A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. *The American Journal of Clinical Nutrition*. 2015;101:1144-1154

[61] Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among us adults. *JAMA Internal Medicine*. 2014

relationship between SSB consumption and diabetes.[62] I discuss the issue of causality in further detail in Section VI, *infra*.

V. HOW SSBs CONTRIBUTE TO OBESITY AND DIABETES

59. Obesity arises as the result of an energy imbalance between calories consumed and calories expended, creating an energy surplus and a state of positive energy balance, which in turn results in excess body weight over time.

60. The caloric intake from commonly consumed serving sizes of SSBs is significant: A typical 12 oz. serving of soda contains on average 140-150 calories and 39 grams of sugar, which is equivalent to about ten teaspoons of table sugar. A typical 20 oz. serving, which became the norm in the early 1990's, provides 65 grams of sugar and 240 calories. These common serving sizes of SSB provide most of or more than the daily recommended maximum of no more than 10% of total energy from all added sugar[63, 64], which is equivalent to about 48 grams or 12 teaspoons of sugar, based on a 2000 calorie per day diet. If these calories are added to the typical diet without compensatory reductions in calories elsewhere, then consuming one 12-oz. can of soda per day, could lead to a weight gain of 5 pounds in one year, and one 20 oz. serving could lead to a weight gain of 8 pounds in one year.[51]

61. There is significant evidence that people who consume SSBs do not fully compensate for these calories by reducing calories elsewhere in their diets.[65] This may be because consumption of SSBs results in less satiety (a feeling of fullness that leads people to stop eating or drinking) than solid foods with similar caloric value. Short-term feeding studies comparing SSBs to non-caloric artificially

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[62] Hu FB. Resolved: There is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obesity Reviews*. 2013;14:606-619

[63] Guideline: Sugar intake for adults and children. Geneva: World Health Organization; 2015.

[64] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th edition. December 2015. Available at http://health.Gov/dietaryguidelines/2015/guidelines/.

[65] Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. 2010;121:1356-1364

sweetened beverages in relation to energy intake[66] and weight change[67, 68, 69, 70, 71] demonstrate this point.

62. Additional evidence supporting incomplete compensation for liquid calories has been provided by studies showing greater energy intake and weight gain after consumption of beverages compared to an equivalent amount of calories from solid food.[72, 73] These studies indicate that calories from sugar in liquid beverages may not suppress intake of solid foods at subsequent meals to the level needed to maintain energy balance. In other words, it is easy to consume an enormous amount of calories from these beverages. These calories are not easy to compensate for with exercise. It has been estimated that it would take 5 miles of walking or 50 minutes of running for a 110 pound adolescent to burn off the calories contained in one typical 20-ounce soda.[74]

63. Kahn appears to embrace the notion that all diets are equally likely or unlikely to contribute to obesity or diabetes, so long foods and beverages are consumed in moderation. (E.g., Kahn ¶¶ 65, 76.) This position is not supported by the evidence. Instead nutritional research, and in

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[66] DellaValle DM, Roe LS, Rolls BJ. Does the consumption of caloric and non-caloric beverages with a meal affect energy intake? *Appetite*. 2005;44:187-193

[67] *Id*.

[68] Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: Different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. *The American Journal of Clinical Nutrition*. 2002;76:721-729

[69] Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *The American Journal of Clinical Nutrition*. 1990;51:963-969

[70] Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: Effects of supplementary sucrose drinks over a 4-week period. *British Journal of Nutrition*. 2007;97:193-203

[71] Raben A, Moller BK, Flint A, Vasilaris TH, Christina Moller A, Juul Holst J, Astrup A. Increased postprandial glycaemia, insulinemia, and lipidemia after 10 weeks' sucrose-rich diet compared to an artificially sweetened diet: A randomised controlled trial. *Food & Nutrition Research*. 2011;55

[72] DiMeglio DP, Mattes RD. Liquid versus solid carbohydrate: Effects on food intake and body weight. *Int J Obes Relat Metab Disord*. 2000;24:794-800

[73] Pan A, Hu FB. Effects of carbohydrates on satiety: Differences between liquid and solid food. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2011;14:385-390

[74] Bleich SN, Barry CL, Gary-Webb TL, Herring BJ. Reducing sugar-sweetened beverage consumption by providing caloric information: How black adolescents alter their purchases and whether the effects persist. *American Journal of Public Health*. 2014;104:2417-2424

particular the cohort studies discussed in ¶¶ 29-30, *supra*, show that some foods should be promoted and some should be limited for optimal health. Added sugar should be limited. According to the USDA 2015 dietary guidelines, based on an extensive review of all available data, a healthy eating pattern limits added sugars to no more than 10% of total energy intake.[75] As previously mentioned SSB's are the greatest contributor to added sugar intake. These beverages have little to no nutritional value and have consistently been associated with adverse health outcomes as described above.

64. In my experience Kahn's views on nutrition have been at odds with mainstream nutrition science in the past. I am familiar with a program launched by the food industry in 2009 called the "Smart Choices Program," in which foods that met specified nutritional criteria were given a front-of-package green checkmark.[76] Unfortunately, the criteria that were used to identify so-called better nutrition choices were set very low; foods such as Froot Loops and Fudgsicles received "Smart Choices" checkmarks on their packages. *Id*. According to published media reports, Kahn was a board member of the organization that administered the Smart Choices program.[77] In a media report published at the time, he defended the inclusion of sugary foods, stating, "If you get someone who has diabetes and they're eating doughnuts for breakfast, anything down the ladder is a better choice."[78] The Smart Choices program was later voluntarily suspended after the FDA wrote a letter announcing its concern that such standardized front-of-package nutritional claims might mislead consumers or encourage them to choose unhealthy foods.[79]

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[75] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th edition. December 2015. Available at http://health.Gov/dietaryguidelines/2015/guidelines/.

[76] Neuman W, For your health, Froot Loops. *N.Y. Times*, Sept. 4, 2009, available at http://www.nytimes.com/2009/09/05/business/05smart.html.

[77] *Los Angeles Times*, Food makers suspend promotion of Smart Choices labeling, Oct. 24, 2009, available at http://articles.latimes.com/2009/oct/24/nation/na-food-labeling24; Ruiz, R. Smart Choices foods: As dumb as they look? *Forbes*, Sept. 17, 2009, available at http://www.forbes.com/2009/09/17/smart-choices-labels-lifestyle-health-foods.html.

[78] *Id*.

[79] Letter from Michael R. Taylor and Jerold R. Mande, FDA, to Sarah Krol, dated Aug. 19, 2009, available at http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm180146.htm.

65. With regard to the mechanisms by which SSBs contribute to the development of diabetes, in part this occurs through their ability to induce weight gain, but also there are likely non-calorically related effects arising from the high amounts of rapidly absorbable sugars. Consumption of SSBs has been shown to induce rapid spikes in blood glucose and insulin levels,[80, 81] which in combination with the volumes typically consumed contribute to a high dietary glycemic load (GL). High GL diets have been shown to lead to hyperinsulinemia and insulin resistance.[82] An increase in GL has also been shown to exacerbate levels of inflammatory biomarkers linked to diabetes and cardiovascular disease.[83] Some evidence also suggests that consuming fructose, a constituent of sucrose and in slightly higher amounts from HFCS may also increase blood pressure and promote the

[80] Raben A, Moller BK, Flint A, Vasilaris TH, Christina Moller A, Juul Holst J, Astrup A. Increased postprandial glycaemia, insulinemia, and lipidemia after 10 weeks' sucrose-rich diet compared to an artificially sweetened diet: A randomised controlled trial. *Food & Nutrition Research*. 2011;55

[81] Janssens JP, Shapira N, Debeuf P, Michiels L, Putman R, Bruckers L, Renard D, Molenberghs G. Effects of soft drink and table beer consumption on insulin response in normal teenagers and carbohydrate drink in youngsters. *Eur J Cancer Prev*. 1999;8:289-295

[82] Ludwig DS. The glycemic index: Physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA: the journal of the American Medical Association*. 2002;287:2414-2423

[83] Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC, Ridker PM. Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity c-reactive protein in middle-aged women. *The American Journal of Clinical Nutrition*. 2002;75:492-498

accumulation of visceral adiposity, dyslipidemia, ectopic fat deposition and insulin resistance.[84, 85, 86, 87] These are all elements of the metabolic syndrome, a precursor of diabetes.

66. These findings, in combination with those from the cohort studies and RCTs described above, demonstrate that SSBs contribute to diabetes partly through effects on body weight and calories but also independently through other metabolic pathways. Kahn's claim that there is mixed or insufficient evidence of any contribution that SSBs make to diabetes independent of calories is therefore inaccurate.

67. Moreover, whether SSBs contribute to obesity and diabetes entirely or partially through calories does not impact the integrity of the warning. The warning's claim is the fact that SSBs contribute to weight gain and diabetes; it does not address how they contribute to these outcomes. Weight gain and increased risk of diabetes occur at typical consumption levels observed in the population, lending further support to the warning's claim.

VI. THERE IS SUFFICIENT EVIDENCE OF THE CONTRIBUTION SSBs MAKE TO OBESITY AND DIABETES TO SUPPORT REGULATORY ACTION

68. To answer the question whether the associations between SSB consumption and obesity and diabetes are causal, I apply the Bradford Hill criteria for causality to the available evidence.[88, 89]

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[84] Teff KL, Grudziak J, Townsend RR, Dunn TN, Grant RW, Adams SH, Keim NL, Cummings BP, Stanhope KL, Havel PJ. Endocrine and metabolic effects of consuming fructose- and glucose-sweetened beverages with meals in obese men and women: Influence of insulin resistance on plasma triglyceride responses. *The Journal of Clinical Endocrinology and Metabolism*. 2009;94:1562-1569

[85] Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beysen C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest*. 2009;119:1322-1334

[86] Stanhope KL, Griffen SC, Bair BR, Swarbrick MM, Keim NL, Havel PJ. Twenty-four-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, sucrose-, fructose-, and glucose-sweetened beverages with meals. *The American Journal of Clinical Nutrition*. 2008;87:1194-1203

[87] Stanhope KL, Havel PJ. Endocrine and metabolic effects of consuming beverages sweetened with fructose, glucose, sucrose, or high-fructose corn syrup. *The American Journal of Clinical Nutrition*. 2008;88:1733S-1737S

[88] Hu FB. Resolved: There is sufficient scientific evidence that decreasing sugar-sweetened beverage consumption will reduce the prevalence of obesity and obesity-related diseases. *Obesity Reviews*. 2013;14:606-619

This set of criteria, commonly used in non-communicable disease epidemiology, evaluates an evidence base according to nine criteria:[90]

1) Strength of the association: Our meta-analysis of cohort studies found that a one serving per day increase in SSB was associated with an additional weight gain of 0.12-0.22 kg over 1 year.[91] Although the effect size seems modest, the unit of exposure is relatively small (i.e. one serving per day). RCTs have shown greater short-term weight gain with the addition of SSBs to the diet and significant benefits of reducing SSB or added sugar consumption on body weight. From our meta-analysis of cohort studies on diabetes we found that daily consumers of SSB had a 26% greater risk of developing diabetes compared to infrequent or nonconsumers.[92] Experimental studies of SSB and biomarkers of diabetes risk support this association.[93]

2) Consistency of the association: The evidence from prospective cohort studies and RCTs for obesity and risk of diabetes is highly consistent. *Supra* ¶¶ 19, 23-25, 32-34, 36-38, 46-47.

3) Specificity of the association: Consumption of SSBs has been associated with risk of hypertension and coronary heart disease and unrelated conditions such as dental caries. This criterion has limited utility since causes of an important effect cannot be expected to lack other effects on any logical grounds.

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[89] Malik VS, Hu FB. Sweeteners and risk of obesity and type 2 diabetes: The role of sugar-sweetened beverages. *Current Diabetes Reports*. 2012

[90] Hill AB. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*. 1965;58:295-300

[91] Malik VS, Pan A, Willett WC, Hu FB. Sugar-sweetened beverages and weight gain in children and adults: A systematic review and meta-analysis. *The American Journal of Clinical Nutrition*. 2013;98:1084-1102

[92] Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: A meta-analysis. *Diabetes Care*. 2010;33:2477-2483

[93] Malik VS, Hu FB. Sweeteners and risk of obesity and type 2 diabetes: The role of sugar-sweetened beverages. *Current Diabetes Reports*. 2012

4) Temporality of the association: The temporal relationships between SSB and obesity and diabetes risk are well established, given that the evidence reviewed here is derived from prospective cohort studies and RCTs.

5) Biological gradient or dose-response: As SSB intake increases, the amount of weight gain increases in a dose-response manner. Similarly as SSB increases, risk of diabetes increases. *Supra* ¶¶ 32, 53.

6) Biological plausibility: SSBs contain large amounts of energy from rapidly absorbable sugars. Consumption of these calories in liquid form is associated with less satiety and an incomplete compensatory reduction in energy intake at subsequent meals, leading to the overconsumption of total daily calories.[94] SSBs lead to diabetes through obesity and independently through glycemic effects from postprandial spikes in blood glucose and insulin and probably also from the metabolic consequences of fructose.[95]

7) Biological coherence: The interpretation of the associations between SSB and obesity and diabetes risk is consistent with what is currently known about the natural history of these conditions.

8) Experimental evidence: RCT's have shown that reducing consumption of SSB's or added sugar significantly decreases weight gain and that adding SSBs to the diet significantly increases weight gain. Short-term mechanistic studies have shown that SSB consumption increases visceral adiposity, dyslipidemia, insulin resistance and plasma concentrations of uric acid and inflammatory cytokines, which are components of the metabolic syndrome, a precursor of diabetes.

9) Analogous evidence or alternate explanations: The positive associations between SSBs and obesity and diabetes risk found in observational studies could be due to confounding by other correlated dietary and lifestyle factors. However, these factors

[94] Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. *Circulation*. 2010;121:1356-1364

[95] *Id*.

were carefully adjusted for in multivariable analyses in most studies. Results from RCTs are not susceptible to such confounding and support conclusions from observational studies.

69. Taken together, the current evidence on SSBs and obesity and diabetes meets all of the key criteria commonly used to evaluate causal relationships in epidemiology. Thus there is compelling evidence that SSB intake is causally related to increased risk of obesity and diabetes.

70. In the absence of large RCTs with clinical disease endpoints, evidence from prospective cohort studies in conjunction with smaller RCTs with intermediate endpoints is often considered in substantiating nutritional claims or establishing policies. For instance, the USDA Dietary Guideline Advisory Committee used evidence from prospective cohort studies extensively, in addition to evidence from RCTs, to evaluate the relations between specific dietary factors and chronic disease risk, which forms one of the foundations for making dietary recommendations for the US population.[96] More broadly, data from observational studies provide the primary basis for policies that protect the public from harms due a wide array of occupational, dietary, environmental, and medical exposures.

71. Kahn appears to believe that because there are limited RCTs linking obesity and diabetes to consumption of SSBs, causality has not been established. As discussed above, *supra* ¶¶ 36 & 55, RCTs are generally considered the gold standard in epidemiology for establishing a causal relationship because they can eliminate confounding and selection bias with a sufficient sample size.[97] However, most trials of SSBs and obesity have been short-term, and it is likely not feasible to examine the relationship between SSB consumption and risk of chronic diseases such as diabetes through RCTs.

72. There are many reasons why RCTs—the gold standard in the pharmaceutical industry—are frequently infeasible in nutritional epidemiology. Unlike classic drug trials in the pharmaceutical industry, RCTs of dietary interventions typically cannot be blinded, leading to the

[96] U.S. Department of Health and Human Services and U.S. Department of Agriculture. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. http://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf

[97] Satija A, Yu E, Willett WC, Hu FB. Understanding nutritional epidemiology and its role in policy. *Advances in Nutrition*. 2015;6:5-18

possibility that the effect of the intervention is due to knowledge of treatment assignment as opposed to the dietary component of the intervention. Dropout rates also tend to be higher in RCTs of nutritional interventions relative to those in drug trials, especially if the intervention is implemented for long periods or is very demanding or both. Dietary interventions to promote weight loss routinely have dropout rates of 30–40% even after just 1 year of follow-up. Such substantial dropout can reduce analytical power in the presence of random loss to follow-up or introduce systematic bias in the effect estimate, usually in unpredictable directions, if the dropout is related to treatment and outcome.[98] Another problem faced to a greater extent in nutritional RCTs relative to drug trials is noncompliance, i.e., insufficient adherence by participants to their assigned intervention. Such noncompliance may become severe in trials of longer duration, which would be necessary for evaluating clinical outcomes like diabetes. Randomized trials of nutritional interventions, although free from confounding and selection bias at baseline, can suffer from similar biases post-baseline that we often observe in observational studies, especially when they are of long duration, complicating their interpretation and diminishing their utility above prospective cohort studies. Unlike drugs, which are designed to have large and targeted effects on individual pathways in relatively short periods of time, individual nutrients or foods usually have modest effects over long periods of time to affect disease risk. Realistically, an ideal RCT may never be conducted in free-living populations for dietary behavioral changes and risk of diseases like diabetes and cardiovascular disease since almost all trials, no matter how well designed, will suffer from one or more of the above mentioned major limitations, such as reduced compliance over time and infeasibility of blinding the interventions.

73. On the other hand, large cohort studies, particularly those with repeated measures that carefully adjust for potential confounders are powerful tools to investigate long-term associations between dietary exposures and chronic disease risk.

74. Thus, evidence from prospective cohort studies of hard clinical endpoints and short-term intervention trials of intermediate outcomes should be used together to infer causality and inform policy. That is what the application of the Bradford Hill criteria does. *See supra* ¶ 68. Based on

[98] Rubin DB. Inference and missing data. *Biometrika* 1976;63:581–92.

application of that criteria, and for the other reasons discussed in this report, it is my opinion that consuming SSBs contributes to obesity and diabetes, that San Francisco's warning is evidence-based and accurate.

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