Sugar Wars, Episode 2: “Fructose Strikes Back”

Effect of Fructose on Established Lipid Targets: A Systematic Review and Meta-Analysis of Controlled Feeding Trials

Introduction

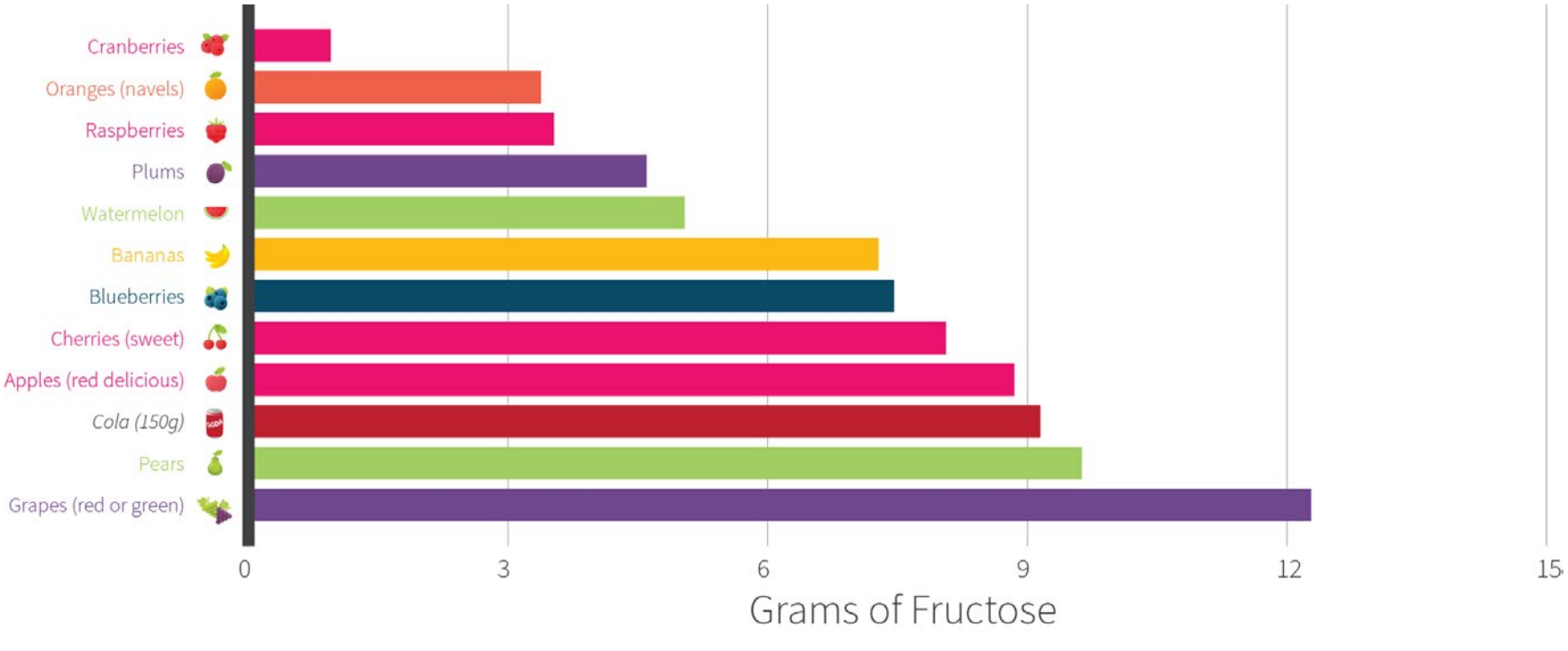
Low-carb diets, saturated fat, and fructose: these constitute the holy trinity of hotly-debated topics in both the scientific literature and popular media. Luckily for us, when these disputes arise we often see an uptick in research as scientists try to fill in any knowledge gaps. In fact, 23 (39%) of the 59 trials included in the current meta-analysis on fructose were published within the past 15 years.

The deliberation over fructose has centered around what its metabolic effects may be, like its impact on diabetes risk or its role in the obesity epidemic. Dr. Robert Lustig has been a leading vocal proponent of the fructose hypothesis, which contends that fructose plays a dominant role in the high rates of obesity, metabolic syndrome, type 2 diabetes, cardiovascular heart disease, non-alcoholic fatty liver disease, cancer, and poor lipid profiles. Dr. Lustig has also proposed fructose as a main mechanism in his "unifying hypothesis of metabolic syndrome" and has drawn parallels between the negative health outcomes of chronic alcohol and fructose consumption. His hypothesis has resonated with many. Dr. Lustig's popular YouTube talk, Sugar: The Bitter Truth, has been viewed nearly six million times.

The concern over fructose has been echoed in public health guidelines provided by the American Heart Association (AHA) and the Canadian Diabetes Association (CDA). The AHA has recommended limiting added sugars to 100 calories a day for women (about 34 grams) and 150 for men (about 51 grams), which is about 5% of daily calories. Their consensus statement also concluded that there were data indicating fructose intakes greater than 50-100 grams per day may elevate triglyceride levels. For reference (and as depicted in Figure 1), 50 grams of fructose would equate to about two 12 ounce cans of cola, 3.5 *large* red delicious apples, or seven cups of blueberries. The CDA has called for added sugars to make up no more than 10% of daily calories (50 grams on a 2,000 calorie diet) and that added fructose consumption above 60 grams a day may moderately increase triglycerides in people with type 2 diabetes. The CDA is careful to note that consuming naturally occurring fructose from fruit has not shown evidence of harm.

The fructose hypothesis has been contested by many scientists, including some of the authors of the current paper. In the present review, Dr. John Sievenpiper and his team examine the effects of fructose on lipid targets,

Figure 1: Fructose content of 1 cup (~150 g) of fruits (and cola as a reference)



Source: USDA National Nutrient Database for Standard Reference Release 27

such as HDL, LDL, and triglycerides, for cardiovascular disease and metabolic syndrome. Two previous reviews on the effect of fructose on lipid profiles have been conducted. A 2008 review by Livesey and Taylor indicated a ≥100 grams per day threshold, above which triglyceride levels were adversely affected. However, the review contained data from trials of both healthy and unhealthy participants, which may confound some of the findings. A second 2009 review conducted by Sievenpiper et al. identified that a fructose intake greater than 60 grams per day in people with diabetes caused triglyceride levels to rise. Since then, 13 additional controlled fructose feeding trials have been conducted. The current review updates and expands on Sievenpiper's previous paper.

Dr. Robert Lustig has proposed that fructose plays a primary role in causing obesity, type 2 diabetes, poor lipid profiles, and cardiovascular heart disease. The American Heart Association and the Canadian Diabetes Association have responded to these worries by proposing upper daily intakes of fructose. Many scientists disagree with the fructose hypothesis, including some of the authors of this review. This study aims to examine the effect that fructose may have on lipid profiles. Fifty-nine controlled feeding trials were examined for this analysis.

Who and what was studied?

A systematic review and meta-analysis is a different type of study than the kind you usually read about in ERD. In these papers, no new studies have been conducted. Instead, the literature has been thoroughly examined for all papers pertaining to a particular topic. In this case, the researchers were looking for two types of controlled feeding trials: trials where calories were kept constant (isocaloric) but included a portion of dietary carbohydrates swapped out for fructose, and trials where calories from fructose were added to the diet (hypercaloric). These hypercaloric trials were not specifically overfeeding trials, but rather studies where a fructose supplement was added to a participant's standard diet to create caloric excess.

The results from all these trials are then standardized so comparisons can be made between studies. Looking at all available data makes it easier to recognize trends and identify where the weight of the evidence may lie. The purpose of this meta-analysis was to determine the effects of fructose on five lipid levels in people who were healthy or had diseases. These lipid targets included:

- Low-density lipoprotein (LDL) – A lipoprotein is a molecule that carries cholesterol through your bloodstream. Lipoproteins like LDL promote the formation of plaques in the arteries. LDLs carry cholesterol particles from the liver to the rest of the body.
- Apolipoprotein B (Apo B) – The primary structural protein of lipoprotein particles such as LDL that have been implicated in the progression of heart disease.
- Non-high-density lipoprotein (Non-HDL-C) – Non-HDL-C is your HDL cholesterol number subtracted from your total cholesterol. It can be used as a marker for heart disease risk.
- High-density lipoprotein (HDL) – Carries cholesterol from the body to the liver. High levels of HDL are associated with lower cardiovascular disease risk.
- Triglycerides – A type of fat found in the blood. High levels are associated with cardiovascular disease risk.

The research team identified 59 controlled trials that used a crossover or parallel study design. In a crossover trial, all participants receive both treatments at different periods and act as their own control group. These 59 trials included 51 isocaloric trials, eight hypercaloric

Randomized trial quality

In this review, the authors evaluated the quality of included trials with the Heyland Methodological Quality Score (MQS). These evaluations are commonly used to help root out the most rigorously conducted studies. There are many different scales used to assess studies (GRADE, PEDro) but they all attempt to do the same thing: evaluate sources of bias that can be introduced through the study's design, execution, and analysis. The score each individual paper receives can help researchers determine what the quality threshold will be for inclusion into a meta-analysis.

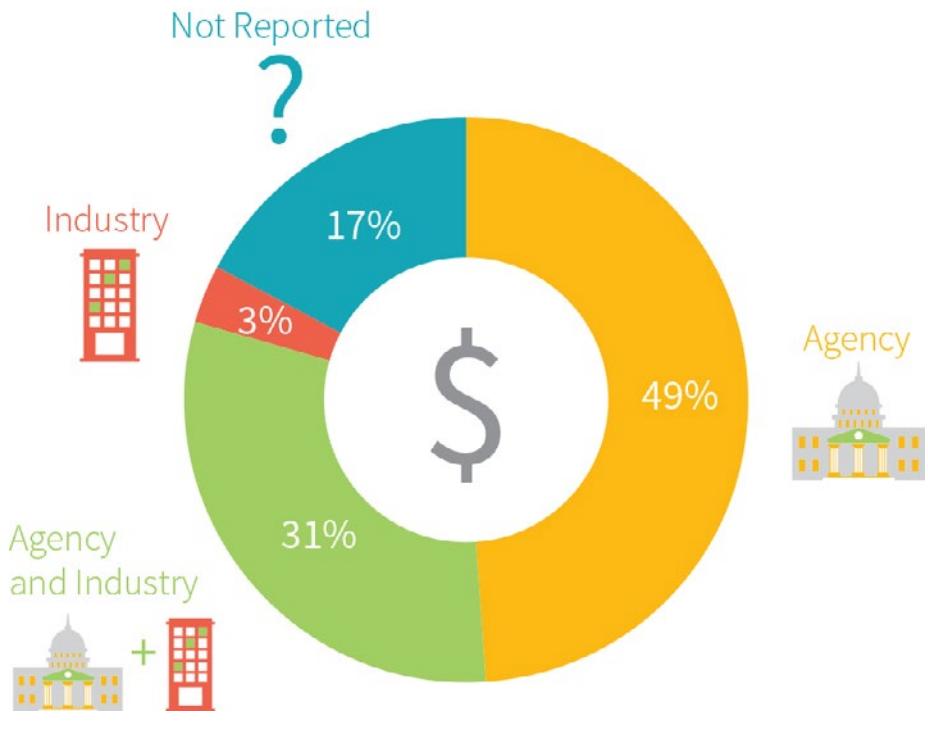
With MQS, studies are judged in nine criteria. Only studies that receive an eight or higher on the 13-point scale are considered to be high in methodological quality. By excluding lower quality trials, like those that do not blind their participants, researchers can avoid overestimating the benefits of an intervention, which tends to occur in poorly-controlled trials.

trials, and had a combined total of 1,068 participants. Trials were excluded if they had a follow-up of fewer than seven days, gave fructose intravenously, did not have a control diet, or reported end-points unsuitable for the analysis. All included trials were reviewed by four researchers to assess methodological quality using the Methodological Quality Score (MQS) system. Trials with a score of eight or higher are considered to be of high methodological quality. The average MQS score of included trials was 6.78.

When conducting their analysis, the researchers separated participants by health status. For each of the five lipid targets assessed, a subgroup analysis was performed for the following groups: participants with diabetes, those with insulin resistance or hypertriglyceridemia, and healthy individuals. By conducting subgroup analyses, the authors were able to eliminate some of the confounding variables present in the 2008 fructose review by Livesey and Taylor. However, due to the limited number of hypercaloric trials, subgroup analysis was not performed for those studies. A combined overall result was also given for each lipid target.

An interesting aside is that the authors reported the funding source of all included trials (summarized in Figure 2), something not typically seen in a meta-analysis. Of the 59 trials, 29 were funded by an agency (government, university, or non-profit), 18 were funded by both agency and industry, two were funded by industry, and 10 did not report their funding source. The mixed agency/industry-funded studies had the highest average MQS score (7.6), followed by agency (7.4), not reported (6.6), and industry (5.5).

Figure 2: Where the funding came from for the studies in this meta-analysis



This paper updates a previous meta-analysis by including 13 additional controlled feeding trials. The authors sought to determine the effects of fructose on lipids in both healthy and unhealthy individuals. Fifty-nine trials including 1,068 participants were assessed. Healthy and unhealthy individuals from isocaloric feeding trials were assessed separately to avoid confounding variables.

What were the findings?

The main findings are summarized in Figure 3. Among the isocaloric trial comparisons, in which part of the dietary carbohydrates were swapped for fructose, no significant changes on any lipid target were seen. In the hypercaloric trials, where fructose was added to the diet to create a caloric excess, an increase in apo B and triglycerides was observed. Fructose could possess the unique ability to modestly raise apo B and triglycerides when eaten in a hypercaloric state, but there is a caveat to this possibility. If fructose has an effect independent of total calories, it should have been observed in the isocaloric comparisons. Because no effect of fructose was observed in the isocaloric trials, it seems likely that most of the increase in apo B and triglycerides seen in the hypercaloric studies was due to the excess calories, as opposed to the fructose.

In the 2008 and 2009 meta-analyses discussed earlier, the researchers had found that fructose was able to increase fasting triglycerides at a dose of 60 grams a day in people with diabetes and 100 grams a day in people with mixed health statuses. The meta-analysis under review was not able to replicate those earlier findings. This is an important discovery, as the AHA and CDA practice guidelines cited one or both of the older meta-analyses as evidence used to help set their daily sugar intake recommendations.

One unexplained finding was that there seemed to be an inconsistent effect on some lipids depending on what form the fructose was delivered in: solid, liquid, or mixed. This is not the first time the form of fructose has led to a curious finding. In a systematic review and meta-analysis of the effects of fructose on body weight in controlled feeding studies, fructose delivered in solid and fluid form had a weight-decreasing effect that differed statistically compared to fructose delivered

Figure 3: Fructose's effects on blood lipids

	ISOCALORIC STUDIES			HYPERCALORIC STUDIES
	People with insulin resistance, diabetes, or high triglycerides	Healthy population	Total population	Total population
HDL-C	—	—	—	—
LDL-C	—	—	—	—
Non-HDL-C	—	—	—	—
Apo B	—	—	—	↑
Triglycerides	—	—	—	↑

in mixed form, which had weight-increasing effects. Furthermore, when looking into prospective cohort studies that examine the relationship between fructose and diabetes, liquids like sugar-sweetened beverages and fruit drinks are correlated with increased risk of diabetes (except not 100% fruit juice, another curiosity) while solid foods like cakes, cookies and fruit are not correlated with increased risk. The researchers have noted that these findings are likely due to the trials being underpowered, differences seen in study populations, and possibly due the observational nature of some studies.

No effect on lipid targets were seen in the isocaloric trials, but apo B and triglycerides were elevated in hypercaloric trials. The dose-response curve for fructose intake on triglycerides established in previous research was not able to be replicated in this analysis. The new data presented may alter future clinical practice guidelines published by health organizations like the AHA and CDA. It is likely that the apo B and triglyceride increases seen in the hypercaloric studies were due to excess calories and not necessarily because of the fructose itself.

What does the study really tell us?

It is important to note the limitations of the evidence when attempting to extrapolate these results to larger populations. The long-term effects of fructose consumption may not yet be fully understood, especially as the average follow-up period for all trials was three weeks. Fructose dosing was also very high in these studies, as the median dose was 96.8 grams per day, way beyond the 95th percentile of American standard intake.

We discussed the issue of non-real world doses of fructose in trials in the ERD #9 Volume 2 article, "Fructose: the sweet truth". Ultra-high fructose intakes in clinical trials may have limited applicability to real-world relevance. But even these high fructose doses were unable to elicit a negative effect in the isocaloric trials, giving credence to the hypothesis that it is the excess calories and not the fructose itself that may be most detrimental. The overall evidence quality was also modest, as 51% of the trials had an MQS of less than eight.

Based on the data analyzed, there does seem to be moderate evidence-quality controlled feeding trials suggesting that when other carbohydrates are replaced by fructose on an energy balanced diet, blood lipids are not likely to change in a way that promotes cardiovascular disease. This same moderate evidence base has indicated that when fructose is consumed to the point of creating a positive caloric balance it may adversely affect some lipids. However, these effects may be due to the excess calories themselves, rather than the fructose.

The short duration of trials, moderate methodological quality, high fructose dose typically administered, and dissimilarities of study populations compared leaves some questions about the effects of fructose. These questions can be answered by future trials that are larger in sample size, longer in duration, of higher methodological quality, and use appropriate "real world" fructose doses. Such trials could greatly increase our understanding of the metabolic effects of fructose and guide our public health policy.

The evidence assessed in this study was of moderate methodological quality. Limitations included short trial duration, unrealistically high fructose dose, and the comparison of dissimilar study participants. Based on the data analyzed, there is moderate evidence that isocaloric fructose consumption does not harm lipid targets while overconsumption may. Negative effects of excess fructose could be due to the extra calories themselves and not the fructose.

The big picture

There has been a concerted effort in the past few years to try and elucidate the role fructose plays in our health. The study we just examined is one part of the puzzle in an ever-expanding line of literature. There are six main areas where scientists have produced systematic reviews and meta-analyses examining the effects of fructose on health markers, many of which have been conducted by Dr. Sievenpiper. They are:

- Blood pressure
- Glycemic control
- Lipids
- Body weight
- Uricemia (Gout)
- Non-Alcoholic Fatty Liver Disease (NAFLD)

To give you a picture of where the weight of the evidence on fructose currently stands, the findings from the most recent reviews are briefly summarized below.

Blood pressure

Two reviews of prospective cohort studies and one of controlled feeding trials have been conducted for blood pressure. The first cohort review looked at the association between fructose-containing sugar-sweetened beverages (SSBs) and the risk of hypertension. The researchers found that one or more SSB per day was associated with a 12% higher risk. The second cohort review looked at total fructose intake but found no association between fructose intake and hypertension risk. Cohort studies are not without their limitations, though they are useful in finding correlations. Luckily, the last review was of controlled feeding trials. When fructose replaced a portion of carbohydrates in an isocaloric diet, significant improvements were seen in diastolic pressure (when the heart relaxes to refill with blood) and mean arterial pressure (average blood pressure) but not systolic pressure (when the heart contracts). The hypercaloric trials saw no overall effect on mean arterial pressure.

Glycemic control

Glycemic control is very important for people with diabetes for maintaining long-term health. Historically, fructose has been suggested to play a role in helping people with diabetes control their blood sugar due to its low glycemic index. A 2012 review of controlled feeding trials examined the effect of fructose on glycemic control in individuals with diabetes. The researchers found that when fructose replaced other carbohydrates under energy balanced diets, participants saw approximately a 0.53% reduction in HbA1c, a measure of average glucose levels over two to three months. It may not seem like much, but a 0.53% reduction in HbA1c is considered clinically significant by the US Food and Drug Administration. Fasting glucose and insulin were not affected.

Lipids

Apart from the study under review, there is one additional review that specifically looked at the effect fructose had on post-meal triglycerides. Isocaloric exchange of carbohydrates for fructose resulted in no significant triglyceride increases for otherwise healthy individuals and participants with diabetes, but researchers did see increases in participants with obesity. When fructose was supplemented hypercalorically,

> “The difference in weight loss could have been partially due to malabsorption of fructose.”

triglycerides did increase. This effect was also observed in the study under review. However, the excessively high dose (about 175 grams per day) could be a confounding variable.

Body weight

Perhaps the most debated area of the fructose hypothesis is its role in weight gain. Two reviews, one by Te Morenga et al. and the other by Sievenpiper et al., found that diets providing similar calories but different fructose intakes did not appear to affect weight gain. Surprisingly, the Sievenpiper review found that a subgroup of participants who were overweight or obese saw significant weight loss on the higher fructose diets. However, this finding became insignificant after a sensitivity analysis. The difference in weight loss could have been partially due to malabsorption of fructose. Participants may not have been fully absorbed the calories from fructose, excreting them instead. It is also possible that fructose may have a higher thermic effect over other carbohydrates like glucose, leading to a slight but insignificant weight loss advantage. Within the hypercaloric fructose arm, there was significant weight gain when given high daily fructose doses (104 to 250 grams a day). In essence, fructose doesn't seem to have any special weight-increasing effects beyond the calories it contains.

Uricemia

When uric acid accumulates in the blood, it can lead to gout, a painful inflammation of the joints. Among the isocaloric trials of fructose reviewed, no effect was seen in uric acid levels. The hypercaloric fructose intake did significantly raise uric acid though. The clinical and practical applications of this remain unclear, as the fructose doses were very high (213 to 219 grams a day).

NAFLD

Non-alcoholic fatty liver disease is a condition characterized by a buildup of excess fat in the liver, affecting 10 to 20% of Americans. NAFLD can progress to cirrhosis, causing permanent liver damage. Both reviews in this area came to similar conclusions: isocaloric exchange of fructose did not induce NAFLD in healthy participants. Fructose overfeeding did negatively affect some markers of liver health, but that was confounded by excessive energy intake, and the overall level of evidence was not robust.

These summaries may help shed some light on the state of the fructose hypothesis. The common theme seen among all these analyses was that negative health effects were not observed until fructose was administered in caloric excess. The overall quality of evidence was consistently rated as poor or moderate. Common limitations included small sample sizes and trials of short duration. Nearly all the authors called for longer and larger trials.

The past five years have produced a flurry of systematic reviews and meta-analyses as scientists try to understand the health implications of fructose consumption. The current evidence indicates that the negative health effects of fructose may be due to the excess calories they can provide in a diet, rather than to the fructose. The call for for better, longer trials was a uniform message across all papers.

Frequently asked questions

Some of the authors have taken money from the food industry. Isn't that a conflict of interest that could bias their interpretation of the data?

At the bottom of the reviewed meta-analysis is a robust conflict of interest disclosure statement. Coming in at over 1,300 words, many of the authors list just about every source of funding they have ever received. Some of them have worked for or received money from large players in the food industry, including Coca-Cola. Dr. Sievenpiper even disclosed that his wife is an employee of Unilever Canada. Lengthy disclosures like this one

are not standard. Typically, the conflict of interest section is used to reveal any financial ties or relationships that may be potential sources of bias of the authors. Dr. Sievenpiper has stated that his super-disclosures were influenced by his mentors, Dr. Vladimir V.V. Vuksan and Dr. David J.A. Jenkins, who highly encouraged full transparency.

You may be worried about the influence of industry on the findings of this paper. It is true that papers published by researchers with ties to industry deserve more scrutiny, but there are some important items to note in this paper's case. The review was not funded by industry, but rather by grants from the Canadian Institutes of Health and the Calorie Control Council. None of the sponsors of this trial had a role in its design or conduct. Additionally, all 16 authors had "access to the study data and reviewed and approved the final manuscript." Lastly, the trial was pre-registered at ClinicalTrials.gov. By registering the study methodology and primary outcome measures before conducting a trial, the researchers have fewer degrees of freedom to change endpoints as the study progressed. Simply put, trial registration makes it easy to see if any drastic changes have been made between the time of registration and publication that could raise any red flags.

What should I know?

Fructose in the diet does not appear to be an issue for lipid targets as long as it is not consumed to the point where a caloric surplus is created. The available evidence suggests that you may see an increase in your apo B and triglyceride levels when you over consume fructose, although this may not be a unique trait to fructose and could be caused by the excess calories themselves. However, naturally occurring fructose from fruit consumption has currently shown no evidence of harm. Increased fruit (and vegetable) intake has long been associated with improved health. Fruit is also packed with fiber, flavonols, anthocyanins, micronutrients, and antioxidants that the vast majority of SSBs lack.

Because the evidence quality is modest, setting strict upper limits on fructose intake may be difficult, based on the current evidence. However, limiting liquid sources of calories from SSBs and fruit juices can be an easy method for reducing overall calorie intake. ◆

Even with all these studies, the fructose picture is not yet crystal clear. What will the next few years of research show? Discuss sugars and metabolic syndrome at the ERD private Facebook forum.

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