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Keller A, O' Reilly EJ, Malik V, et al. Substitution of sugar-sweetened beverages for other beverages and the risk of developing coronary heart disease: Results from the Harvard Pooling Project of Diet and Coronary Disease. *Preventive Medicine*. 2020;131:105970.

What We Know, Think We Know, or Are Starting to Know

We can say with a lot of confidence that sugar is Public Enemy No.1 in the modern diet debates. It has also become a darling of Quacks, for whom sugar provides the perfect bait-and-switch ploy to justify their narratives that everything we know about cardio-metabolic disease as it relates to dietary fat is "wrong".

But there is a grain of truth to the role of sugar in the modern food supply; it *is* drastically different to 50-years ago. If you scrutinise the historical trends for sugar, it has constantly been high [where "high" means >10% energy], however, the food sources have shifted [(1)]. In the post-Second World War period, sugar in the typical UK diet was a nutrient consumed primarily within the home, with the main food sources being table sugar, preserves, cakes and pastries [(1)].

By the 1990's this had shifted, with an increase of sugar consumed outside the home and a rise in the consumption of sugar-sweetened beverages [SSB] and 100% fruit juices [(1)]. In both the U.S. and UK populations, high intake of SSB and sugar as a percentage of energy are associated with significant increases in cardiovascular disease and all-cause mortality [(2,3)].

The role of isolated added sugar, and the contribution of added sugar to energy excess, has led to interest in the use of non-nutritive sweeteners or low-calorie sweeteners, often simply referred to as 'artificial sweeteners' [AS]. Despite extensive toxicology studies and both pre and post-market research, concerns continue to be raised in relation to the potential for AS to increase risk for cardio-metabolic disease [(4,5)].

However, adjusting for BMI may negate any such associations [(4)], suggesting that high AS intake may correlate with BMI and that associations with cardio-metabolic disease may reflect the latter, not the former. While previous research has looked at AS *per se* as an exposure of interest, no studies have specifically investigated the effects of replacing SSB with AS and other beverages.

The Study

The present study was a pooled analysis of 6 studies included in the Harvard Pooling Project [HPP], which includes only studies with validated dietary assessment methods.

Of the 6 studies, 4 were prospective cohorts and 2 were RCTs with long-term observational follow-up. 5 studies were in the U.S., and one was in Finland.

The primary exposure of interest was sugar-sweetened beverages [SSB]. The aim of the study was to model the effects of replacing SSB with other beverages, including artificially-sweetened beverages [ASB], milk, tea, coffee, and 100% fruit juice.

The outcomes of interest were coronary heart disease [CHD] events and mortality, and nonfatal myocardial infarction [MI].

The analysis adjusted for fibre, trans-fats, polyunsaturated and saturated fats, total energy intake, BMI, hypertension, and high cholesterol.

*Geek Box: Pooled Analysis

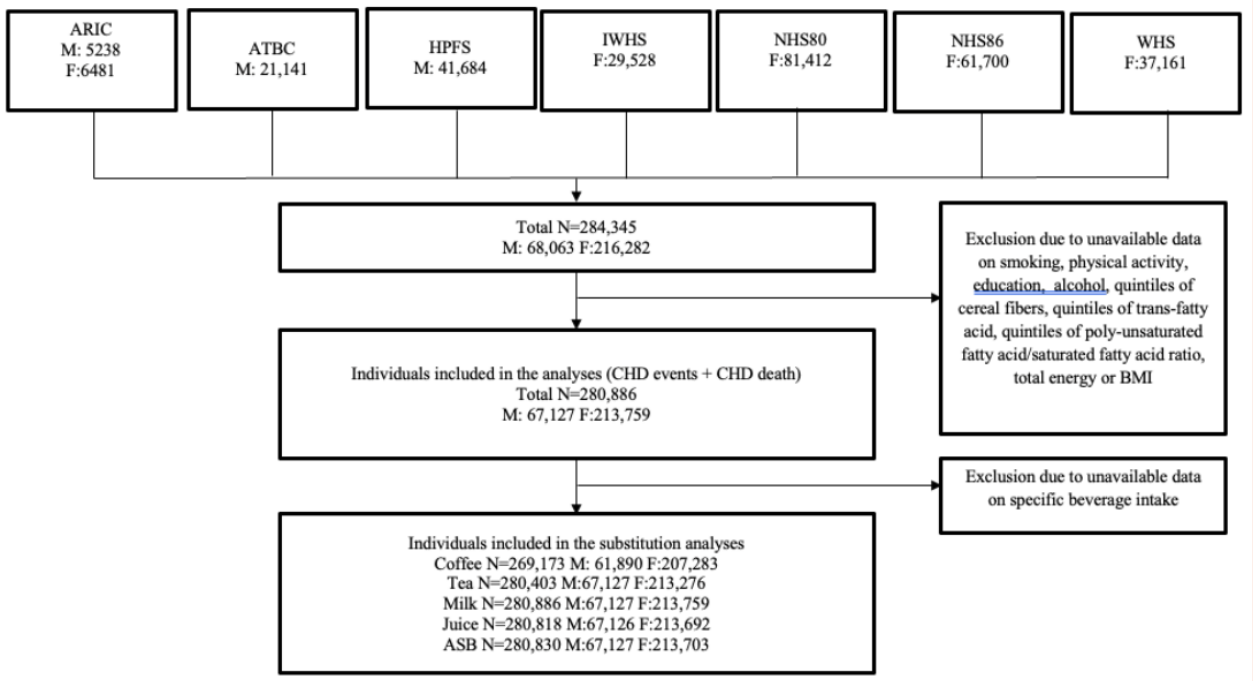
You'll have come across meta-analysis over and over in reading research, but a pooled analysis is same-same-but-different. Both meta and pooled analysis are similar insofar as they are condensing multiple published studies into an overall analysis, to obtain a summary of the effect of an exposure on an outcome of interest.

In a meta-analysis, the results of each primary study are included, and the analysis is conducted by combining all these results together to obtain a single summary estimate of the overall effect. This is an attractive methodology where the primary included studies are relatively similar in design, and where the exposure is similar in dose, two criteria that are more easily met in medical interventions.

A pooled analysis is another method of summarising results, but rather than use the overall result of the primary study, use the individual data from the participants in that study, and combine - 'pool' - all this individual data together. This provides increased statistical power, and allows for testing different aspects of the relationship between an exposure and outcome by doing sensitivity analysis [i.e., testing a specific variable within an overall analysis on the outcome], performing sub-group analysis [i.e., studies with >10yrs follow-up or studies with men and women separately], and investigating dose-responses.

Pooling itself if all individual data is just all lumped together can yield spurious results. Thus, just like meta-analysis, real care must be taken in the methodology, and the studies included must have clear inclusion/exclusion criteria, similar laboratory analysis methods for the primary data and biomarkers measured, and the data must be standardised for analysis. If these criteria can be met, then pooling individual data together can, in effect, act as one very large cohort [vs. combining individual study results, where smaller studies may be considered less reliable].

The flow chart below from the present study provides a good visual representation of this pooling process, with each of the 6 included studies being combined into an individual-data pooled analysis with nearly 290,000 participants – a huge sample size.



Results: A total of 280,886 [67,127 men and 213,759 women] participants were included in the final analysis. Over an average of 8.2yrs follow-up, there were 4,248 CHD events and 1,630 CHD deaths.

Mean SSB intake was 137ml and 115ml in men and women, respectively, while median intake was 52ml and 29ml in men and women, respectively. The 90th percentile of intake for SSB was 371ml and 370ml in men and women, respectively.

There were no significant associations between SSB, or replacing SSB with either ASB, tea, coffee, milk, or fruit juice, and CHD deaths. Thus, the following results are for CHD events only.

- ***SSB*:** Per 355ml increase in SSB, there was an overall 8% [HR 1.08, 95% CI 1.02 to 1.14] increased risk for CHD events in all participants. When stratified by sex, however, this was only significant in men with a 10% [HR 1.10, 95% CI 1.02 to 1.17] higher risk. Women had a 6% higher risk [HR 1.06, 95% CI 0.97 to 1.15] that was not statistically significant [the direction of effect, however, is overall similar to men].

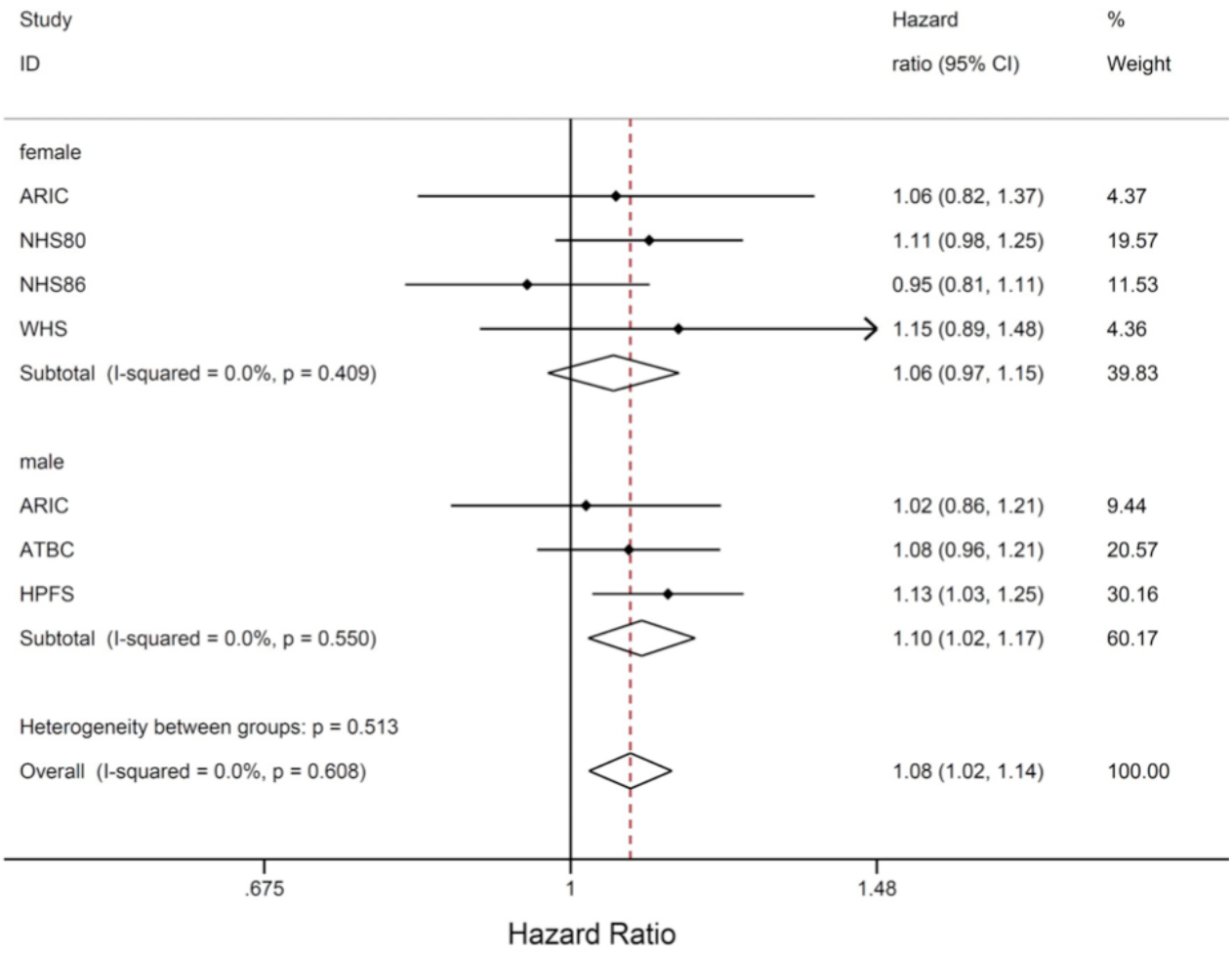


***Figure** from the paper illustrating the associations between SSB intake per 355ml increase and CHD event risk in women [**top**] and men [**bottom**]. The red dashed vertical line shows the overall average effect across all participants. As you can see, the effect overall stronger in men. However, the difference in the estimate of effect was not huge, a 4% differential, and you can see that the confidence intervals for women and men are also not hugely dissimilar, except for the finding for women crossing the 1.0 mark. It could be that the lower overall intakes of SSB among women yielded weaker effect estimates. Overall, however, the magnitude of effect and precision of that effect is not mind-blowing.*

- ***Substituting ASB for SSB*:** Replacing SSB with ASB was associated with a 12% [HR 0.88, 95% CI 0.82 to 0.96] lower risk for CHD events in all participants. This was significant in men, with a 13% [HR 0.87, 95% CI 0.77 to 0.97] lower risk. In women there was a 10% [HR 0.90, 95% CI 0.81 to 1.01] lower risk, which was not statistically significant [again, the direction of effect is similar to men].

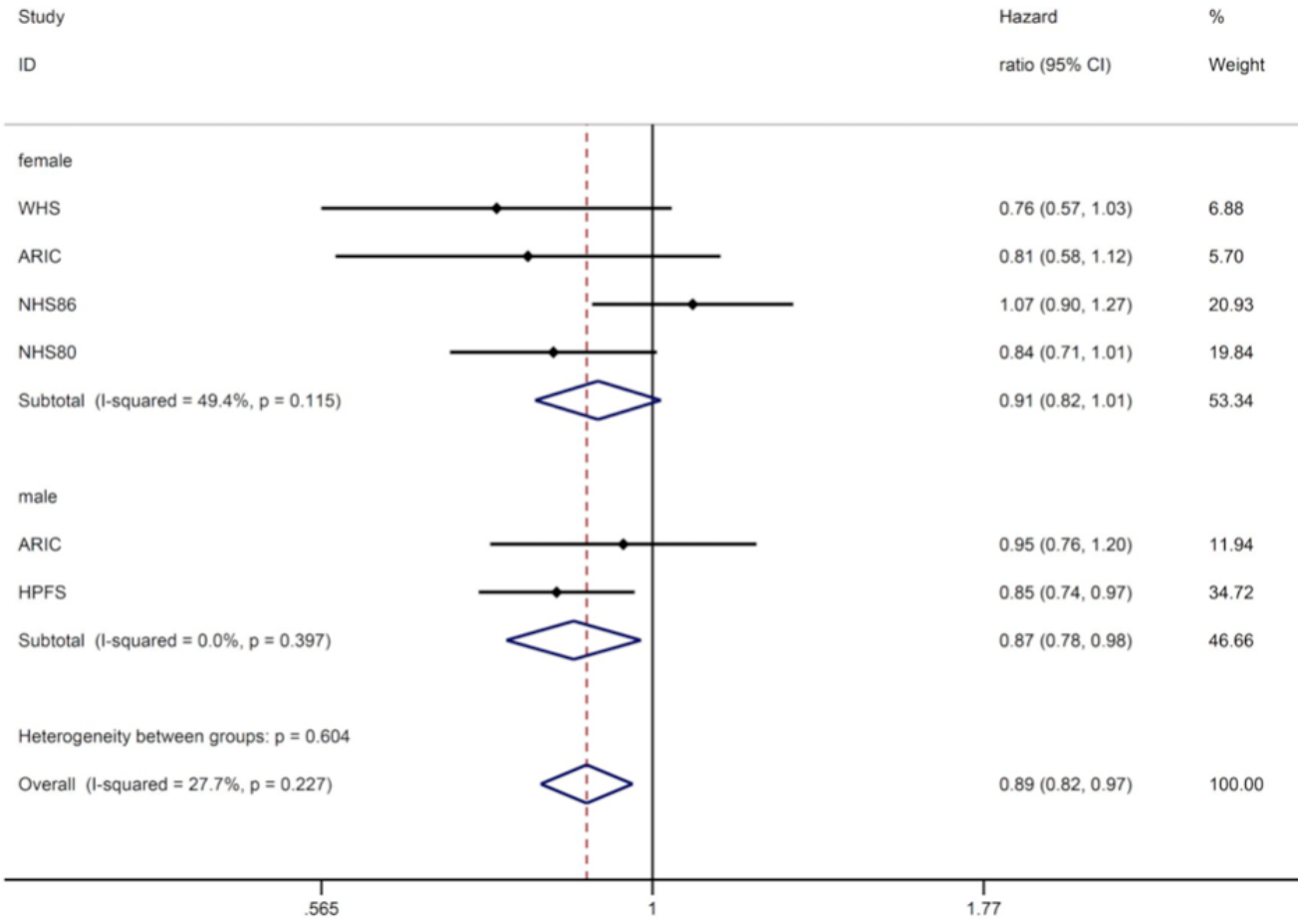


***Figure** from the paper illustrating the effect of replacing SSB with ASB on CHD events. Again, you can see that the magnitude of effect was slightly greater in men and the precision of the effect estimate just crossing 1.0 in women. As can be seen from the summary estimate [blue triangle] for women, men, and overall, the direction of effect is largely similar for both sexes.*

- ***Substituting Coffee for SSB*:** Replacing SSB with caffeinated coffee was associated with a 6% [HR 0.94, 95% CI 0.87 to 0.99] lower risk for CHD events in all participants. For total coffee intake [caffeinated or decaffeinated], there was a 7% [HR 0.93, 95% CI 0.87 to 1.00] lower risk for CHD events in all participants, an effect which was slightly stronger in women with a significant 9% [HR 0.91, 95% CI 0.84 to 0.98] lower risk, while men exhibited no significant association [HR 1.00, 95% CI 0.87 to 1.15].

There were no significant effects of replacing SSB with tea, milk, or fruit juice.

The Critical Breakdown

Pros: The inclusion criteria were clearly defined, and the HPP included studies only with validated dietary assessment methods. The final sample size was very large, and the follow-up period was adequate. The analysis added total energy intake and BMI into the adjustment model individually; this allowed for any change in the association, and the magnitude of that change, to be evident for that specific variable, rather than including it with other variables in which case any change represents the sum effect of all those variables together. Given sex differences in CHD risk, each analysis was stratified according to sex. The final adjustment model included important potential effect moderators, including total energy intake and BMI.

Cons: While the follow-up period was adequate, there may have been a lack of power to detect stronger associations, particularly for CHD deaths which were very low. Added to that is the fact that 37% of participants reported consuming no SSB in the previous year, and the strength of the study is attenuated again. Further, the median intake of SSB was also low, around ~48ml/d, and only the 90th percentile of participants [both sexes] were consuming levels of intake that might have ecological validity, e.g., 1 can of Pepsi. The included studies were all older cohorts and interventions from the late 1980' s and early 1990' s, which factoring in that beverage intake was only assessed at baseline, may have mischaracterised the exposure relative to current levels of intake. Only 23.8% of participants were male, which may also have influenced the sex-specific outcomes.

Key Characteristic

In nutritional epidemiology, standard practice is to rank participants according to levels of intake from highest to lowest, often in quintiles of fifths of intake, then compare the highest category to the lowest to assess risk associated with a disease outcome. And this approach has its strengths, particularly when we consider that controlled intervention trials in nutrition often lack any meaningful difference in nutrient intakes between groups, *even* the nutrient they are trying to compare. Thus, comparing high vs. low levels of intake is an advantage to nutritional epidemiology, particularly where there are large differences in these levels of intake.

However, one advantage of RCTs is the ability to control total energy intake *and* specific macronutrients, in order to determine differences between dietary composition. But how do you do this in epidemiological research? The answer is what are known as "substitution models". This is analogous to an RCT controlling for total energy, and involves modelling the effects of isocaloric replacement of one nutrient [or food] with another.

However, when the substitution model is of a food – or beverage in the case of the present study – then some caution is required to properly interpret the outcomes [6,7]. Let' s take the example of the present study, which modelled the substitution of SSB with ASB, while adjusting for total energy intake, trans-fats, PUFA:SFA, and fibre. This means that the analysis is looking at a 1-unit higher intake of ASB and 1-unit lower intake of SSB at the same level of energy intake, fibre, trans-fats, and PUFA:SFA.

But what about, as one example, whole fruit intake? Or non-starchy vegetable intake? Is it possible that consuming both ASB and SSB are associated with different underlying dietary patterns? The answer is 'yes' [6,7]. If the two underlying dietary patterns are similar, then the substitution may reflect more of a 'true' effect of replacing Food/Beverage A with Food/Beverage B. Otherwise, the magnitude of effect of substituting SSB for ASB must also be interpreted *as whatever other aspects of diet correlate with ASB intake beyond the factors adjusted for in the model.*

Interesting Finding

Let's stick with the theme and say that the most interesting finding of the present study is the one that should be intuitive, yet based on the hyperbole surrounding AS is not: that replacing SSB with ASB was associated with lower risk for CHD events. This may seem to some to be a counter-intuitive finding due to some associations between ASB and *increased* risk of adverse health outcomes [4,5]. However, the epidemiology of AS intake and health outcomes is fraught with several known confounders, particularly reverse causality: higher adiposity is associated with high levels of ASB intake, rather than higher ASB intake *leading* to higher adiposity [8,9].

The fact is that no analysis prior to the present study had considered the effects of substitution. However, substitution is *precisely* the entire rationale for the use of AS in the food supply. By modelling substitution, the present study was the first in epidemiology to demonstrate the purported role of AS, i.e., replacing SSB with ASB. The modest 12% overall risk reduction [13% and 10% in men and women, respectively], as stated above under ***Key Characteristic***, must also be interpreted as reflecting an underlying dietary pattern that may associate with ASB use. And overall, this is a pattern that was associated with lower risk of CHD events compared to SSB [and related dietary pattern].

Relevance

Overall, the present study could be considered a more appropriate approach to the role of AS in the food supply, i.e., replacing sugar-sweetened products. Given the complexity of the associations between ASB intake and wider lifestyle and dietary characteristics, even well-considered adjustment models may be prone to reverse causality with this particular exposure. Analysing the effects of replacing SSB with ASB thus allowed for a more ecologically valid test of the relationship between SSB, ASB, and disease risk.

This is important because whatever debate exists, and may continue, in relation to ASB, the associations with sugar intake are clear. In the UK Biobank cohort, an analysis of ~198,000 participants showed that >2 servings of SSB per day was associated with a whopping 84% [HR 1.84, 95% CI 1.42 to 2.37] higher risk all-cause mortality [(2)]. And Yang *et al*. [(3)] showed that risk for CVD mortality associated with added sugar intake increased exponentially over 25% energy from sugar.

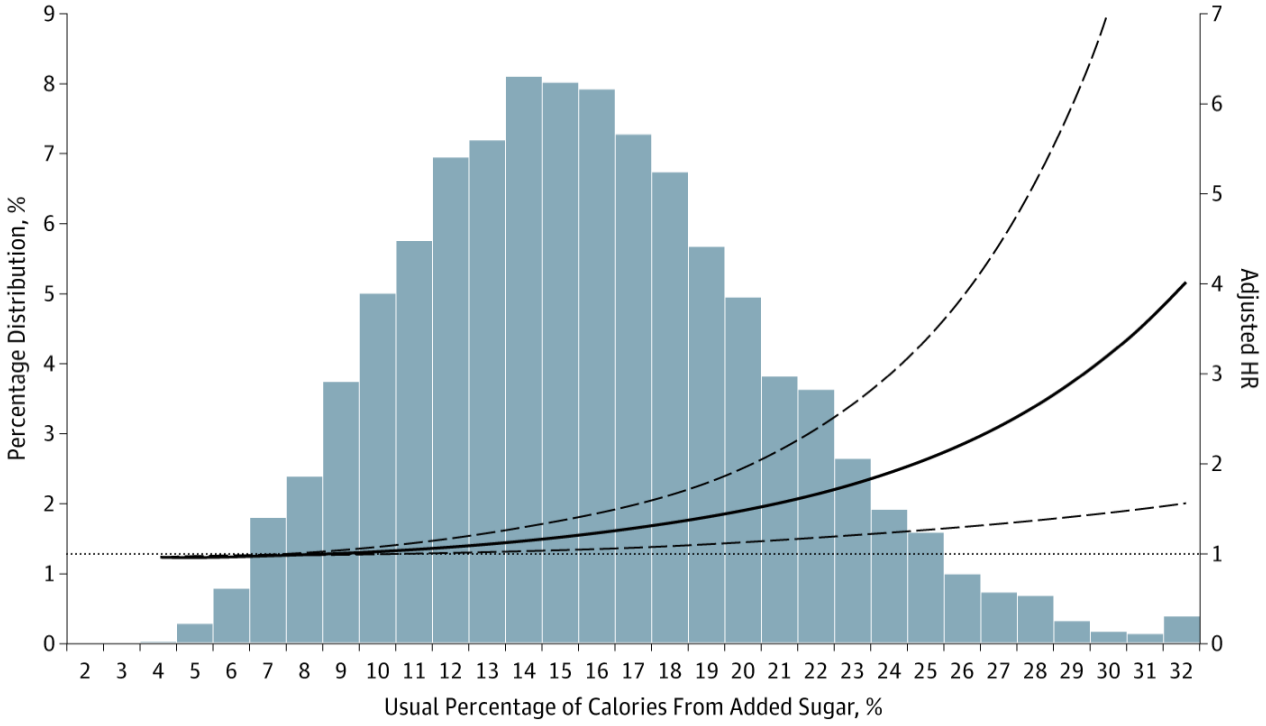


Figure *from Yang et al.* [(3)] *illustrating the distribution of sugar intake in a U.S. cohort as a percentage of energy with the corresponding risk for CVD mortality [**black line**]. For context, the average UK intake of added sugar is 12%, while in the U.S. it is 14-15%.*

In the analysis by Yang *et al*. [(3)], there was a 30% higher risk in people consuming 10-24% energy from sugar, which jumped up to a 175% higher risk in those consuming >25% energy from added sugars. The point here is that in many Western countries, current population averages of added sugar are >10%. Thus, the findings of the present study have some important relevance if the replacement of SSB with non-caloric/AS alternatives would lower that total added sugar intake into a lower risk range.

Application to Practice

It is important to state that AS are not biological benign. But there is a substantial difference between anything in the food supply not being entirely benign vs. having adverse effects. Much of the supposed adverse effects of AS, from impacts on glucose and insulin homeostasis to 'tricking the brain' into wanting actual sugar-containing foods, are not supported by any weight of evidence [10–14]. In the context of CHD management risk, much of the dietary low-hanging fruit is ready to implement; replacing saturated with unsaturated fats, particularly plant-sourced mono/polyunsaturated fats; increasing dietary fibre; increasing fruit and vegetable intake. There is no good evidence to suggest that a Diet Coke on top of such a dietary pattern poses any concern.

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