Association or Causation of Sugar Sweetened Beverages and Coronary Heart Disease: Recalling Sir Austin Bradford Hill

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Association or Causation?

In this issue of *Circulation*, de Koning and colleagues evaluate the association between sugar-sweetened beverage (SSB) consumption, incident coronary heart disease (CHD), and biomarkers associated with cardiovascular risk using data from the Health Professionals’ Follow-up Study.\(^1\) This analysis is similar to this research group’s previous evaluation using data from the Nurses' Health Study, with similar longitudinal follow-up of \(>20\) years.\(^2\) The results mirror those previously reported (RR=1.19 [95% CI: 1.11, 1.28] for incident CHD associated with one serving per day higher SSB consumption in the Health Professionals’ Study and add to the growing body of information that suggests an independent association between SSBs and worse cardiovascular health.

Data from the National Health and Nutrition Examination Survey (NHANES) suggest that approximately two out of every three Americans drink SSBs daily, with rates reaching as high as four in five among young (20-44 years) black men.\(^3\) Calorie intake from SSBs among individuals who drink SSBs has also risen from 239 kcal per day in 1988-1994 to 294 kcal per day in 1999-2004, highlighting the relevance of the authors’ research question. The analyses appear internally valid, but the question remains as to whether these associations are causal or not, which may be particularly difficult to discern given the risk of residual confounding present in many dietary studies, especially those that rely upon self-reported data, as was done in both the Health Professionals’ Follow-up Study and Nurses’ Health Study. A review using criteria to assess causation, as outlined by the famed British epidemiologist and biostatistician Sir Austin Bradford Hill (b. 1897 – d. 1991) in his 1965 presidential address to the United Kingdom’s Royal Society of Medicine, may help place this research into perspective.\(^4\)
Bradford Hill Criteria

**Strength of association:** Bradford Hill’s research legacy lay in the association between tobacco and lung cancer, which had a relative risk nine to ten times higher in smokers compared with non-smokers. However, he was keen to point out that “slight” associations should not be dismissed. Therefore, the authors’ results of an adjusted relative risk of 1.18 (95%CI 1.06, 1.31) in the risk of incident CHD between individuals with the highest quartile of SSB consumption (median intake=6.5 servings/week) compared with individuals with the lowest quartile of consumption (median intake=never) might be considered sufficiently strong to be considered causal.

**Consistency:** Consistency of effect is achieved by finding a similar direction and strength of association using different methods. The authors’ use of a longitudinal cohort to evaluate the association between SSB and incident CHD has been similarly shown in the Nurses’ Health Study, providing consistency across sex groups but not across a wide range of race/ethnic or socioeconomic groups. Other studies have evaluated the association between SSBs and surrogate outcomes. For example, the International Study of Macro/Micronutrients and Blood Pressure (INTERMAP) demonstrated a 1.6/0.8 mmHg increase in blood pressure for every SSB consumed per day, while the PREMIER trial has shown that blood pressure decreases by 0.7/0.4 mmHg for every SSB removed from the daily diet of individuals who had a baseline median of 8.5 SSB servings per week. Currently, there are few types of studies that describe the independent association between SSBs and CHD.

**Specificity:** The association between smoking and lung cancer was initially considered non-specific, given the overall increase in mortality rates among smokers compared with non-smokers. SSB intake is associated with adverse cardiometabolic changes, so are the authors’
results due to residual confounding or is there an independent, specific effect of SSBs on CHD? De Koning and colleagues have anticipated this question by controlling for potential confounders (including energy intake, body mass index, and self-reported high blood pressure, among others) and by evaluating the association of SSB consumption and biomarkers of CVD risk such as triglycerides, HDL cholesterol, C-reactive protein IL-6, TNF-alpha, and leptin. The authors were not able to adjust for socioeconomic position (SEP) within this cohort of male health professionals of presumably higher SEP, but SEP may be an important confounder or effect modifier. Interestingly, no association between SSB consumption and mean hemoglobin A1c was found in this analysis, though there was an inverse association with lipoprotein (a). These findings support the specificity of the relationship between SSB consumption and incident CHD, but the question remains as to whether there is something specific about SSBs that leads to CHD or if residual confounding persists.

**Temporality:** While the prospective nature of this study makes the concept of temporality appear self-evident, the potential for “protopathic bias” remains. That is, could preclinical cardiovascular disease or abnormalities in biomarkers of CVD risk lead individuals to consume more SSBs? Recent ecologic data would suggest that this scenario is implausible given the decline in age-adjusted CHD mortality rates in the US over the past 50 years despite rising SSB consumption over the past 30 years. Since the exposure appears to precede the outcome, the criterion of temporality seems to have been met.

**Biological gradient:** A dose-response gradient provides additional support for causality, beyond an association between any exposure and the outcome of interest compared with no exposure. The authors’ use of quartiles (Tables 2) appears to suggest a potential threshold effect wherein only individuals who have the highest quartile of SSB consumption (median intake=6.5
servings/week) experience increased CHD risk compared with individuals with lowest quartile of consumption. Does that mean that anything less than approximately one serving per day is not associated with increased risk? The authors try to answer that question in their regression models shown in Table 3 where SSB consumption is treated as a continuous variable, which demonstrates a 19% increased risk of incident CHD for every SSB serving consumed per day. The lack of non-linearity using regression models with cubic splines further suggests that there does not appear to be a specific threshold of SSB consumption that increases risk for CHD.

**Plausibility:** Bradford Hill warned against dismissing associations that were perceived as too “odd”.

The biological plausibility of SSB consumption independently causing incident CHD may seem limited to some, who would point to the growing body of literature that shows an association between SSB consumption and intermediate factors such as childhood overweight/obesity, adult weight gain, high blood pressure, diabetes, and dyslipidemia, all of which are associated with increase cardiovascular risk. Skeptics might argue that the authors’ results are simply a matter of residual confounding, particularly when evaluating similarities in BMI across SSB consumption quartiles in these data, despite higher caloric intake and lower physical activity reported in the highest SSB consumption quartile compared with the lowest SSB consumption quartile. While the association may be difficult to disentangle from an individual’s overall dietary pattern, the association appears to be plausible.

**Coherence:** The authors provide data that demonstrate an independent association between SSB consumption and biochemical mediators such as lipids, inflammatory markers, cytokines, and adipokines to suggest a causal pathway between SSBs and CHD, but are these associations present because of the aforementioned residual confounding or are they, in fact, independent changes secondary to SSBs? Is there something special about SSBs themselves that are
particularly harmful or is it simply increased caloric intake over time that was not captured through the authors’ semi-quantitative food frequency questionnaire sent to participants every four years? On the other hand, do these data suggest that SSBs are “the causes of the causes”, a key target of epidemiologic investigation espoused by Rose?13

**Experiment (Reversibility):** Even though an association between an exposure (SSBs) and outcome (CHD) may be present, does removing (or reversing) that exposure lead to a decrease in the risk of that same outcome? There are no controlled trials where individuals are randomized to receive SSB or alternative (water, diet beverage, or better yet, a calorie-neutral alternative beverage) with CHD as an outcome. The recently published Choose Health Options Consciously Everyday (CHOICE) trial14 randomized 318 overweight/obese individuals who consumed 330-390 kcal/day of SSBs (more than twice the median intake of the highest quartile in the Health Professionals’ Follow-Up Study) to replace caloric beverages (including SSBs, but not exclusive of them) with water or diet beverage (provided by the investigators) or to serve as attentive controls. There were no differences in weight loss at six-month follow-up, though there were differences in likelihood of achieving more than 5% weight loss (19.5% in intervention arm; 10.5% in attentive control arm; OR=2.07 [95% CI: 1.02, 4.22]). Even though the length of follow-up may have been insufficient to demonstrate changes in anthropometry or other markers of cardiovascular risk (such as blood pressure) and given that the CHOICE trial was not powered to evaluate the effect of the intervention on CHD events, there does not appear to be supporting experimental evidence to strengthen de Koning and colleagues’ data at present.

**Analogy:** If other beverages were implicated in causing CHD, then the case for SSBs would be considered analogous. The protective effect of moderate alcohol use notwithstanding,15 there does not appear to be a sufficient analogy that supports de Koning and colleagues’ data. Their
comparison of SSB with artificially sweetened beverages supports the specificity of their argument but does not seem to be a coherent analogy for independently implicating SSB consumption in CHD, particularly given the inherent calorie differences.

Results in Context

The American Heart Association (AHA) recommends that SSB consumption should be limited to \( \leq 450 \text{ kcals/week} \) (or approximately three 12-oz servings per week) as part of its healthy diet metric for measuring cardiovascular health, as outlined in the AHA’s 2020 Strategic Impact Goals.\(^ {16} \) The AHA’s Scientific Statement on dietary sugar intake recommends reducing \textit{total} dietary sugar intake from 355 kcal/day to less than 150 kcal/day for most men and less than 100 kcal/day for most women, or half of the daily discretionary calorie allowance.\(^ {17} \) The subsequent Added Sugars Conference in 2010 further reflects the AHA’s attempt to translate these recommendations into action, including through engagement with the food and beverage industry, among many other stakeholders from academia, government, and other groups.\(^ {18} \)

Unlike high-fiber containing carbohydrates, SSBs are nutrient-poor. Further, SSB consumption is correlated with salt consumption, reflecting a dietary pattern where SSBs are combined with high salt foods.\(^ {19} \) The high prevalence of SSB intake, even with a modest effect size on CHD risk, may suggest a large population attributable risk burden. Few would argue that SSB consumption should not decrease, particularly given high consumption rates and the current obesity epidemic, and de Koning and colleagues’ findings are a provocative page in the evolving story of SSBs and CHD. As additional research explores this relationship, the Bradford Hill criteria may be useful guideposts in placing future results into context.
Conflict of Interest Disclosures: None

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