Dominik D. Alexander, PhD, MSPH
Principal Epidemiologist
EpidStat Institute

Dr. Alexander has extensive experience in health research methodology and disease causation, particularly in the conceptualization, design, analysis, and interpretation of epidemiologic studies. He has published on a diverse range of topics and types of studies, including original epidemiologic research, qualitative reviews, systematic weight-of-evidence assessments, and quantitative meta-analyses.

Review of Epidemiologic Methodology Used in the SACN Report: A Focus on Sugar and Health Outcomes

Overall impressions:
The SACN Draft Report (including the extensive supplementary documents) is a large and ambitious summary of carbohydrates and health outcomes. As an epidemiologist, I evaluated critically the methodology used to synthesize the literature, the quantitative analytical summaries of the data, and how interpretations and evidence judgments were formulated. My review is specific to the evidence on sugars and health outcomes.

Although comprehensive in scope, there are concerns regarding the application of systematic methodology, and the development of evidence judgments that do not appear to be clearly supported by the evidence base. Specifically, the review methodology used to synthesize the evidence and formulate conclusions is not transparent in the SACN report. The methodological protocol is summarized comprehensively in the Cardiometabolic Health Protocol supporting document and the SACN Framework for Evaluation of Evidence document, but the application of analytical and interpretive methodologies for specific topic areas is somewhat unclear.

Perhaps the foremost concern is the judgment of the evidence – because of the rather limited volume of studies, inconsistency of the data and methods across the studies, relatively weak associations, and the likelihood of bias (e.g., dietary recall, selection bias) and confounding (e.g., influence of other dietary and lifestyle factors) as acknowledged by SACN, the conclusions pertaining to sugar intake and health outcomes, particularly body composition and type 2 diabetes, appear to be overstated. A more cautious approach to interpreting the currently available evidence should be undertaken.

Judgment of the Evidence in the SACN Report

The SACN grading system for judging the evidence is discussed beginning in Annex 2 (A2.12). It is indicated that a grading system was devised specifically for use in the report (A2.12). The authors state that, "Expert judgement was used to determine the exact grading. This included taking account of study quality, study size and methodological considerations, which may have resulted in the upgrading or downgrading of evidence, where appropriate" (A2.15, pg. 222). Although expert judgment is of utmost importance in interpreting the evidence, it is unclear how

the judging process was implemented from the content of the SACN report. This is a concern when attempting to interpret the underlying evidence as reported in the SACN document. Some information is provided in the Cardiometabolic Health Protocol supporting document but the specific application of judgment criteria is not transparent. In addition some relevant guidance information is reported in the SACN Framework for Evaluation of Evidence document, but this document does not describe the application of the framework. Some components of the well-established criteria for evaluating the evidence, namely the Sir Bradford Hill guidelines, were reportedly used, such as the magnitude of association, temporality and dose-response but again, it is unclear how these were applied directly to the topic areas summarized in the SACN draft report.

Hill, A. B. (1965). "The Environment and Disease: Association or Causation?". Proceedings of the Royal Society of Medicine 58 (5): 295–300

Based on the SACN report, the evidence was considered either Adequate, Moderate, or Limited (A2.16). This was apparently based on the number of available studies as well as study methodology. However, it is unclear how such grades were implemented based on the content of the SACN report. For example, was information bias considered and if so, how was this methodological factor 'weighed' against other study quality characteristics, such as inadequate adjustment for potential confounding factors? These are very important concepts in a systematic weight-of-evidence approach. Again, some of this information is provided in the supplementary materials but the judgment process lacks clarity.

The authors state that, "Evidence was deemed inconsistent according to statistical considerations i.e. in a meta-analysis, when I^2 >75%, the confidence intervals do not overlap or if the results of individual studies are not in the same direction. When the I^2 was greater than 75%, but the forest plot suggested there was evidence of a direction for an outcome expert judgement was used to upgrade the conclusion, where appropriate" (A2.19, pg. 223). This approach to evaluate consistency/inconsistency is not sufficient to appreciate the concept of between-study variation because this approach is based only on statistical heterogeneity, where an I^2 tests indicates the amount of unexplained between-study variation in a meta-analysis model. This is acceptable for looking at statistical variation in a 'specific' meta-analysis model. If significant heterogeneity is apparent, additional sub-group analyses must be conducted to identify potential sources of between-study variation. It is unclear if these necessary analytical steps were taken. To appropriately evaluate consistency/inconsistency, methodological variability needs to be assessed prior to conducting a meta-analysis and producing I^2 statistics (see Althuis et al. 2014 for example). If significant between-study variability is identified *a priori*, a meta-analysis model shouldn't be generated in the first place unless the authors transparently discuss methodological heterogeneity and then use a meta-analysis to explore sources of between-study variation. This does not appear to be the case in the SACN report.

Althuis MD, Weed DL, Frankenfeld CL. Evidence-based mapping of design heterogeneity prior to meta-analysis: a systematic review and evidence synthesis. Syst Rev. 2014 Jul 23;3:80. doi: 10.1186/2046-4053-3-80.

Use of Meta-Analysis Methodology in the SACN Report

Meta-analysis methodology is discussed (in brief) under the data analysis sub-heading beginning in section A2.6 of the SACN report. Very little information is presented regarding the utilization and analytical methodology of meta-analyses in the context of the SACN draft report, however, more relevant information is provided in the Cardiometabolic Health Protocol supporting document.

A meta-analysis is a systematic quantitative method whereby results data from individual studies are combined to produce an overall, or weighted, estimate of relative risk. A meta-analysis serves many vital functions when synthesizing, summarizing, and interpreting a body of scientific evidence (see Modern Epidemiology, 2008). Specifically, a meta-analysis can be used to estimate risk with greater precision (enhancing statistical power), evaluate consistency of findings across studies, examine potential sources of heterogeneity (between-study variation), analyze and discern potential dose-response patterns, and assess the potential for publication bias. Meta-analyses are a very complex analytical methodology, but many researchers attempt to conduct meta-analyses without fully understanding the methodological complexities. Although meta-analysis methodology served an instrumental role of synthesizing and summarizing the evidence, very little precious information is provided in the SACN draft report. While more comprehensive meta-analysis information is provided in the extensive supporting documents, it would be beneficial to the reader if a section on meta-analysis application and evidence review was included in the SACN report (prior to the summary of the evidence). This would provide a framework for evaluation in a more transparent fashion. An exorbitant amount if information is provided in the supportive documents, however, a clear and transparent application of meta-analysis methodology and review synthesis remains for specific topic areas. While I fully acknowledge and appreciate the comprehensive effort of the authors, the following concerns are raised:

- The literature search for the specific topic areas are not provided in the SACN draft report. In addition, it is unclear if they are provided in the supportive documents. An appropriate literature search protocol is provided in the Cardiometabolic Health Protocol supporting document but a systematic flow chart of the process is lacking for individual topic areas.
- The protocol for study inclusion and exclusion is provided in the Cardiometabolic Health Protocol supporting document but again, it is not clear how this was applied to specific topic areas.
- The methods for data extraction are lacking in the SACN draft report, thus it is unclear how the researchers identified and synthesized relevant information and data for specific topic areas. Further, it is unclear how the authors synthesized the studies on an individual basis as well as collectively. The methodological considerations with specific factors, such as length of follow-up and sample size, are listed in the SACN Framework for Evaluation of Evidence document, but it is uncertain/unclear how these relevant factors were considered for each topic area and how these factors played a role in the interpretation of the evidence.
- Importantly, the meta-analytic model building process is absent for each topic area. This is a main feature of assessing methodology heterogeneity – a necessary and fundamental feature of conducting a meta-analysis. While a great deal of meta-analysis framework information is provided in the Cardiometabolic Health

Protocol supporting document, the SACN draft report lacks this important information for evidence review.

- The types of meta-analysis appear to be somewhat limited. For example, the authors state that for, "meta-analyses of cohort studies, a dose response approach was used to quantify the relationship between dietary intakes on particular health outcomes." A dose-response approach is definitely warranted but this should be done with respect to numerous other analyses. For example, an extreme-quantile analysis should be conducted, and other (not just the categorical dose-response regression analysis) types of dose-response analyses should be performed (e.g., stratified intake analyses, cumulative dose-response analyses, etc.). In addition, sub-group analyses should be conducted to identify potential sources of between-study variation, sensitivity and influence analyses should be performed, and publication bias assessments should be generated. The supporting documents do present this information but such analyses should also be considered at the design phase. Finally, it would be beneficial for the reader if this type of information was reported in the SACN draft document so the reader could garner a better appreciation of analytical consistency.
- It is unclear if an evaluation of methodological heterogeneity was conducted (this should be a fundamental step before the analyses are performed) [see Althuis 2014].
- It is stated that, "if the result produced an I^2 of more than 75%, the pooled estimate would not be presented because it indicates that there is excessive heterogeneity and the result would have little meaning" (A2.8, pg. 221). While it is true that this is evidence of statistical heterogeneity, it is not clear how the identification of sources of between-study variability were explored. Furthermore, it is not clear if/how such secondary analyses fit into the development of evidence judgments.

While a great deal of relevant meta-analysis and methodological information is provided in the Cardiometabolic Health Protocol supporting document and the SACN Framework for Evaluation of Evidence document, the direct application to specific topic areas summarized in the SACN draft report is somewhat lacking. Thus, it is not clear how the analytical results summarized in the supporting documents were used to formulated conclusions and evidence judgments.

Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 2008. Lippincott Williams & Wilkins, 758 pages.

Althuis MD, Weed DL, Frankenfeld CL. Evidence-based mapping of design heterogeneity prior to meta-analysis: a systematic review and evidence synthesis. Syst Rev. 2014 Jul 23;3:80

SACN Chapter 6. Sugars, Sugar Alcohols, Sugars-Sweetened Foods and Beverages

The studies pertaining to sugars and various health endpoints are discussed in Chapter 6 of the SACN report. Several studies were claimed to be identified and reviewed, and the authors indicate that the links to the individual systematic reviews and updated search are provided in Annex 1. However, it is not clear if this is yet to be provided or if the SACN draft report is referring to: Update Search, Evidence tables updating the systematic reviews on cardio-metabolic health, colorectal health & oral health from the supporting documents. The SACN draft report in its current form provides no scientific perspective on the specific methodology

used to evaluate topic areas. In the SACN draft report it is stated that, "Evidence on health/disease outcomes have been discussed in detail only where there are sufficient data for a conclusion to be drawn, from studies meeting the pre-agreed inclusion criteria" (6.2, pg. 82). The report does not contain detailed discussions or reviews for any topic area. Each sugar-outcome topic area is summarized in an insufficiently brief paragraph that includes the number of studies and minimal characteristics. There is no evidence on the review process for each of the topic areas, no discussion of study quality, no discussion on how the studies were evaluated quantitatively, and no discussion of how the evidence was judged. Some additional information is provided in the supportive documents but it is unclear how the totality of the evidence was synthesized to formulate conclusions.

Energy intake and body composition

The authors report an 'effect' with 'adequate evidence' demonstrating that greater consumption of sugars is detrimental to health (6.19, pg. 86). This conclusion is based primarily on seven studies, with variable methodology, study populations, and follow-up periods. Of the seven, only two studies had comparable interventions (Raben et al., 2002; Reid et al., 2007). The other five had interventions that involved substitution of the macronutrient content of the diet, but these interventions were highly variable (i.e., "low-fat high- "complex" carbohydrate diet" and "low-fat, high-"simple" carbohydrate diet" (Poppitt et al., 2002) versus "advised to reduce fat" and "advised to reduce fat and NMES" (Drummond et al., 2003)). Study populations ranged from 12 to 83 allocated with completers ranging from "completers not reported" to 100% of participants, and follow-up periods ranged from two weeks to six months (pg. 107-110, Consultation Supporting Documents Ch. 6). In addition, the sample sizes are relatively small. Given these important concerns, the evidence should not be considered adequate and a conclusion of an 'effect' is not warranted based on the underlying data sources. Indeed, positive correlations may have been observed in the sparse evidence base of studies, but there is clearly not enough relevant information to formulate conclusive opinions. Furthermore, their findings were not substantiated by all lines of evidence, i.e., data from cohort studies. In addition, for the cohort studies conducted among children, the SACN authors concluded no association between SSBs and increasing BMI, and no association between SSBs and increased body fatness (6.51-6.53, pg. 94, summary boxes). The authors reported an effect, with limited evidence, that SSBs increase BMI in the randomized controlled trials (pg. 96, summary box).

Raben A, Vasilaras TH, Moller AC & Astrup A (2002) Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. American Journal of Clinical Nutrition 76, 721-729.

Reid M, Hammersley R, Hill AJ & Skidmore P (2007) Long-term dietary compensation for added sugar: effects of supplementary sucrose drinks over a 4-week period. British Journal of Nutrition 97, 193-203

Poppitt SD, Keogh GF, Prentice AM, Williams DE, Sonnemans HM, Valk EE, Robinson E & Wareham NJ (2002) Long-term effects of ad libitum low-fat, high-carbohydrate diets on body weight and serum lipids in overweight subjects with metabolic syndrome. American Journal of Clinical Nutrition 75, 11-20.

Drummond S, Kirk T, Jackson J, Hendry J, Panton S & Gray F (2003) Effectiveness of dietary advice given by community dietitians to men with elevated blood cholesterol in a clinical setting: a pilot study. Journal of Human Nutrition and Dietetics 16, 81-83.

Sugars and T2D

Of note, the authors concluded no association between sugars or individual sugars and risk of T2D (pg. 86, summary box). By extension, it makes no scientific/epidemiologic sense that SSBs would therefore increase the risk of T2D [see the section on SSBs and T2D below].

Chapter 6 synopsis

There appears to be a disconnect between the level and evidence and the recommendations being made (in later sections) in the SACN report. Specifically, the totality of available scientific and epidemiologic evidence does not clearly support an independent relationship between SSB intake and energy, body composition parameters, or T2D. There have been some positive associations, effects, and correlations observed in the literature, however, because of significant methodological limitations and variability, the evidence based does not support the formulation of recommendations. Indeed, the associations between SSB intake and health outcomes are weak in magnitude, relatively inconsistent, based on rather sparse data, and are likely strongly confounded by other dietary and lifestyle factors. Thus, a cautious approach to interpreting the evidence should be made.

In addition, numerous, but related topic areas for which there is/was insufficient evidence are noted in the SACN draft report. For example, in the cohort studies, there is insufficient evidence between SSBs and body weight change, weight gain, body fatness and fat distribution, energy intake, etc. (pg. 102, table). For the randomized controlled trials, there is insufficient evidence between SSBs and body weight, weight gain, energy intake, etc. (pg. 103, table). Thus, making recommendations on these topic areas is clearly not supported or warranted by the scientific foundation.

Table 6.1 Insufficient evidence-cohort studies

Risk factor/health outcome/measure	Exposure
cardiovascular disease events	monosaccharides disaccharides
Coronary events	monosaccharides disaccharides sugars rich foods sugars-sweetened beverages
Stroke	total sugars monosaccharides disaccharides sugars-sweetened beverages
Incident hypertension	fructose sugars-sweetened beverages
Blood pressure	sugars rich foods
Total cholesterol	sugars rich foods
HDL-cholesterol	sucrose sugars-sweetened beverages
Body weight change	sucrose sugars rich foods sugars-sweetened beverages
Weight gain	sucrose sugars rich foods sugars-sweetened beverages
Body fatness and fat distribution	sugars rich foods sugars-sweetened beverages
Energy intake	sugars-sweetened beverages
Type 2 diabetes mellitus	sugars rich foods
Impaired glucose tolerance	total sugars
Glycaemia	sugars-sweetened beverages
Insulinaemia	total sugars sugars-sweetened beverages
Insulin resistance/sensitivity	sugars sugars-sweetened beverages
Colo-rectal, colon and rectal cancer	sugars, fructose, sucrose lactose (colon cancer only)
Caries in the deciduous dentition	frequency of sugars intake sweetened comforter (dummy) fruit juice
Caries in the mixed and permanent dentition	frequency of sugars-sweetened beverages
Oral cancer	sugars-sweetened beverages

Table 6.2 Insufficient evidence-randomised controlled trials

Risk factor/health outcome/measure	Exposure
Vascular compliance	sugars
Fasting blood lipids	glucose, fructose sucrose sugars-sweetened beverages
CRP, haptoglobin and transferrin	sugars
Body weight	sugars-sweetened beverages
Weight gain	sugars-sweetened beverages
Energy intake	sugars rich foods sugars-sweetened beverages
Eating motivation	sucrose
Impaired glucose tolerance	sugars
Glycosylated blood proteins	sugars
Glycaemia	sugars-sweetened beverages
Insulinaemia	sugars-sweetened beverages
Insulin resistance	sugars-sweetened beverages
Transit time	sugar alcohols polydextrose
Constipation	polydextrose
Caries in the deciduous dentition	monosaccharides sugar alcohols
Caries in the mixed and permanent dentition	sugars rich foods
Periodontal disease	sugars

Table 6.3 Inconclusive evidence

Measure	Exposure
Faecal pH	polydextrose
Faecal SCFA	polydextrose

In fact, the authors appropriately conclude that, "Due to the paucity of studies, there is a lack of evidence to draw conclusions on the impact of sugars intake on the majority of cardio-metabolic outcomes in adults, including body weight. There is also a lack of evidence to assess the impact of sugars intake on oral health in adults, as all included studies and trials were conducted in children and adolescents. With observational studies there is substantial potential for biases and

the possibility of confounding by an extraneous variable that correlates with both the dependent variable and the independent variable (residual confounding) and any associations must be interpreted with caution" (6.72, pg. 104).

The authors continue to state that, "Randomised controlled trials conducted in adults indicate that increasing sugars intake when consuming an ad libitum diet, either through the substitution of other macronutrient components or by replacement of non-caloric sweeteners by sugars, leads to an increase in energy intake" (6.75, pg. 104). However, this is not in complete concert with the table shown above, nor by support from other lines of evidence as mentioned previously.

Given the information presented above, there appears to be a disconnect between the collective evidence and the conclusions in the SACN draft report. Complicating interpretation is the fact that numerous specific topic areas are reviewed, most with insufficient levels of evidence (e.g., body weight change and SSB), but some specific areas indicate adequate evidence. It is not clear how a conclusion for this level of evidence was formulated, especially when the totality of evidence does not appear to support a firm conclusion. Based on how the SACN draft report is organized and summarized, it is unclear whether and/or how the very important concepts of consistency or coherence were considered when judging the evidence.

Epidemiology of Sugar-Sweetened Beverages (SSB) and Type 2 Diabetes (T2D)

Despite some strong assertions that SSBs may increase the risk of T2D, the available epidemiologic evidence is relatively sparse. In fact, results data for SSB and T2D risk has been reported in only eight mutually exclusive study populations, with specific SSB categories reported in only five to six study populations. Considerable heterogeneity exists in the study populations, SSB definitions, intake metrics, T2D outcome validation, and level of adjustment of relevant confounding factors. Based on review of the SACN supporting documents, it is indicated that no RCTs reported outcomes concerning sweetened beverages and incident T2D. Thus, SACN based their conclusions on six cohort studies, all of which were large and ranged in size from 6841 to 116671 participants. All but one study was conducted outside the United States. One study reported no association between intakes of full calorie sweetened beverages and T2D, although the authors noted that no risk estimates or consumption data were provided in that paper (Nettleton et al., 2009) (note: data were actually reported at the highest intake levels). Another study also reported no consistent association with incident T2D. Hazard ratios in that study were reported as being close to 1.0 for both men and women (Paynter et al., 2006). The remaining four studies selected by the authors provided some evidence of increased risk of T2D with increasing intakes of the sweetened beverages that were analyzed. However, considerable variability and inconsistency were noted, especially in terms of beverages defined by the study authors as "sugar-sweetened-beverages." Sugar sweetened beverages included fruit juices, fruit punches, and carbonated beverages, both diet and non-diet. Groupings and definitions of these beverages varied. Also of concern is the issue of servings sizes, which varied from study to study. One study reported that consumers of sugar-sweetened beverages were different from low to non-consumers of said beverages in aspects of lifestyle such as smoking, sedentary lifestyle, and energy intake (Schulze et al., 2004b). All of these attributes are potential confounders and were important adjustments in the studies selected by the authors, although residual confounding

is a concern. One study did not adjust for energy intake (Schulze et al., 2004b). These considerable inconsistencies results in low confidence that the studies should be combined in a meta-analysis without a resulting problem of significant heterogeneity. As noted in the SACN supportive document, observational studies have a high potential for biases and should always be interpreted with caution.

Nettleton JA, Lutsey PL, Wang Y, Lima JA, Michos ED, Jacobs J (2009) Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the multi-ethnic study of atherosclerosis (MESA). Diabetes Care 32 (4): 688-694

Paynter NP, Yeh HC, Voutilainen S, Schmidt MI, Heiss G, Folsom AR, Brancati FL, Kao WH (2006) Coffee and sweetened beverage consumption and the risk of type 2 diabetes mellitus: the atherosclerosis risk in communities study. Am J Epidemiol 164 (11): 1075-1084

Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB (2004b) Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA 292 (8): 927-934

The following sub-sections include a critical evaluation of the Greenwood et al. (2014) meta-analysis, a review of the meta-analysis data reported in the SACN report, and a summary of the evidence on this topic based on internal analyses of the epidemiologic data.

Greenwood et al. 2014

Recently, Greenwood et al. (2014) published a meta-analysis of prospective studies of SSB and T2D (the authors' also analyzed artificially sweetened beverages, but they are not covered in detail herein). Greenwood and colleagues acknowledge in the opening of the abstract that there have been some positive associations between SSBs and T2D but it is "unclear whether this is because of the sugar content or related lifestyle factors, whether similar associations hold for artificially sweetened soft drinks, and how these associations are related to BMI." These postulations have not been answered based on their analyses. Furthermore, Greenwood appropriately suggests that their results should be interpreted cautiously, and that there may be alternative explanations for the results, such as lifestyle factors or reverse causality. In the following section of bullet points, Greenwood's own concerns about interpreting their data are summarized as it directly relates to meta-analysis methodology and valid statistical analyses.

- Because of a "range of definitions" in the soft drink categories across studies, Greenwood and colleagues estimated a linear dose-response trend for each study before combining studies into a meta-analysis. What this means is that they made significant assumptions about linear risk patterns in each study rather than utilizing the actual data reported by the authors in the individual studies. Thus, risk estimates for increased consumption levels may not be representative of the underlying data foundation from the studies themselves. This approach is commonly used by meta-analysts, however, this should be used in conjunction with numerous other analytical methods. For example, an extreme-quantile comparison should be conducted whereby high vs. low intake levels are compared. Stratified intake dose-response analyses should be conducted, which use the 'actual' data from the studies rather than assumed data generated for the dose-response method by Greenwood. Specifically:
    - In a typical epidemiologic study, risk estimates are reported for specific intake levels, such as <1 SSB per week (referent group), 1-6 SSBs per week, daily SSB intake, 2 or more SSBs per day (highest intake group). Thus, an extreme group comparison would be the highest intake level vs. the lowest (referent group). It would be expected that if a difference were to exist, it would be at the highest

level of intake. However, not all studies report the same intake metrics, e.g., the highest level in one study may be the middle level in another study. Thus, other methods are suggested to utilize all groups of data, such as dose-response analyses. All methods should be utilized to facilitate a better understanding of potential relationships. Greenwood et al. used a single analytical strategy – a type of dose-response analysis that includes assumptions. Therefore, consistency of results across analytical strategies could not be appreciated.

- Furthermore (and importantly), if a study does not report risk data for all categories (such as for the MESA cohort, where a decreased risk of T2D was observed at the 1 or more servings of SSB per day category; note: they also included non-alcoholic beer in their SSB category), then it would be excluded by Greenwood. There are essentially ignoring relevant data that could serve a useful role in a meta-analysis.
- Greenwood et al. assumes a linear pattern of risk in each individual study. Thus, if the highest category of SSB is 1+ per day, they would assume a linear relationship above and beyond 1 serving of SSB per day. This may not be an accurate reflection of the true pattern of associations. Further, they transformed servings to ml/d, which may introduce another dimension of bias if a 'self-reported' serving does not translate to the pre-specified criteria set-forth by the authors. These factors may lead to a spurious appearance of a dose-response trend, or an inflated estimate of risk at higher consumption levels. A preferred method given the data variability across studies is to conduct categorical dose-response analyses for each specific exposure metric, that is, dose-response for the servings/unit time studies and dose-response for the volume studies. [see comments below on meta-analysis of SSB and T2D]

- Given the single primary type of meta-analysis that Greenwood performed, a RR of 1.20 (95% CI: 1.12-1.29) per 330ml per day of SSB and T2D was reported. This is a very weakly elevated association that is likely influenced by confounding, bias, and colinearity with other dietary and lifestyle factors. Indeed, the authors noted that when BMI was adjusted, the association attenuated to 1.16. In addition, SSB intakes (as well as other dietary and lifestyle factors) are based on self-reported recall via a food frequency questionnaire. Thus, information bias (misclassification) may result in modifying the association in either direction, as indicated by the authors. Thus, the level of evidence supporting a role between SSB intake and risk of T2D should be considered weak.
- Another important factor that contributes to the lack of confidence in the SSB-T2D relationship is statistical heterogeneity. Statistical heterogeneity reflects unexplained variation between the risk estimates and variability measures between studies. A meta-analysis model with statistically significant heterogeneity may not be a valid representation of the actual association (or lack thereof) between an exposure and outcome. Greenwood noted statistically significant heterogeneity in their analyses of SSBs and T2D.
- The summary relative risks between SSBs and artificially sweetened beverages on T2D risk were indistinguishable based on similar magnitudes of effect (RR for SSB = 1.20, RR for artificially sweetened beverages = 1.13) and overlapping confidence intervals (CI

for SSB = 1.12-1.29, CI for artificially sweetened beverages = 1.02-1.25).This is a very important observation, which may be supported by the following logical statement:

- If sugar sweetened beverages contain sugar (they do), and artificially sweetened beverages do not contain sugar (they don't)
  AND
  If there is no difference in relative risk between sugar sweetened beverages and artificially sweetened beverages on type 2 diabetes risk
  THEN
  Sugar from sugar sweetened beverages would not be a cause of type 2 diabetes

- Because the association between SSBs and T2D was attenuated after adjusting for BMI, the authors suggest that this is consistent with BMI being in the causal pathway. This is a flawed assumption. First, it assumes that SSBs *cause* an increase in BMI (this is not an established causal relationship). Second, it assumes that all study participants with a high BMI have a high BMI because of SSB intake. Third, it assumes that any attenuation in risk is due solely to SSBs being in the causal pathway (rather than any confounding influence). Fourth, it ignores the potential for reverse causality, that is, individuals who already have a high BMI consume SSBs – SSB intake is a consequence (or a behavior) of persons with high BMI rather than a cause of high BMI. Fifth, it completely ignores the fact that high BMI/obesity is an independent causal factor of T2D, and that adjustment for BMI would in fact attenuate the observed associations because of the relationship between BMI and T2D. Sixth, even under an assumption that SSBs cause increased BMI (note: this is not supported by the evidence), SSBs are clearly not the only causative factor. Thus, a complex analytical framework would need to be in place to adequately account for the role of the major contributors to increased BMI, independent of SSB intake, in order to better understand the causal pathway hypothesis. At this point, the current state-of-the-science is not well understood.
  - In some studies (of the relatively few on this topic), adjusting for BMI did not result in an appreciable reduction in risk compared with not adjusting for BMI. This demonstrates that BMI did not act as a mediating factor on the SSB-T2D relationship. Therefore, an entire spectrum of possible risks factors for T2D should be appropriately considered and included in analytical modes of SSBs and T2D to fully understand any potential associations.

de Koning L, Malik VS, Rimm EB, Willett WC, Hu FB. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. Am J Clin Nutr. 2011;93(6):1321-1327.

Sakurai M, Nakamura K, Miura K, et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. Eur J Nutr. 2013:1-8.

Paynter NP, Yeh H-, Voutilainen S, et al. Coffee and sweetened beverage consumption and the risk of type 2 diabetes mellitus: The atherosclerosis risk in communities study. Am J Epidemiol. 2006;164(11):1075-1084.

Nettleton JA, Lutsey PL, Wang Y, Lima JA, Michos ED, Jacobs DR,Jr. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the multi-ethnic study of atherosclerosis (MESA). Diabetes Care. 2009;32(4):688-694.

- In the textbook, Obesity Epidemiology, the author indicates that T2D is an obesity-related disease. Specifically, it is stated that, "Among all lifestyle risk factors for type 2 diabetes, overweight and obesity are the most important." In fact, in the textbook and a published paper, RRs for BMI levels of 30-34.9kg/m^2 and 35+kg/m^2 were 20.1 and 38.8, respectively, for T2D risk (Hu et al. 2001). In a recent meta-analysis, an RR of 7.19 was

reported for obesity and T2D risk (Abdullah et al. 2010). These are very strong relative risks, and in contrast, the general patterns of RRs for SSBs and T2D range between 1.0 and 1.3 – orders of magnitude lower than the relationship between high BMI/obesity and T2D risk.

- Based on the available epidemiologic evidence, BMI should be evaluated as a confounder rather than a factor in the alleged causal pathway, especially given the strong relationship between BMI and T2D.
- The authors concluded that the estimates for SSBs show "strong" dose-response trends. This is NOT true. The risk estimates reported by Greenwood et al. are actually very weak in the context of epidemiologic associations (Miller 2014). Given the weakly elevated associations, the role of chance, bias, confounding, and colinearity cannot be ruled out. Furthermore, the risk estimates reported by Greenwood are based on only a handful of studies, with mixed methodology such as variable BMI adjustment.
- Greenwood et al. conclude that, "Recommendations to limit the consumption of sugar-sweetened soft drinks by promoting the supply of sugar-free alternatives depend, in part, on the nature of the association with obesity and whether alternatives to artificially sweetened soft drinks also have negative consequences." Thus, the authors appear to acknowledge (at least in part) the fact that the relationship between SSBs and T2D remain questionable. The facts are:
    - Collectively, BMI plays a role in attenuating the association between SSBs and risk of T2D
    - SSBs are not an established causal factor for T2D
    - The associations between SSBs and T2D are similar to the associations between artificially sweetened beverages and T2D
    - Thus, other dietary and lifestyle factors (rather than SSBs) appear to play the biggest role in T2D risk

Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. Diabetes Res Clin Pract. 2010 Sep;89(3):309-19.

Greenwood DC, Threapleton DE, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C & Burley VJ (2014) Association between sugar-sweetened and artificially sweetened soft drinks and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. Br J Nutr, 1-10.

Hu, FB, Manson, JE, Stampfer MJ, et al. Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women. N Engl J Med 2001; 345:790-797.

Hu, FB. Obesity Epidemiology. 2008; Oxford University Press.

Miller, PE, Alexander, DD, Weed, DL. Uncertainty of Results in Nutritional Epidemiology. Nutrition Today: May/June 2014, Volume 49, Issue 3, p 147-152.

SSB and T2D analysis reported in the SACN report

The authors of the SACN report conducted their own meta-analysis on SSBs and T2D (6.34, pg. 90, text and summary box; supportive documents file). Five cohorts were included in their meta-analysis, resulting in a summary association of 1.07 (95% CI 1.05-1.08) for each 100ml/day increase, with statistically significant heterogeneity. The authors then present the following synopsis:

Sugars-sweetened beverages (ml/day) and type 2 diabetes mellitus
• Association • Moderate evidence • The direction of the association indicates that greater consumption of sugars-sweetened beverages is detrimental to health • The association is biologically relevant

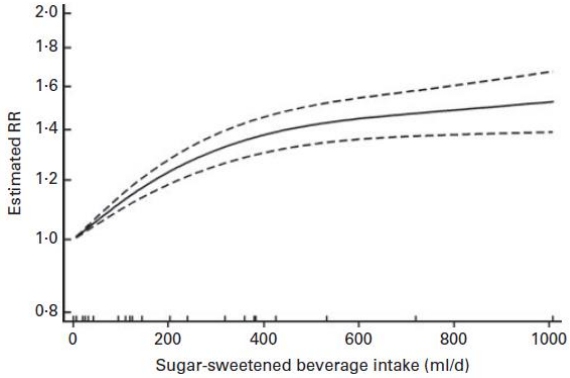
This synopsis is unclear in many aspects. The four summaries in their synopsis (pg. 90) are discussed in brief as follows:

- *Association*: The authors of the SACN report indicate that there is an association but they do not qualify this association. Specifically, the association of 1.07 per SSB intake unit is extremely weak in magnitude and does not address the likelihood of chance, bias, or confounding on this association (see Miller 2014). That is, the possible role of alternative explanations is not given sufficient weight. There is a distinction of an association and an 'independent' association. Given the strong likelihood of influence by bias and confounding, and given the fact that the association is weak in magnitude and based on a handful of studies, any observed association should not be considered independent based on the currently available evidence. An independent association is necessary before a determination of causation can be made, and it is acknowledge that the SACN authors do not make a causal statement. Of importance is that the exercise of performing a meta-analysis does not overcome the limitations of the individual studies. More specifically, results from a meta-analysis are only as valid as the validity of the individual studies included in a meta-analysis. The authors note methodological limitations in the studies, thus, a very careful and cautious interpretation is necessary.
- *Moderate evidence*: This appears to be more of a "volume" of studies factor rather than a "quality" of studies factor. Moderate (based on the SACN judgments) means that there are approximately 3 to five cohort studies for a particular topic (see A2.16, pg. 222). Judging of evidence needs to objectively and transparently include study quality, methods, and interpretation of results across the body of evidence – not merely a number of studies. It is not readily apparent in the SACN draft report whether/how this was performed.
- *The direction of the association indicates that greater consumption of sugars-sweetened beverages is detrimental to health*: It is true that a positive association was observed but again (emphasis added) – the association is very weak in magnitude, based on relatively few studies, and is likely influenced by bias and confounding.
- *The association is biologically relevant*: Yet again, it is unclear what is meant by this statement. It is not known whether a comprehensive evaluation of biological plausibility (not likely) was conducted or if an assumption is being made that SSB intake is clearly associated with risk of T2D, in which case would suggest the human health effects are biologically meaningful. This is not specific. Any time a health effect would ostensibly be increased or reduced, it would be biologically relevant. However, the blanket statement lacks specificity and the reported association suffers from the limitations describe above.

Miller, PE, Alexander, DD, Weed, DL. Uncertainty of Results in Nutritional Epidemiology. Nutrition Today: May/June 2014, Volume 49, Issue 3, p 147-152.

Dose-response meta-analysis of SSB and T2D

I conducted an independent stratified intake dose-response meta-analysis. For this analysis, linearity was not assumed nor were risk estimates generated in the individual studies under the assumption of a linear pattern of risk by increasing intake levels. Rather, actual data reported in similar intake strata from the individual studies were combined. For example, data for SSB intake categories were combined that included the actual intake groupings in the studies (e.g., 1-2 servings per day). By doing this, assumptions were not made about the linear risk pattern of the data, and an attempt to harmonize intake levels across the literature was made. This analysis produced summary risk estimates for dose-response that were considerably lower than those extrapolated by Greenwood et al. (see their dose-response curve below).



Based on this figure, risk increases in a non-linear fashion as intake increases. However, based on the stratified intake analysis for dose-response, the individual studies do not report risk data at these increasing levels of intake. Specifically, the highest intake level for most studies is 1-2 servings per day. Thus, Greenwood should not extrapolate data out to these levels that are not even analyzed across the epidemiologic studies. For example, assuming that a typical soft drink is 350-360 ml, then results (based on actual data from the individual studies) for 1 to 2 servings per day would equate to a relative risk of approximately 1.15 for a range of 355 to 720ml per day. This is in direct contrast to Greenwood's data that suggest the risk for this same intake level would range between 1.25 and 1.45.

Overview of the epidemiology of SSBs and T2D

Collectively, the available epidemiologic evidence does not support an independent association between SSB intake and risk of type 2 diabetes. The conclusion is based on the follow:

- Associations are weak in magnitude.
- The possible relationship between SSBs and T2D is confounded by other dietary and lifestyle factors, such as BMI.

- Disentangling any potential associations between SSBs and T2D is complicated by the fact that dietary intake of SSBs is highly correlated with other foods, nutrients, and behavioral choices.
- Bias likely plays a significant role in the reported associations between SSB intake and T2D. For example, dietary and lifestyle information is based on self-report, which may result in exposure misclassification that would bias associations in unpredictable directions.
- Methodological heterogeneity is prevalent across the studies. Definitions of SSBs vary across studies, intake levels vary across studies, outcome validation procedures vary across studies, the level of identification and adjustment for potential confounding factors varies across studies, etc.
- Interpretation is severely limited by data from a handful of studies. For a potentially complex relationship, such as SSBs and T2D, a large volume of studies with high-quality and uniform methodology is needed to make informed decisions on a body of evidence. Indeed, there are well over 40 active epidemiologic cohorts, however, only 5 to 8 have reported data for SSBs and T2D.
- Finally, associations between SSBs and T2D are indistinguishable from associations between artificially sweetened beverages and T2D. Thus, there is no epidemiologic basis to claim that "sugar" sweetened beverages cause T2D.

SACN Chapter 11. Dietary Reference Values

In Chapter 11 of the SACN draft report, the authors propose carbohydrate dietary reference values for adults and children 2 or more years of age (pg. 199). It is indicated that these propositions have been made in the context of an energy intake appropriate to maintain a healthy weight. However, these recommendations are either 1) not clearly supported by the underlying evidence, or 2) completely lack evidence for some recommendations. Some key points are summarized in brief as follows:

- The authors of the SACN draft report suggest that the "quality of the evidence" has strengthened regarding adverse health outcomes pertaining to free sugars (11.8, pg. 200). However, it is not clear if the authors are actually referring to study quality (as a detailed summary of methodological quality appears to be absent in the SACN draft report; the application of judgment criteria is somewhat tenuous) or an increase volume of studies. The latter would not be a matter of quality, but number. In this case, the original underlying methodological concerns would still be present – just in greater number.
- The authors suggest that in regards to a mere handful of studies, "The data show a clear dose response relationship such that total energy intake increases as the percentage of energy from sugars increases. Although there is limited evidence relating to sugars intakes below 10% of energy intake, there is little reason to doubt that the relationship continues to be approximately linear at lower percentages of energy from sugars" (11.9, pg. 200). However, and as mentioned previously, there are few studies and they have methodological variability, different study populations and follow-up periods, relatively small sample sizes, and they lack a clear control for other factors that may be related to energy intake. In fact, the SACN authors themselves suggest a cautious interpretation.

Specifically, they state, "This figure assumes no dietary compensation for the additional energy supplied in the higher sugars diets, which may not reflect true dietary behaviour and, therefore, the estimate should be treated with some caution" (11.10, pg. 201). They say further that there are "few data at this level [5% of energy] of intake to draw firm conclusions" (11.10, pg. 201).
    - These are crucial factors that they acknowledge in their own assessment.
    - The bottom line from both, an epidemiologic perspective and a regulatory perspective, is that recommendations should not be made in the absence of data nor should they be made in light of the significant methodological limitations that they indicate.
    - The validity of the conclusions and recommendations may be considered questionable.
- It is implied that the proposed dietary reference value for sugars is justified because "the evidence in this report found that sugars sweetened beverages are associated with a higher risk of type 2 diabetes mellitus and that obesity is also linked with this outcome" (11.12, pg. 202). However, based on all of the reasons detailed in this commentary, including a lack of clear scientific evidence supporting a role of SSBs on either T2D risk or increased BMI risk, the proposed dietary reference values are based on a limited evidence base replete with methodological shortcomings and inconsistencies.

Brief synopsis of dietary reference values for sugars

- Few studies with inconsistent methodology and variability/limitations in terms of the study population, sample sizes (all are relatively small), differing follow-up periods of rather short durations, and assessment of other factors that may influence energy intake are being relied upon to formulate recommendations.
- There are no (or sparse) data points relating sugar intake at 5% of energy intake.
- There is no scientific rationale to isolate sugars in terms of a reduction to achieve a 100kcal dairy deficit. The authors of the SACN report did not do a formal analysis of other relevant sources of energy in this context, such as fat or alcohol. Thus, the SACN report provides no reliable basis to compare potential human health implications resulting from dietary modifications.
- The singling out of SSBs is unwarranted and not supported by the available evidence.
- The SACN authors themselves point out serious limitations and suggest a cautious approach to interpreting the evidence.
- Thus, if such limitations are acknowledged and a cautious approach is recommended, then based on sound scientific rationale, recommendations should not be made at this time.

Methodological Limitations of Nutritional Epidemiology

Because of the well-known, well-established, and well-documented limitations of interpreting evidence from nutritional epidemiology studies, a large body of evidence is required to examine methodological variability across studies with respect to patterns of associations across the

literature. The epidemiology on SSBs/sugars and health outcomes is rather limited (for example, only 5 to 8 cohorts with mutually exclusive study populations and heterogeneous methods have been published for SSBs and T2D); thus, more studies with improved and uniform methodology are needed to provide a better understanding of any potential relationships between SSBs and health outcomes. Not until then should recommendations be made that pertain directly to intake of SSBs/sugars.

Miller, PE, Alexander, DD, Weed, DL. Uncertainty of Results in Nutritional Epidemiology. Nutrition Today: May/June 2014, Volume 49, Issue 3, p 147-152.

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